Suspected Cancer:

recognition and management of suspected cancer in children, young people and adults

Update of clinical guideline 27

Appendix J1:

Sections from NICE clinical guideline 27 full version that have been removed

NCC-PC

The National Collaborating Centre for Primary Care

REFERRAL GUIDELINES FOR SUSPECTED CANCER IN ADULTS AND CHILDREN.

PART ONE

CHAPTERS 1 - 12

April 2011
A recommendation in this guideline (see page 69) has been updated and replaced by section 1.1.1 in 'Ovarian cancer' (NICE clinical guideline 122, 2011). Available from www.nice.org.uk/guidance/CG122

Contents

Preface 5

Acknowledgements 7

Glossary of Terms 18

1 Introduction *20*

1.1 Guideline aims 20

1.2 Referral of patients with suspected cancer 20

1.3 Principles underlying the guideline development 23

1.4 Who should use this guideline 23

1.5 Structure of guideline documentation 23

1.6 Guideline limitations 24

1.7 Scope 26

2 Methods *30*

2.1 Introduction 30

2.1 The developers 30

2.3 The Guideline Development Group 31

2.4 Developing key clinical questions (KCQs) 32

2.5 Identifying the evidence 32

2.6 Health economics 34

2.7 Review of clinical audits 35

2.8 Reviewing and grading the evidence 36

2.8.1 Details of levels of evidence and grading of recommendations 39

2.8.2 The role of risk factors in decisions about referral for suspected cancer 41

2.8.3 What is a risk factor? 41

2.8.4 When is a risk factor relevant to a referral decision? 43

2.8.5 Specificity of the symptoms and signs 43

2.8.6 Patient concern 44

2.8.7 Health economics 44

2.9 Developing recommendations 45

2.10 External review 46

3 Key Priorities for implementation 47

4 Executive Summary 49

4.1.Support and Information needs of people with suspected cancer at the time of referral 49
4.2.The Diagnostic Process 53

4.3.Lung Cancer 56

4.4.Upper Gastrointestinal Cancer 59

4.5.Lower Gastrointestinal Cancer 62

4.6.Breast Cancer 65

4.7.Gynaecological Cancer 68

4.8.Urological Cancers 71

4.9.Haematological Cancers 75

4.10.Skin Cancer 78

4.11.Head and Neck Cancer 82

4.12.Brain and CNS Cancer 86

4.13.Bone Cancer and Sarcoma 86

4.14.Children's Cancer 86

5 Algorithms 86

6 Audit Criteria 86

7 Support and Information needs of people with suspected cancer at the time of referral 86
8 The Diagnostic Process 86

9 Lung cancer 86

9.1 Symptoms and Signs 86

9.2 Investigations 86

9.3 Delay and diagnostic difficulties 86

10 Upper gastrointestinal cancer 86

10.1 Symptoms and Signs 86

10.2 Investigations 86

10.3 Delay and Diagnostic Difficulties 86

11 Lower gastrointestinal cancer 86

11.1 Symptoms and Signs 86

11.2 Investigations 86

11.3 Delay and Diagnostic Difficulties 86

12 Breast cancer 86

12.1 Signs and Symptoms 86

12.1.2 Men 86

12.2 Investigations 86

12.3 Delay and Diagnostic Difficulties 86

12.4 Support and Information needs 86

Reference List 382

Chapters 13 – 21 as a separate document

Appendices as separate documents

Appendix A: Evidence Tables
Appendix B: Evidence Tables
Appendix C: Health Economics
Appendix D: Example Search Strategy

Preface

As a practicing GP, I will see seven or eight new patients with cancer in a year, but may see hundreds of patients who have a possible diagnosis of cancer. Diagnosis is relatively straightforward when the presentation is obvious but when symptoms are vague or inconclusive – as is often the case- it becomes much more difficult. In such cases, I know that I would find it helpful to have information that would help me decide which patients to refer for further investigation and what clinical priority to accord.

Whilst greater vigilance is needed, it is important not to routinely over- investigate or make inappropriate referrals. The role of the GP[1] is to *'tolerate uncertainty, explore probability and marginalise danger'*. In contrast, the role of the secondary care specialist is to *'reduce uncertainty, explore possibility and marginalise error'*.

Almost one million people visit their GP every day in the UK and making an accurate diagnosis can often be difficult. It is one of the strengths of general practice that uncertainty is managed so effectively. The RCGP[2] in its seminal document *The Future General Practitioner* says, *"A correct diagnosis is a crucial achievement which opens the way to prognosis and treatment."* Delayed or missed diagnosis is the most common reason for medico-legal claims in general practice[3].

Improvements in medical practice are therefore needed and indeed possible. However, the solutions sometimes proposed are too simplistic. But these guidelines are in a different league. They clearly understand the culture of general practice.

I therefore welcome these referral guidelines. They offer a practical way forward to improve cancer diagnosis. I liked the emphasis on support for patients, learning and peer review, communication and consulting skills, the appropriate use of investigations and the section dealing with children.

I commend these referral guidelines to primary health care teams and urge primary care organisations to implement them comprehensively.

Mayur Lakhani FRCGP, GP
Leicestershire, Chairman of Council, Royal College of General Practitioners, London.

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The Project Team would like to thank Dr Ivan Cox, chairman of the guideline group, for his skilled leadership, and all the co-optees who had an essential role in providing the group with expert advice. We thank Ms Cluley for her organisational support.

Glossary of Terms

Equivocal: A symptom and/or sign that has more than one equally plausible explanation, or in which the explanation is uncertain.

Odds Ratio (OR): The odds of an event among an exposed population to the odds among the unexposed.

Persistent: 'Persistent' as used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional. In many cases, the upper limit the

[1] Marinker M Looking and Leaping. In Clinical Futures. Marinker M, Peckham
[2] RCGP. 1972. The Future General Practitioner: Learning and Teaching BMJ Books London
[3] http://www.rcgp.org.uk/quality_unit/insaferhands/ISH6.pdf

professional will permit symptoms and/or signs to persist before initiating referral will be 4-6 weeks.

Progressive: Getting worse over a long or short period of time.

RCT: Randomised controlled trial.

Recurrent: A symptom and/or sign that resolves then returns at least once.

Relative risk (RR): Ratio of the risk of an event among an exposed population to the risk among the unexposed.

Trigger for referral: A symptom or sign that is sufficient to indicate the need for either urgent or non-urgent referral.

Watch and wait: A strategy that may sometimes be employed when the symptom(s) and/or sign(s) suggest a benign condition, although do not rule out the possibility of cancer. It is important to review the patient at intervals until the possibility of cancer is ruled out, to limit the duration of the watch and wait policy to a predetermined period, and to refer if the patient's condition changes or if the predetermined period expires without a resolution of the patient's problem.

Unexplained: When used in a recommendation, unexplained refers to a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any).

Urgency of referral
Immediate/emergency: an acute admission or referral occurring within a few hours, or even more quickly if necessary.

Urgent: the patient is seen within the national target for urgent referrals
(currently two weeks).

Non-urgent: all other referrals.

Prompt: This term has been occasionally used in the guideline in connection with referrals that are non-urgent, but delay should nevertheless be avoided. The upper limit for 'prompt' referrals will vary according to the particular case, but if delay beyond six weeks is likely, the primary care professional should discuss the case and the need for an early appointment with the specialist.

The category of 'soon' referral is no longer generally used and therefore is not used in this guideline.

Introduction

1.1 Guideline aims
Clinical guidelines are defined as "*systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances*".(1) This guideline offers advice on the referral of patients with suspected cancer to specialist services. It updates previously published guidelines,(2) following a commitment in the NHS Cancer Plan(3) that these guidelines would be reviewed by NICE. The new guideline takes account of new research evidence and the findings of audits{969] undertaken since the publication of the previous guideline.

1.2 Referral of patients with suspected cancer
A key aim for the NHS is improvement in the care of people with cancer, including a reduction in mortality by 20% in people under 75 by 2010 in comparison with a 1995-97 baseline. Progress is being made towards this objective, and death rates are falling.{970} In England and Wales in 2003, 136,030 people died from cancer(4). The cancers causing most deaths are shown in *Table 1*.

Table 1 Deaths from cancer males and females, all ages, in England and Wales(4)

Cancer		Deaths all
Trachea, bronchus and lung	M	17,1
	F	11,6
Colorectal cancers	M	7,49
	F	6,58
Breast	M	6
	F	11,2
Prostate	M	9,16
Oesophagus	M	4,13
	F	2,28
Pancreas	M	3,06
	F	3,17
Stomach	M	3,28
	F	2,00
Non-Hodgkin's lymphoma	M	2,21
	F	1,93
Ovary	F	3,97
Leukaemia	M	2,23
	F	1,68
Bladder	M	2,90
	F	1,50
Multiple myeloma and	M	1,19
malignant plasma cell	F	1,14
Brain	M	1,69
	F	1,24
Liver, intrahepatic bile ducts,	M	1,53
gallbladder and biliary tract	F	1,22
Kidney	M	1,71
	F	1,10
Mesothelioma	M	1,37
	F	2
Lip, oral cavity, pharynx, and	M	1,57
	F	7
Cervix uteri	F	9
Malignant melanoma of skin	M	8
	F	7

*Permission to reproduce being

Five-year survival rates for some cancers are increasing. For example, rates for breast cancer rose from 72.8% in the period 1991-5 to 77.5% in the period 1996-9; for colon cancer the improvement was from 42.1% in men and 42.8% in women to 46.9% in men and 47.9% in women over the same period. However, in cancers survival rates have been relatively unchanged, for example certain

types of cancers of the bladder, brain, and cervix.(5)

Early referral has a role to play in the improvement of care for people with cancer, and in some cancers early referral may improve survival rates. In addition to its roles in prevention, support and long-term management of people with cancer, primary health care has particular responsibility for the early detection of cancer and the initiation of speedy referral to specialist services. To assist primary healthcare professionals identify people with suspected cancer as early as possible, the Department of Health issued guidelines on the topic in 2000.(2)

A recent report by the National Audit Office(6) on cancer services in England observed that patients in England tended to have more advanced cancer at the time of diagnosis than some other countries, at least for breast and bowel cancer. Older people and those from deprived areas were more likely to be diagnosed with cancer at a more advanced stage.

The national Audit Office accepted that more action was needed to reduce delay in the presentation of patients for treatment. Delay may be explained by the failure of some patients to seek help quickly, and by the difficulties general practitioners can face in identifying people with cancer. An electronic survey was circulated to the several thousand subscribers of a general practitioner information network. The survey attracted 814 responses, just under half of whom had read the Department of Health guidelines published in 2000 and found them useful. Some respondents reported that the guidelines had not added to their existing knowledge. A survey of consultants indicated that respiratory physicians reported that 80% of referrals from general practitioners were appropriate, but colorectal surgeons reported 50% that only were appropriate. The National Audit Office recommended that the updated guidelines should be widely disseminated and acted upon, and that stronger joint working relationships between general practitioners and hospitals should be encouraged through the continued development of standardised referral procedures and feedback to general practitioners on appropriateness of referrals.

1.3 Principles underlying the guideline development

The key principles behind the development of this guideline were that it should:

- take full account of the perspective of the person with suspected cancer and their family and/or carers
- consider all the issues that are important in the primary care assessment and referral of people with suspected cancer
- base the recommendations on the published evidence that supports them, with explicit links to the evidence
- be useful and usable by all health care professionals dealing with people with suspected cancer
- indicate areas of uncertainty requiring further research.

1.4 Who should use this guideline

The guideline is intended for use by individual healthcare professionals in primary care, people with suspected cancer and their carers, the wider general public, and health care commissioning organisations and provider organisations.

Separate short form documents for people with suspected cancer and healthcare professionals are available without details of the supporting evidence. The guideline does not consider health promotion or education of the public about cancer.

1.5 Structure of guideline documentation

The guideline is divided into sections which cover in detail specific topics relating to twelve groups of cancers:

- lung
- upper gastrointestinal cancers
- lower gastrointestinal cancers
- breast cancer
- gynaecological cancers
- urological cancers
- haematological cancers
- skin cancers
- head and neck including oral cancers

- brain/central nervous system cancers
- bone and sarcoma, and
- children's and young people's cancers.

In each section, the symptoms, signs and risk factors relevant to initial assessment in primary health care are considered. The role of investigations in primary care is then addressed, and the sections conclude with consideration of factors related to delay and difficulties in diagnosis.

Two additional sections are included at the beginning of the guideline. The first deals with the needs of patients with suspected cancer at the time of referral. The second considers the process followed by healthcare professionals in reaching an initial diagnosis, and interventions to help healthcare professionals improve their ability to identify patients who should be suspected of having cancer.

Important general methodological issues are flagged up as appropriate. Where appropriate, full details of the papers reviewed are presented in the evidence tables (see Appendix A and B).

1.6 Guideline limitations

The guideline documentation and recommendations are limited to the detection of people who may have cancer in primary care, and do not address the assessment or investigation of patients after referral. The guideline will be relevant to professionals in general practice, walk-in centres, accident and emergency departments and other open access services that may be consulted by patients with symptoms or signs caused by undiagnosed cancers.

1.7 Scope

Guideline title

Referral guidelines for suspected cancer.

Short title

Referral guidelines for suspected cancer.

Background

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework is to be published. The statements in each NSF reflect the evidence that was available at the time the Framework was prepared.

The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop referral guidelines for suspected cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The guideline will be an update of previously published guidelines,(2) following a commitment in the NHS Cancer Plan that these guidelines would be reviewed by NICE. The new guideline will take account of new research evidence and the findings of audits undertaken since the publication of the previous guideline.
Both the Department of Health and the Welsh Assembly Government have introduced policies on the urgent referral of patients with suspected cancer.

Clinical need for the guideline

Cancer was responsible for a quarter of all deaths in England and Wales in 1997, and for over half of all deaths among women between 45 and 55 years of age.(7) The incidence of new cases of cancer increased by 12% in males and 28% in females between 1960 and 1997. For some cancers, mortality rates in the UK compare unfavourably with those in other countries.

Delays of three to six months between the onset of symptoms and diagnosis are associated with worse survival rates in breast cancer.(8) However, evidence about the influence of relatively short delays in other cancers is less clear. The initial symptoms of some cancers can be difficult to

distinguish from the symptoms of other more common disorders,(9) and delays can occur between the first presentation and referral for suspected cancer. In a study of the time between presentation and treatment of six common cancers in general practice, the median number of days between presentation of the first symptom or sign and initiation of referral was 0 days for breast, 28 days for large bowel, 31 days for lung, 84 days for oesophageal, 20 days for prostate and 66 days for stomach cancer.(10)

Survival rates for some cancers are lower than elsewhere in Europe, and patients in the UK may have more advanced disease at the time of diagnosis or treatment.(11;12)

The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information').

The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline. This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups and categories that will be covered

Patients in all age groups suspected of having one of the cancers covered by the guideline will be included.

The guideline will cover the following cancers:

- lung
- upper gastrointestinal cancers
- lower gastrointestinal cancers
- breast cancer
- gynaecological cancers
- urological/renal cancers
- haematological malignancies
- skin cancers
- head and neck including oral cancers
- brain/central nervous system malignancies
- sarcomas
- children's and young people's malignancies.

Groups and categories that will not be covered

The guideline will not cover:

- the organisation or effectiveness of screening schemes for cancer
- the tests undertaken after referral, therefore definitive diagnosis will not be covered
- referral for suspected recurrence or metastases in previously diagnosed cancer, or referral for palliative care.

Healthcare setting

The guideline will cover the care received from primary healthcare professionals who have direct contact with, and make decisions concerning, the referral of people with suspected cancer.

The guideline will address care in primary care prior to referral for specialist assessment, but will not address care after referral in secondary and tertiary centres.

The guideline will also be relevant to healthcare professionals in secondary care who suspect a patient they are managing for another condition also has cancer, and in whom referral to another specialist would be indicated.

The guideline will also be relevant to the work, but will not cover the practice, of those working in:

- accident and emergency departments
- walk-in centres
- NHS Direct
- voluntary sector

- occupational health
- other health professionals who may encounter patients with symptoms of cancer, for example allied health professionals, dentists, clinicians in secondary care and pharmacists.

Clinical management
The guideline will address:

1. the symptoms, signs and other factors that should prompt consideration of the need for referral, taking into account variation in risk by age and ethnic group
2. the initial investigations that contribute to the assessment of patients prior to, or in association with, urgent referral for suspected cancer
3. interventions intended to help healthcare professionals appropriately identify patients needing urgent referral for suspected cancer
4. the need for urgent referral, and the consequences of delay in referral
5. the information and support needs of patients who are referred for suspected cancer and their families
6. the monitoring of patients after referral but before the first specialist assessment will be considered in the guideline

Audit support within guideline
The guideline will include review criteria and advice.

2 Methods

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the National Institute for Clinical Excellence (the Institute) in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at: http://www.nice.org.uk).

2.1 The developers

The National Collaborating Centre for Primary Care (NCC-PC)
The National Collaborating Centre for Primary Care (NCC-PC) is hosted by the Royal College of General Practitioners (RCGP), and involves the following partners: Royal College of General Practitioners, Royal Pharmaceutical Society of Great Britain, Community Practitioners and Health Visitors Association, and the Clinical Governance Research and Development Unit (CGRDU), Division of General Practice and Primary Health Care, Department of Health Sciences, University of Leicester. The Collaborating Centre was set up in 2000, to undertake commissions from the National Institute for Clinical Excellence to develop clinical guidelines for the National Health Service in England and Wales. The two partners – University of Leicester and the RCGP unit – undertake this work on behalf of the NCC-PC.

This guideline was developed by the Clinical Governance Research and Development Unit (CGRDU), Department of Health Sciences, University of Leicester.

The methodology team
The methodology team was led by the Director of the NCC-PC Leicester, Professor of Quality in Health Care (the project lead). Other members of the team were the Deputy Director of the NCC-PC Leicester, a clinical lecturer, a systematic reviewer, an information librarian and a health economist. Where appropriate, the advice and opinion of the Chief Executive of the NCC-PC, the appointed Chair of the Guideline Development Group (GDG, see below) and members and co-opted experts of the GDG was sought. Editorial responsibility for the guideline rested solely with the methodology team.

2.3 The Guideline Development Group

Nominations for group members were invited from various stakeholder organisations who were

selected to ensure an appropriate mix of health care professionals and delegates of patient groups. In view of the number of organisations who needed to contribute to the guideline it was decided that there should be two groups: nominated members of the Guideline Development Group (GDG) and co-opted experts. Each nominated member was expected to serve as an individual expert in their own right and not as a representative of their parent organisation, although they were encouraged to keep their nominating organisation informed of the process. The co-opted experts contributed to aspects of the guideline development. For each group of cancers two experts were identified: one a specialist in the field and the other a general practitioner with a particular interest in that group of cancers. These experts were sent copies of the evidence reviews, were invited to sit within the GDG and entered fully into any discussion. Details of the experts can be found in the preface to the guideline. Group membership details can be found in the preface to the guideline.

The GDG met at six weekly intervals for 18 months to review the evidence identified by the methodology team, to comment on its quality and completeness and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the GDG.

All GDG members made a formal “Declaration of Interests” at the start of the guideline development and provided updates throughout the development process.

2.4 Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope (see chapter 1) into a series of key clinical questions (KCQs) which reflected the clinical care pathway for adults and children with symptoms and signs suggestive of suspected cancer seen in primary care. These KCQs formed the starting point for the subsequent systematic reviews and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG, with input as appropriate from co- optees and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The methodology team and the GDG agreed that a full literature search and critical appraisal process could not be undertaken for all of these KCQs due to the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Reasons for this included awareness that the evidence was conflicting or that there was a particular need for evidence-based guidance in that area. The KCQs prioritised for detailed searching were the symptoms and signs of cancers presenting in primary health care, primary care investigations, and diagnostic difficulties leading to delay in primary health care.

2.5 Identifying the evidence

Literature Search Strategy

The aim of the literature review was to seek to identify all available, relevant published evidence in relation to the key clinical questions generated by the GDG. The prioritised KCQs were turned into EBQs by the project lead and systematic reviewer. Literature searches were conducted using generic search filters and modified filters, designed to best address the specific question being investigated. Searches included both medical subject headings (MeSH terms) and free-text terms. Details of all literature searches are available from the NCC-PC, University of Leicester and an example can be seen in Appendix D.

The information librarian developed a search strategy for each question with the assistance of the systematic reviewer and the project lead. Searches were re-run at the end of the guideline development process, thus including evidence published up to the end of June 2004.

Depending on the clinical area, some or all of the following databases were searched: Cochrane Library (up to Issue 2, 2004) was searched to identify any relevant systematic reviews, and for reports of randomised controlled trials, MEDLINE (for the period January 1966 to June 2004, on the OVID interface), EMBASE (for the period January 1980 to June 2004, on the OVID interface), the Cumulative Index of Nursing and Allied Health Literature (for the period January

1982 to November 2003, on the Dialog DataStar interface), PsycINFO (for the period 1887 to June 2004, on the OVID and the Dialog DataStar interfaces), the Health Management Information Consortium database (HMIC), the British Nursing Index (BNI), and the Allied and Complementary Medicine Database (AMED). Searches for non-systematic reviews of the literature were limited to 1997 – June 2004. This was a pragmatic decision that draws on the search strategies used by the North Of England Evidence Based Guideline Development Project. No systematic attempt was made to search 'grey literature' (such as conference proceedings, abstracts, unpublished reports or trials, etc.).

Existing systematic reviews and meta-analyses relating to referral for suspected cancer were identified. Recent (last six years) high quality reviews of referral for suspected cancer were also identified. New searches, including identification of relevant randomised controlled trials (RCTs), were conducted in areas of importance to the guideline development process, for which existing systematic reviews are unable to provide valid or up to date answers.

The search strategy was dictated by the exact EBQ the GDG wished to answer. Expert knowledge of group members was also drawn upon to corroborate the search strategy.

The National Research Register (NRR), National Guidelines Clearinghouse (NGC), New Zealand Guidelines Group (NZGG) and the Guidelines International Network (GIN) were searched to identify any existing relevant guidelines produced by other organisations. The reference lists in these guidelines were checked against the methodology team's search results to identify any missing evidence.

The titles and abstracts of records retrieved by the searches were scanned for relevance to the GDG's clinical questions. Any potentially relevant publications were obtained in full text. These were assessed against the inclusion criteria and the reference lists were scanned for any articles not previously identified. Further references were also suggested by the GDG. Evidence submitted by stakeholder organisations that was relevant to the GDG's KCQs, and was of at least the same level of evidence as that identified by the literature searches, was also included.

2.6 Health economics

A separate systematic literature review was conducted to assess the state of the economic evidence, given that in the main searches this evidence was limited. The systematic reviewer and the health economist carried out these searches for health economics evidence. Economic search filters were used - including the one developed by the Centre for Reviews and Dissemination - in the following bibliographic electronic databases MEDLINE, PreMEDLINE, EMBASE, PsycINFO, CINAHL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Review of Effectiveness (DARE), the Cochrane Controlled Trials Register (CCTR) and the NHS R&D Health Technology Assessment Programme and special health economic databases Office of Health Economics – OHE - Health Economic Evaluations Database (HEED) and NHS Economic Evaluation Database (NHS EED) were searched.

Given the limited economic evidence in the area it was decided to perform a broad search for evidence that was designed to identify information about the costs or resources used in providing a service or intervention and /or the benefits that could be attributed to it. No criteria for study design were imposed a priori. In this way the searches were not constrained to RCTs or formal economic evaluations. Papers included were limited to studies of referral for suspected cancer published after 1990, written in English, and reporting health economic information that could be generalized to UK.

2.7 Review of clinical audits

The Centre for Reviews and Dissemination (CRD) has undertaken a review of clinical audits(13) to assess the implementation and effectiveness to the two week waiting time referral system to inform the cancer referral guideline. The summary findings relating to each group of cancers are outlined in each chapter of the guideline.

The review included audits undertaken following the adoption of the two week standard and the publication of the Department of Health's guidelines in 2000. Audits were identified by direct contact with all NHS Trusts, a detailed search of relevant internet sites, and by a search of electronic

bibliographies. This broad strategy was required because many audits would not have been published in medical journals. The audits identified were assessed for quality, and data were extracted into a database. The findings were reported in relation to each cancer site.

Two hundred and forty-one audits met the inclusion criteria. The majority of the audits were poorly reported, and only 44% provided sufficient detail on methods for the audit to be reproducible. Less than 20% provided an action plan outlining recommended changes to service delivery, or how changes would be implemented. In the review, only the findings from the 173 most reliable audits were presented in detail.

The reviewers found that under the two week wait system, there was wide variation in the proportion of referrals seen within two weeks for each cancer site, and in the proportion of referrals that were found to be in accordance with the symptoms listed in the guidelines.(2) Improved reporting of audits was recommended, and it was suggested that the methods and reporting of cancer referral audits should be standardised across the NHS.(13)

Despite these qualifications about the quality of the audits, the findings do indicate that the proportion of patients referred under the two week wait system who turn out to have cancer is often low. Moreover, a variable proportion of patients who have cancer are not diagnosed after a two week referral. The explanations for these findings will vary according to the cancer concerned, for example some cancers may be more likely to be diagnosed following acute admission or in screening programmes. Nevertheless, guidelines appear to have a role to play in informing decisions about referral for suspected cancer.

2.8 Reviewing and grading the evidence

General

The studies identified following the literature search were reviewed to identify the most appropriate evidence to help answer the KCQs and to ensure that the recommendations were based on the best available evidence. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results and grading of the evidence.

The searches were first sifted by the information librarian and systematic reviewer to exclude papers that did not relate to the scope of the guideline. The abstracts of the remaining papers were scrutinised for relevance to the EBQ under consideration. Initially both the systematic reviewer and project lead reviewed the abstracts independently. This proved impractical as the guideline progressed and the task was delegated to the systematic reviewer. The project lead was asked to review the abstracts in cases of uncertainty.

One of the challenges in this guideline was defining inclusion and exclusion criteria for retrieved studies. There were very few studies in which presenting symptoms and signs of suspected cancer were assessed prospectively or in a primary care setting. In addition, there was concern about the applicability and generalisability of studies conducted in countries other than the UK to the NHS in England and Wales. Therefore, a pragmatic, inclusive approach was adopted so the GDG were able to consider a wider body of evidence than if a stricter, more exclusive approach had been taken. The GDG then considered the evidence within the context of primary care in the NHS.

The papers chosen for inclusion were obtained and were assessed for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differ according to study type and were based on the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). Critical appraisal was carried out by the systematic reviewer. Further appraisal was provided by the GDG members at the relevant GDG meeting.

The data were extracted to a standard template on an evidence table. The findings were summarised by the systematic reviewer into a series of evidence statements and an accompanying narrative review. The project lead independently assessed the accuracy of the derived evidence statements. None of the EBQs required the preparation of a quantitative synthesis (meta- analysis) by the project team.

The evidence statements were graded by the project lead according to the established hierarchy of evidence table presented in section 0 of this chapter. This system reflects the susceptibility to bias

inherence in particular study designs.

The type of EBQ dictates the highest level of evidence that may be sought. For questions relating to therapy/treatment the highest possible level of evidence is a systematic review or meta-analysis of RCTs (evidence level Ia) or an individual RCT (evidence level Ib). For questions relating to prognosis, the highest possible level of evidence is a cohort study (evidence level IIb). For diagnostic tests, the highest possible level of evidence is a test evaluation study using a quasi-experimental design that uses a blind comparison of the test with a validated reference standard applied to a sample of patients who are representative of the population to whom the test would apply (evidence level IIb). For questions relating to information needs and support, the highest possible level of evidence is a descriptive study using either questionnaire survey or qualitative methods (III).

For each clinical question, the highest level of evidence was selected. If a systematic review, meta-analysis or RCT existed in relation to an EBQ, studies of a weaker design were ignored.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables (Appendices A and B).

A number of KCQs could not appropriately be answered using a systematic review, for example, where the evidence base was very limited. These questions were addressed by the identification of ‘published expert’ narrative reviews by the project team and/or GDG, which formed the basis of discussion papers written either by the project lead or a member of the GDG. This approach has been used on the sections dealing with “breaking bad news”, how primary care practitioners should make a diagnosis and patient information and support needs. Systematic reviews or expert narrative reviews were also used to summarise the risk factors for each of the groups of cancers.

2.8.1 Details of levels of evidence and grading of recommendations

Table 2 Levels of evidence

Hierarchy of evidence	
Ia	Systematic review or meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomisation
IIb	At least one well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, case-control studies, and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities
NICE	NICE guidelines or Health Technology Appraisal programme

Table 3 Grades of recommendation

Grading of recommendations	
A	Based directly on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence
A NICE	Recommendation taken from NICE guideline or Technology Appraisal
GPP	Good practice point based on the clinical experience of the GDG

Table 4 Levels of evidence for studies of the accuracy of diagnostic tests

Levels of evidence	Type of evidence

Ia Systematic review (with homogeneity)† of level-1 studies‡
Ib Level-1 studies‡
II Level-2 studies
Systematic reviews of level-2 studies§

III Level-3 studies§§

Systematic reviews of level-3 studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research or 'first principles'.

†Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.
‡Level-1 studies are studies:

that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply
§Level-2 studies are studies that have only one of the following:

narrow population (the sample does not reflect the population to whom the test would apply) use a poor reference standard (defined as that where a 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
the comparison between the test and reference standard is not blind case-control studies
§§Level-3 studies are studies that have at least two or three of the features listed above§

(from the NICE Technical Manual, and adapted from The Oxford Centre for Evidence-based Medicine Levels of Evidence(14) and the Centre for Reviews and Dissemination Report Number 4(15))

Table 5 Classification of recommendations for studies of the accuracy of diagnostic tests

Class	Level of evidence (see Table 4)
A (DS)	Studies with level of evidence Ia or Ib
B (DS)	Studies with level of evidence II C (DS) Studies with level of evidence III
D (DS)	Based on studies with level of evidence IV (DS – diagnostic studies).

2.8.2 The role of risk factors in decisions about referral for suspected cancer

Risk factors are often included in reviews of the presenting features of cancers, and the guideline group considered the role of selected risk factors in decisions about referral for suspected cancer. However, the place of risk factors in making decisions about referral for suspected cancer was found by the guideline group to be unclear. The guideline group recognised that in a patient with symptoms or signs suggestive of cancer, the presence or absence of risk factors was usually irrelevant to the referral decision. The following paragraphs outline the issues taken into account by the guideline group in considering the place of risk factors in referral decisions.

2.8.3 What is a risk factor?

Risk factors are generally viewed as factors that increase the likelihood of development of a disease or condition. One definition is 'those patient characteristics associated with the development of the disease in the first place'.(16) For example, regular smoking increases the risk of lung cancer, cardiovascular disease, and so forth. Prognostic risk factors are also sometimes described, and these are defined as 'patient or study participant characteristics that confer increased or decreased risk of a positive or adverse outcome'.(16)

However, a rather different question is relevant in the context of identifying people who have

cancer, namely does the presence of certain features in a person presenting to primary care with certain symptoms and signs increase the likelihood of cancer? The risk factor of increasing age for breast cancer illustrates the issue.

Figure 1 Incidence of breast cancer among females, in England and Wales, 1997(17)

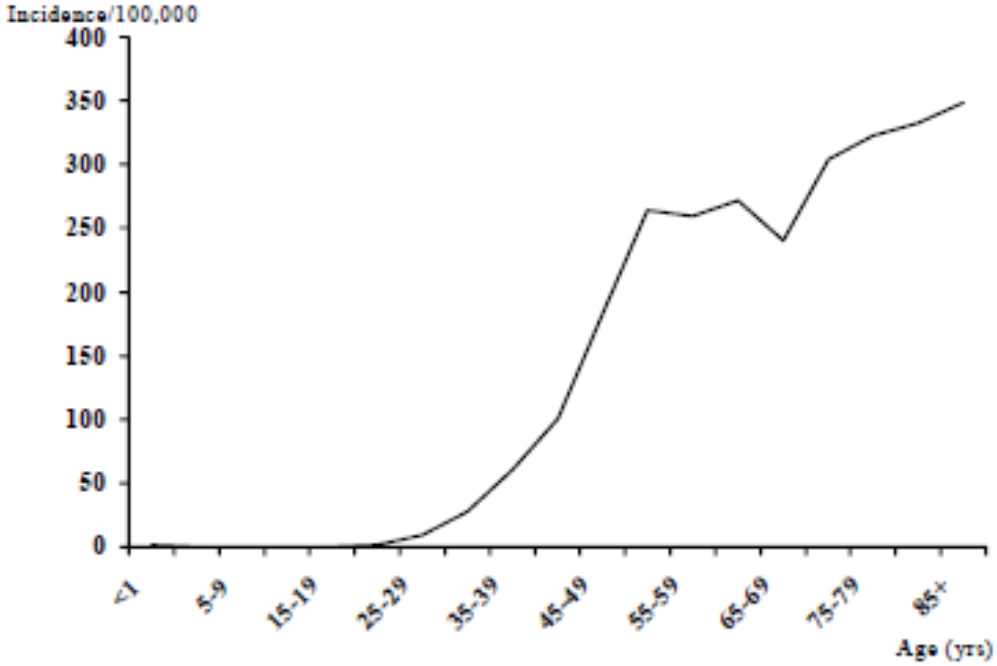


Figure 1 shows the risk of breast cancer to be around 50/100,000 at age 35, and around 275/100,000 at age 55. However, the data do not indicate the proportion of breast lumps at different ages that will be cancer, since they do not include information about the total numbers of patients presenting in primary care with benign lumps. Consequently, the guideline group required judgement in interpreting the breast cancer incidence data. Because breast lumps are 'common' in the 30-35 age group, but cancer uncommon, then referral of all patients below aged 30 cannot be recommended. However, cancer was judged by the group to be not only more common at age 55, but also to constitute a greater proportion of those cases presenting with breast lumps.

2.8.4 When is a risk factor relevant to a referral decision?

Relative risk (RR) is the 'ratio of the risk of an event among an exposed population to the risk among the unexposed'. Is the RR of conditions occurring when a risk factor is present helpful in making referral decisions?

Although age has been taken into account in making recommendations about referral in some cancers, small increments in age do not confer high relative risks. However, the fact that cancer is rare below a certain age was regarded by the group as important. The group has not found information about risk factors with low RRs helpful. In the case of haematological cancers, Epstein-Barr virus was found to have a RR for Hodgkin's disease of 2.4,(18) high birth weight had an RR of 1.7 for ALL,(19) and farm labourers had a RR of 1.8 for myeloma.(20) The group considered these findings as irrelevant to the referral decision.

Risk factors with high RRs are not necessarily helpful either. It is uncommon for patients to have such risk factors, and the absence of the risk factor in someone who presents with symptoms and signs does not mean that cancer is ruled out.

2.8.5 Specificity of the symptoms and signs

If the symptoms and/or signs are reasonably specific for the condition, the presence of an additional risk factor would be unlikely to be helpful in making a referral decision. Thus, in a patient aged 60 with weight loss, change in bowel habit, rectal bleeding and a palpable abdominal mass, a past history of ulcerative colitis will not influence the referral decision. However, if the symptoms and/or signs are less specific, risk factors might be considered relevant. Thus, it could be argued that in a patient of 48 who incidentally reports 7lbs weight loss only, a past history of ulcerative

colitis might be taken into account in decisions about further investigation, although probably not referral in the first instance.

2.8.6 Patient concern

The presence of a risk factor could increase patient concern, even though it does not increase the likelihood that the presenting symptoms and signs could be explained by cancer. In this case, the primary care practitioner may or may not be able to provide adequate reassurance. Referral decisions should involve patients, and therefore patient concern was accepted as appropriate by the guideline group as a factor that would contribute to the decision on referral.

The guideline group concluded that for the majority of symptoms and/or signs or initial investigations suggestive of the need for referral for cancer, risk factors other than age are not helpful to the decision to refer or the urgency of referral. If an individual has a risk factor indicating a substantially increased risk of a particular cancer, this may increase the health care professional's index of suspicion of cancer, but in the majority of symptomatic cases it should not influence referral decisions or the urgency of a referral if made. For example, a family history of breast cancer or parity would not be factors that would influence the referral decision in the case of a woman presenting with a breast lump. In assessing the significance of risk factors, the guideline group decided to seek good quality reviews rather than undertake primary searches for studies of risk factors, most of which would have no bearing on referral decisions.

2.8.7 Health economics

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraisal by the health economist using a standard validated checklist. A general descriptive overview of the studies, their qualities, and conclusions was presented and summarized in the form of a short narrative review. The economic evidence was not summarized in the form of meta- analyses given the limited evidence found.

The GDG identified the economics of referral of people with suspected lower gastrointestinal cancer as an important area where further analysis was needed. This area was chosen because there is a high prevalence of the primary symptoms of bowel cancer in the community (rectal bleeding, changes in bowel habit and abdominal pain) relative to the low incidence of bowel cancer. The results of this analysis are presented in Appendix C.

2.9 Developing recommendations

For each KCQ, the recommendations were derived from the evidence statements presented to the GDG. The link between the evidence statement and recommendation was made explicit. The GDG were able to reach their agreed recommendations through a process of informal consensus.

Each recommendation was graded according to the level of evidence upon which it was based using the established grading of recommendations table presented in section 12 of this chapter. For questions relating to therapy/treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For questions relating to prognosis and diagnostic tests, the generally appropriate level of evidence (a cohort study) would equate to a grade B recommendation. For questions relating to information needs and support, the generally appropriate level of evidence (descriptive study) would equate to a grade C recommendation. It is important that the grading in such areas is not treated as inferior to those of therapy as it the existence of relevant evidence.

Many recommendations in this guideline are graded C or D. This is an inevitable consequence of the focus in the guideline on symptoms and signs rather than clinical interventions, and it would be inappropriate to infer from the grade given to most of the recommendations in this guideline that the recommendations are not important. The relevant studies have usually described the presenting symptoms and signs in patients with the cancer of interest, and some studies have compared the findings among patients who were subsequently found to either have or not have cancer. It is essential to note that the guideline group has been able to use this evidence to make recommendations it regards as highly important.

2.10 External review

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline, the first draft of the full and short form guideline and the final draft of the guideline. In addition, the first draft was reviewed by nominated individuals with an interest in cancer and an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented anonymously for consideration by the GDG. All comments were considered systematically by the GDG and the project team recorded the agreed responses.

3 Key Priorities for implementation

Making a Diagnosis

- The primary care professional should recognise that the diagnosis of any cancer on clinical grounds alone can be difficult.
- Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them.
- Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients who are thought to not have cancer fail to recover as expected. Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary care professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical.
- Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are the best observers of their children, and should listen carefully to their concerns. Professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected.

Investigations

- In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made.

The need for support and information

- When referring patients with suspected cancer, primary healthcare professionals should assess the patient's need for continuing support whilst awaiting a specialist opinion, and should provide appropriate information about the possible diagnosis, what to expect from the service the patient will be attending, and how to obtain further information or help prior to the specialist appointment.
- In assessing the need of the patient for support, the primary healthcare professional should take account of the needs of people from different cultural groups, social factors, including family circumstances or isolation, and the needs of people of different ages.

Continuing education for health professionals

- Primary healthcare professionals should take part in education, peer review and other activities to improve or maintain the clinical consulting skills they need to identify patients who may have cancer at an early stage and should be aware of the methods of communicating the possibility of cancer to the patient. Current guidance for advising patients and breaking bad news should be followed (taking into account the personal characteristics of the patient).

4 Executive Summary

4.1. Support and Information needs of people with suspected cancer at the time of referral

1 Patients should be able to consult a primary healthcare professional of the same sex if preferred. D

2 Primary healthcare professionals should discuss with patients (and carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations (including their potential risks and benefits), and ensure they have the time for this. D

3 When cancer is suspected in a child, the referral decision and information to be given to the child should be discussed with the parents or carers (and the patient if appropriate). D

4 Adult patients who are being referred with suspected cancer should normally be told by the primary healthcare professional that they are being referred to a cancer service, but if appropriate they should be reassured that most people referred will not have a diagnosis of cancer, and alternative diagnoses should be discussed. D

5 Primary healthcare professionals should be willing and able to give the patient information on the possible diagnosis (both benign and malignant) in accordance with the patient's wishes for information. Current advice on communicating with patients and/or their carers and breaking bad news[4] should be followed. D

6 The information given to patients, family and/or carers as appropriate by the primary healthcare professional should cover, among other issues: D
- where patients are being referred to
- how long they will have to wait for the appointment
- how to obtain further information about the type of cancer suspected or help prior to the specialist appointment
- who they will be seen by
- what to expect from the service the patient will be attending
- what type of tests will be carried out, and what will happen during diagnostic procedures
- how long it will take to get a diagnosis or test results
- whether they can take someone with them to the appointment
- other sources of support, including those for minority groups.

7 When referring a patient with suspected cancer to a specialist service, primary healthcare professionals should assess the patient's need for continuing support while waiting for their referral appointment. This should include inviting the patient to contact the primary healthcare professional again if they have more concerns or questions before they see a specialist. D

8 Consideration should be given by the primary healthcareprofessional to meeting the information and support needs of parents and carers. Consideration should also be given to meeting these particular needs for the people for whom they care, such as children and young people, and people with special needs (for instance, people with learning disabilities or sensory impairment). D

9 The primary healthcare professional should be aware that some patients find being referred for suspected cancer particularly difficult because of their personal circumstances, such as age, family or work responsibilities, isolation, or other health or social issues. D

10 Primary healthcare professionals should provide culturally appropriate care, recognising the potential for different cultural meanings associated with the possibility of cancer, the relative importance of family decision- making and possible unfamiliarity with the concept of support outside the family. D

11 The primary healthcare professional should be aware that men may have similar support

[4] *Improving communication between doctors and patients*. A report of the working party of the Royal College of Physicians (1997) www.rcplondon.ac.uk/pubs/brochures/pub_print_icbdp

needs to women but may be more reticent about using support services. D

12 If the patient has additional support needs because of their personal circumstances, the specialist should be informed (with the patient's agreement). D

13 All members of the primary healthcare team should have available to them information in a variety of formats on both local and national sources of additional support for patients who are being referred with suspected cancer. D

14 In situations where diagnosis or referral has been delayed, or there is significant compromise of the doctor/patient relationship, the primary healthcare professional should take care to assess the information and support needs of the patient, parents and carers, and make sure these needs are met. The patient should be given the opportunity to consult another primary healthcare professional if they wish. D

15 Primary healthcare professionals should promote awareness of key presenting features of cancer when appropriate. D

4.2. The Diagnostic Process

1 Diagnosis of any cancer on clinical grounds alone can be difficult. Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them. D

2 Cancers usually present with symptoms commonly associated with benign conditions. The primary healthcare professional should be ready to review the initial diagnosis in patients in whom common symptoms do not resolve as expected. D

3 Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients thought not to have cancer fail to recover as expected. In such circumstances, the primary healthcare professional should systematically review the patient's history and examination, and refer urgently if cancer is a possibility. D

4 Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are usually the best observers of their children, and should listen carefully to their concerns. Primary healthcare professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected. D

5 Primary healthcare professionals should take part in continuing education, peer review and other activities to improve and maintain their clinical consulting, reasoning and diagnostic skills, in order to identify at an early stage, patients who may have cancer, and to communicate the possibility of cancer to the patient. C

6 Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical (for example, by telephone or email). D

7 There should be local arrangements in place to ensure that letters about non-urgent referrals are assessed by the specialist, the patient being seen more urgently if necessary. D

8 There should be local arrangements in place to ensure a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements. D

9 There should be local arrangements in place toidentify those patients who miss their appointments so that they can be followed up. D

10 The primary healthcare professional should include all appropriate information in referral correspondence, including whether the referral is urgent or non-urgent. D

11 The primary healthcare professional should use local referral proformas if these are in use. D

12 Once the decision to refer has been made, the primary healthcare professional should make sure that the referral is made within 1 working day. D

13 A patient who presents with symptoms suggestive of cancer should be referred by the primary healthcare professional to a team specializing in the management of the particular type of cancer, depending on local arrangements. D

14 In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary, but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made. D

4.3. Lung Cancer

1 A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. D

Specific recommendations

2 An urgent referral for a chest X-ray should be made when a patient presents with:
- haemoptysis, or
- any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs:
  - -chest and/or shoulder pain
  - -dyspnoea
  - -weight loss
  - -chest signs
  - -hoarseness
  - -finger clubbing
  - -cervical and/or supraclavicular lymphadenopathy
  - -cough with or without any of the above
  - -features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).

A report should be made back to the referring primary healthcare professional within 5 days of referral. D

3 An urgent referral should be made for any of the following:
- persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation). D

4 Immediate referral should be considered for the following:
- signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)
- stridor. C

Risk Factors

5 Patients in the following categories have a higher risk of developing lung cancer:
- are current or ex-smokers
- have smoking-related chronic obstructive pulmonary disease (COPD)
- have been exposed to asbestos
- have had a previous history of cancer (especially head and neck).

An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients (see 1.3.1 above) but may be considered sooner, for example if symptoms or signs have lasted for less than 3 weeks. C

Investigations

6 Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray. D

7 If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral. D

8 In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made. C

4.4. Upper Gastrointestinal Cancer

General recommendations

1 A patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specializing in the management of upper gastrointestinal cancer, depending on local arrangements. D

Specific recommendations

2 An urgent referral for endoscopy or to a specialist with expertise in upper gastrointestinal cancer should be made for patients of any age with dyspepsia[5] who present with any of the following:
- chronic gastrointestinal bleeding
- dysphagia
- progressive unintentional weight loss
- persistent vomiting
- iron deficiency anaemia
- epigastric mass
- suspicious barium meal. C

3 In patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made. D

4 In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms. D

5 In patients presenting with dysphagia (interference with the swallowing mechanism that occurs within 5 seconds of having commenced the swallowing process), an urgent referral should be made. C

6 Helicobacter pylori status should not affect the decision to refer for suspected cancer. C

7 In patients without dyspepsia, but with unexplained weight loss or iron deficiency anaemia, the possibility of upper gastrointestinal cancer should be recognised and an urgent referral for further investigation considered. C

8 In patients with persistent vomiting and weight loss in the absence of dyspepsia, upper gastro-oesophageal cancer should be considered and, if appropriate, an urgent referral should be made. C

9 An urgent referral should be made for patients presenting with either:
- unexplained upper abdominal pain and weight loss, with or without back pain, or
- an upper abdominal mass without dyspepsia. C

10 In patients with obstructive jaundice an urgent referral should be made, depending on the patient's clinical state. An urgent ultrasound investigation may be considered if available. C

Risk Factors

11 In patients with unexplained worsening of their dyspepsia, an urgent referral should be

[5] The definition of dyspepsia is taken from the NICE guideline on *Dyspepsia: management of dyspepsia in adults in primary care* (www.nice.org.uk/CG017). Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting.

considered if they have any of the following known risk factors:

- Barrett's oesophagus
- known dysplasia, atrophic gastritis or intestinal metaplasia
- peptic ulcer surgery more than 20 years ago. C

Investigations

12 Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H2 receptor antagonists, for a minimum of 2 weeks. C

13 In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements. D

14 All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia. D

4.5. Lower Gastrointestinal Cancer

General recommendations

1 A patient who presents with symptoms suggestive of colorectal or anal cancer should be referred to a team specializing in the management of lower gastrointestinal cancer, depending on local arrangements. D

2 In patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of 'treat, watch and wait' as a method of management. D

3 In patients with unexplained symptoms related to the lower gastrointestinal tract, a digital rectal examination should always be carried out, provided this is acceptable to the patient. C

Specific Recommendations

4 In patients aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, an urgent referral should be made. C

5 In patients aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms, an urgent referral should be made. C

6 In patients aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding, an urgent referral should be made. C

7 In patients presenting with a right lower abdominal mass consistent with involvement of the large bowel, an urgent referral should be made, irrespective of age. C

8 In patients presenting with a palpable rectal mass (intraluminal and not pelvic), an urgent referral should be made, irrespective of age. (A pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist.) C

9 In men of any age with unexplained[6] iron deficiency anaemia and a haemoglobin of 11 g/100 ml or below, an urgent referral should be made. C

10 In non-menstruating women with unexplained6 iron deficiency anaemia and a haemoglobin of 10 g/100 ml or below, an urgent referral should be made. C

Risk Factors

11 In patients with ulcerative colitis or a history of ulcerative colitis, a plan for follow-up should

[6] 'Unexplained' in this context means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (for example, non-steroidal anti- inflammatory drug treatment or blood dyscrasia).

be agreed with a specialist and offered to the patient as a normal procedure in an effort to detect colorectal cancer in this high-risk group. C

12 There is insufficient evidence to suggest that a positive family history of colorectal cancer can be used as a criterion to assist in the decision about referral of a symptomatic patient. C

Investigations

13 In patients with equivocal symptoms, a full blood count may help in identifying the possibility of colorectal cancer by demonstrating iron deficiency anaemia, which should then determine if a referral should be made and its urgency. C (DS)

14 In patients for whom the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be in accordance with local arrangements. D

15 In patients for whom the decision to refer has been made, no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended as this may delay referral. D

4.6. Breast Cancer

General recommendations

1 A patient who presents with symptoms suggestive of breast cancer should be referred to a team specialising in the management of breast cancer. D

2 In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. However, primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will be naturally concerned. C

3 People of all ages who suspect they have breast cancer may have particular information and support needs. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them. D

4 Primary healthcare professionals should encourage all patients, including women over 50 years old, to be breast aware7 in order to minimise delay in the presentation of symptoms. D

Specific Recommendations

5 A woman's first suspicion that she may have breast cancer is often when she finds a lump in her breast. The primary healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of age. C

6 In a woman aged 30 years and older with a discrete lump that persists after her next period, or presents after menopause, an urgent referral should be made. C

7 Breast cancer in women aged younger than 30 years is rare, but does occur. Benign lumps (for example, fibroadenoma) are common, however, and a policy of referring these women urgently would not be appropriate; instead, non-urgent referral should be considered. However, in women aged younger than 30 years with:

- a lump that enlarges, [C] or
- a lump that has other features associated with cancer (fixed and hard), [C] or
- in whom there are other reasons for concern such as family history. [D]

an urgent referral should be made. C/D

8 The patient's history should always be taken into account. For example, it may be appropriate, in discussion with a specialist, to agree referral within a few days in patients reporting a lump or other symptom that has been present for several months. D

9 In a patient who has previously had histologically confirmed breast cancer, who presents with a further lump or suspicious symptoms, an urgent referral should be made, irrespective of

age. C

10 In patients presenting with unilateral eczematous skin or nipple change that does not respond to topical treatment, or with nipple distortion of recent onset, an urgent referral should be made. C

11 In patients presenting with spontaneous unilateral bloody nipple discharge, an urgent referral should be made. C

12 Breast cancer in men is rare and is particularly rare in men under 50 years of age. However, in a man aged 50 years and older with a unilateral, firm subareaolar mass with or without nipple distortion or associated skin changes, an urgent referral should be made. C

Investigations

13 In patients presenting with symptoms and/or signs suggestive of breast cancer, investigation prior to referral is not recommended. D

14 In patients presenting solely with breast pain, with no palpable abnormality, there is no evidence to support the use of mammography as a discriminatory investigation for breast cancer. Therefore, its use in this group of patients is not recommended. Non-urgent referral may be considered in the event of failure of initial treatment and/or unexplained persistent symptoms. [B (DS)]

4.7. Gynaecological Cancer

General recommendations

1 A patient who presents with symptoms suggesting gynaecological cancer should be referred to a team specializing in the management of gynaecological cancer, depending on local arrangements. D

Specific recommendations

2 The first symptoms of gynaecological cancer may be alterations in the menstrual cycle, intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding or vaginal discharge. For a patient who presents with any of these symptoms, the primary healthcare professional should undertake a full pelvic examination, including speculum examination of the cervix. C

3 In patients found on examination of the cervix to have clinical features that raise the suspicion of cervical cancer, an urgent referral should be made. A cervical smear test is not required before referral, and a previous negative cervical smear result is not a reason to delay referral. C

4 Ovarian cancer is particularly difficult to diagnose on clinical grounds as the presentation may be with vague, non-specific abdominal symptoms alone (bloating, constipation, abdominal or back pain, urinary symptoms). In a woman presenting with any unexplained abdominal or urinary symptoms, abdominal palpation should be carried out. If there is significant concern, a pelvic examination should be considered if appropriate and acceptable to the patient.
NOTE: This recommendation has been updated and replaced by section 1.1.1 in 'Ovarian cancer' (NICE clinical guideline 122, 2011). Available from www.nice.org.uk/guidance/CG122

5 Any woman with a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids or not of gastrointestinal or urological origin should have an urgent ultrasound scan. If the scan is suggestive of cancer, or if ultrasound is not available, an urgent referral should be made. C

6 When a woman who is not on hormone replacement therapy presents with postmenopausal bleeding, an urgent referral should be made. C

7 When a woman on hormone replacement therapy presents with persistent or unexplained postmenopausal bleeding after cessation of hormone replacement therapy for 6 weeks, an urgent referral should be made. C

8 Tamoxifen can increase the risk of endometrial cancer. When a woman taking tamoxifen presents with postmenopausal bleeding, an urgent referral should be made. C

9 An urgent referral should be considered in a patient with persistent intermenstrual bleeding and a negative pelvic examination. D

Vulval cancer

10 When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made. C

11 Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently. D

12 Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms, it is reasonable to use a period of 'treat, watch and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer. C

4.8. Urological Cancers

General recommendations

1 A patient who presents with symptoms or signs suggestive of a urological cancer should be referred to a team specialising in the management of urological cancers, depending on local arrangements. D

Specific recommendations

Prostate cancer

2 Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate specific antigen (PSA) test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive. C

3 Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms:

- erectile dysfunction
- haematuria
- lower back pain
- bone pain
- weight loss, especially in the elderly.

These patients should also be offered a DRE and a PSA test. C

4 Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection. C

5 If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients do not need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range[7]. C

6 In a male a patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age-specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other comorbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate. C

[7] The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50−59 years ≥ 3.0 ng/ml; aged 60−69 years ≥ 4.0 ng/ml; aged 70 years and older ≥ 5.0 ng/ml. (Note that there are no age-specific reference ranges for men aged over 80 years. Nearly all men of this age have at least a focus of cancer in the prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment.)

7 Symptomatic patients with high PSA levels should be referred urgently. C

8 If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently. D

Bladder and renal cancers

9 Male or female adult patients of any age who present with painless macroscopic haematuria should be referred urgently. C

10 In male or female patients with symptoms suggestive of a urinary infection who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed the patient should be referred urgently. D

11 In all adult patients aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria, an urgent referral should be made. C

12 In patients under 50 years of age with microscopic haematuria, the urine should be tested for proteinuria and serum creatinine levels measured. Those with proteinurea or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made. C

13 In patients aged 50 years and older who are found to have unexplained microscopic haematuria, an urgent referral should be made. C

14 Any patient with an abdominal mass identified clinically or on imaging that is thought to be arising from the urinary tract should be referred urgently. C

Testicular cancer

15 Any patient with a swelling or mass in the body of the testis should be referred urgently. C

16 An urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished. D

Penile cancer

17 An urgent referral should be made for any patient presenting with symptoms or signs of penile cancer. These include progressive ulceration or a mass in the glans or prepuce particularly, but can involve the skin of the penile shaft. Lumps within the corpora cavernosa not involving penile skin are usually not cancer but indicate Peyronie's disease, which does not require urgent referral. D

4.9. Haematological Cancers

General recommendations

1 A patient who presents with symptoms suggesting haematological cancer should be referred to a team specialising in the management of haematological cancer, depending on local arrangements. D

2 Primary healthcare professionals should be aware that haematological cancers can present with a variety of symptoms that may have a number of different clinical explanations. D

3 Combinations of the following symptoms and signs may suggest haematological cancer and warrant full examination, further investigation (including a blood count and film) and possible referral:

- fatigue
- drenching night sweats
- fever
- weight loss
- generalised itching
- breathlessness

- bruising
- bleeding
- recurrent infections
- bone pain
- alcohol-induced pain
- abdominal pain
- lymphadenopathy
- splenomegaly.

The urgency of referral depends on the severity of the symptoms and signs, and findings of investigations. C

Specific Recommendations

4 In patients with a blood count or blood film reported as acute leukaemia, an immediate referral should be made. D

5 In patients with persistent unexplained splenomegaly, an urgent referral should be made. C

Investigations

6 Investigation of patients with persistent unexplained fatigue should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or Creactive protein (according to local policy), and repeated at least once if the patient's condition remains unexplained and does not improve. [B(DS)]

7 Investigation of patients with unexplained lymphadenopathy should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [B(DS)]

8 Any of the following additional features of lymphadenopathy should trigger further investigation and/or referral:

- persistence for 6 weeks or more
- lymph nodes increasing in size
- lymph nodes greater than 2 cm in size
- widespread nature
- associated splenomegaly, night sweats or weight loss. [C(DS)]

9 Investigation of a patient with unexplained bruising, bleeding, and purpura or symptoms suggesting anaemia should include a full blood count, blood film, clotting screen and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [B(DS)]

10 A patient with bone pain that is persistent and unexplained should be investigated with full blood count and X-ray, urea and electrolytes, liver and bone profile, PSA test (in males) and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [C(DS)]

11 In patients with spinal cord compression or renal failure suspected of being caused by myeloma, an immediate referral should be made. C

4.10. Skin Cancer

1 A patient presenting with skin lesions suggestive of skin cancer or in whom a biopsy has been confirmed should be referred to a team specialising in skin cancer. D

2 All primary healthcare professionals should be aware of the 7-point weighted checklist (see recommendation 1.10.8) for assessment of pigmented skin lesions. C

3 All primary healthcare professionals who perform minor surgery should have received appropriate accredited training in relevant aspects of skin surgery including cryotherapy, curettage, and incisional and excisional biopsy techniques, and should undertake appropriate continuing professional development. D

4 Patients with persistent or slowly evolving unresponsive skin conditions in which the diagnosis is uncertain and cancer is a possibility should be referred to a dermatologist. D

5 All excised skin specimens should be sent for pathological examination. [C(DS)]

6 On making a referral of a patient in whom an excised lesion has been diagnosed as malignant, a copy of the pathology report should be sent with the referral correspondence, as there may be details (such as tumour thickness, excision margin) that will specifically influence future management. D

Specific recommendations

Melanoma

7 Change is a key element in diagnosing malignant melanoma. For low-suspicion lesions, careful monitoring for change should be undertaken using the 7-point checklist (see recommendation 1.10.8) for 8 weeks. Measurement should be made with photographs and a marker scale and/or ruler. D

8 All primary healthcare professionals should use the weighted 7-point checklist in the assessment of pigmented lesions to determine referral:
Major features of the lesions:
- change in size
- irregular shape
- irregular colour.
- Minor features of the lesions:
- largest diameter 7 mm or more
- inflammation
- oozing
- change in sensation.

Suspicion is greater for lesions scoring 3 points or more (based on major features scoring 2 points each and minor features scoring 1 point each). However, if there are strong concerns about cancer, any one feature is adequate to prompt urgent referral. C

9 In patients with a lesion suspected to be melanoma (see recommendation 1.10.8), an urgent referral to a dermatologist or other suitable specialist with experience of melanoma diagnosis should be made, and excision in primary care should be avoided. C

Squamous cell carincomas

10 Squamous cell carcinomas present as keratinizing or crusted tumours that may ulcerate. Non-healing lesions larger than 1 cm with significant induration on palpation, commonly on face, scalp or back of hand with a documented expansion over 8 weeks, may be squamous cell carcinomas and an urgent referral should be made. C

11 Squamous cell carcinomas are common in patients on immunosuppressive treatment, but may be atypical and aggressive. In patients who have had an organ transplant who develop new or growing cutaneous lesions, an urgent referral should be made. C

12 In any patient with histological diagnosis of a squamous cell carcinoma made in primary care, an urgent referral should be made. C

Basal cell carcinomas

13 Basal cell carcinomas are slow growing, usually without significant expansion over 2 months, and usually occur on the face. Where there is a suspicion that the patient has a basal cell carcinoma, a nonurgent referral should be made. C

Investigations

14 All pigmented lesions that are not viewed as suspicious of melanoma but are excised should have a lateral excision margin of 2 mm of clinically normal skin and cut to include subcutaneous fat in depth. [B(DS)]

4.11. Head and Neck Cancer

General recommendations

1 A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements. D

2 Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after 6 weeks, an urgent referral should be made. D

3 Primary healthcare professionals should advise all patients, including those with dentures, to have regular dental checkups. D

Specific recommendations

4 A patient who presents with unexplained red and white patches (including suspected lichen planus) of the oral mucosa that are:

- painful, or
- swollen, or
- bleeding
- an urgent referral should be made.

A non-urgent referral should be made in the absence of these features. If oral lichen planus is confirmed, the patient should be monitored for oral cancer as part of routine dental examination[8]. C

5 In patients with unexplained ulceration of the oral mucosa or mass persisting for more than 3 weeks, an urgent referral should be made. C

6 In adult patients with unexplained tooth mobility persisting for more than 3 weeks, an urgent referral to a dentist should be made. C

7 In any patient with hoarseness persisting for more than 3 weeks, particularly smokers aged 50 years and older and heavy drinkers, an urgent referral for a chest X-ray should be made. Patients with positive findings should be referred urgently to a team specialising in the management of lung cancer. Patients with a negative finding should be urgently referred to a team specialising in head and neck cancer. C

8 In patients with an unexplained lump in the neck which has recently appeared or a lump which has not been diagnosed before that has changed over a period of 3 to 6 weeks, an urgent referral should be made. C

9 In patients with an unexplained persistent swelling in the parotid or submandibular gland, an urgent referral should be made. D

10 In patients with unexplained persistent sore or painful throat, an urgent referral should be made. D

11 In patients with unilateral unexplained pain in the head and neck area for more than 4 weeks, associated with otalgia (ear ache) but with normal otoscopy, an urgent referral should be made. D

Investigations

12 With the exception of persistent hoarseness (see recommendation 1.11.7), investigations for head and neck cancer in primary care are not recommended as they can delay referral. D

Thyroid cancers

[8] See: National Institute for Clinical Excellence (2004) Dental recall: recall interval between routine dental examinations. *NICE Clinical Guideline* No. 19. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG019

13 In patients presenting with symptoms of tracheal compression including stridor due to thyroid swelling, immediate referral should be made. D

14 In patients presenting with a thyroid swelling associated with any of the following, an urgent referral should be made:
- a solitary nodule increasing in size
- a history of neck irradiation
- a family history of an endocrine tumour
- unexplained hoarseness or voice changes
- cervical lymphadenopathy
- very young (pre-pubertal) patients
- patients aged 65 years and older. D

15 In patients with a thyroid swelling without stridor or any of the features indicated in recommendation 1.11.14, the primary healthcare professional should request thyroid function tests. Patients with hyper- or hypothyroidism and an associated goitre are very unlikely to have thyroid cancer and could be referred, non-urgently, to an endocrinologist. Those with goitre and normal thyroid function tests who do not have any of the features indicated in recommendation 1.11.14 should be referred nonurgently. D

16 Initiation of other investigations by the primary healthcare professional, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and is not recommended. D

4.12. Brain and CNS Cancer

General recommendations

1 A patient who presents with symptoms suggestive of brain or CNS cancer should be referred to an appropriate specialist, depending on local arrangements. D

2 If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with a local specialist should be considered. If rapid access to scanning is available, this investigation should also be considered as an alternative. D

Specific Recommendations

3 In patients with new, unexplained headaches or neurological symptoms, the primary healthcare professional should undertake a neurological examination guided by the symptoms, but including examination for papilloedema. The absence of papilloedema does not exclude the possibility of a brain tumour. D

4 In any patient with symptoms related to the CNS (including progressive neurological deficit, new onset seizures, headaches, mental changes, cranial nerve palsy, unilateral sensorineural deafness) in whom a brain tumour is suspected, an urgent referral should be made. The development of new signs related to the CNS should be considered as potential indications for referral. C

Headaches

5 In patients with headaches of recent onset accompanied by either features suggestive of raised intra-cranial pressure (for example, vomiting, drowsiness, postural related headache, headache with pulse synchronous tinnitus) or other focal or non-focal neurological symptoms (for example, blackout, change in personality or memory), an urgent referral should be made. C

6 In patients with unexplained headaches of recent onset, present for at least 1 month but not accompanied by features suggestive of raised intracranial pressure (see recommendation 1.12.5), discussion with a local specialist or referral (usually non-urgent) should be considered. D

7 In patients with a new, qualitatively different unexplained headache that becomes progressively severe, an urgent referral should be made. C

8 Re-assessment and re-examination is required if the patient does not progress according to expectations. D

Seizures

9 A detailed history should be taken from the patient and an eyewitness to the event if possible, to determine whether or not a seizure is likely to have occurred[9]. C

10 In patients presenting with a seizure, a physical examination (including cardiac, neurological, mental state) and developmental assessment, where appropriate, should be carried out. C

11 In any patient with suspected recent onset seizures, an urgent referral to a neurologist should be made. C

Other neurological features

12 In patients with rapid progression of:
   a. subacute focal neurological deficit [B]
   b. unexplained cognitive impairment, behavioural disturbance, or slowness or a combination of these [C]
   c. personality changes confirmed by a witness (for example, a carer, friend or a family member) and for which there is no reasonable explanation even in the absence of the other symptoms and signs of a brain tumour [D]

   An urgent referral to an appropriate specialist should be considered. B/C/D

Risk Factors

13 In patients previously diagnosed with any cancer an urgent referral should be made if the patient develops any of the following symptoms:
   a. recent onset seizure
   b. progressive neurological deficit
   c. persistent headaches
   d. new mental or cognitive changes
   e. new neurological signs. C

4.13. Bone Cancer and Sarcoma

1 A patient who presents with symptoms suggesting bone cancer or sarcoma should be referred to a team specialising in the management of bone cancer and sarcoma, or to a recognised bone cancer centre,depending on local arrangements. D

2 If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with the local specialist should be considered. D

3 Patients with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest (and especially if not in the joint), or an unexplained limp should be investigated by the primary healthcare professional urgently. The nature of the investigations will vary according to the patient's age and clinical features.
   - In older people metastases, myeloma or lymphoma, as well as sarcoma, should be considered. [C(DS)]

Specific Recommendations

Bone tumours

4 A patient with a suspected spontaneous fracture should be referred for an immediate X-ray. [B(DS)]

5 If an X-ray indicates that bone cancer is a possibility, an urgent referral should be made. [C(DS)]

[9] National Institute for Clinical Excellence (2004) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. *NICE Clinical Guideline* No. 20. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG020

6 If the X-ray is normal but symptoms persist, the patient should be followed up and/or a repeat X-ray or bone function tests or a referral requested. [C(DS)]

Soft tissue sarcomas

7 In patients presenting with a palpable lump, an urgent referral for suspicion of soft tissue sarcoma should be made if the lump is:
- greater than about 5 cm in diameter
- deep to fascia, fixed or immobile
- painful
- increasing in size
- a recurrence after previous excision.

If there is any doubt about the need for referral, discussion with a local specialist should be undertaken. C

8 If a patient has HIV disease, Kaposi's sarcoma should be considered and a referral made if this is suspected. C

4.14. Children's Cancer

General Recommendations

1 Children and young people who present with symptoms and signs of cancer should be referred to a paediatrician or a specialist children's cancer service, if appropriate. D

2 Childhood cancer is rare and may present initially with symptoms and signs associated with common conditions. Therefore, in the case of a child or young person presenting several times (for example, three or more times) with the same problem, but with no clear diagnosis, urgent referral should be made. D

3 The parent is usually the best observer of the child's or young person's symptoms. The primary healthcare professional should take note of parental insight and knowledge when considering urgent referral. D

4 Persistent parental anxiety should be a sufficient reason for referral of a child or young person, even when the primary healthcare professional considers that the symptoms are most likely to have a benign cause. D

5 Persistent back pain in a child or young person can be a symptom of cancer and is indication for an examination, investigation with a full blood count and blood film, and consideration of referral. C

6 There are associations between Down syndrome and leukaemia, neurofibromatosis and CNS tumours, and between other rare syndromes and some cancers. The primary healthcare professional should be alert to the potential significance of unexplained symptoms in children or young people with such syndromes. D

7 The primary healthcare professional should convey information to the parents and child/young person about the reason for referral and which service the child/young person is being referred to so that they know what to do and what will happen next. D

8 The primary healthcare professional should establish good communication with the parents and child/young person in order to develop the supportive relationship that will be required during the further management if the child/young person is found to have cancer. D

Specific Recommendations

Leukaemia (children of all ages)

9 Leukaemia usually presents with a relatively short history of weeks rather than months. The

presence of one or more of the following symptoms and signs requires investigation with full blood count and blood film:

- pallor
- fatigue
- unexplained irritability
- unexplained fever
- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- persistent or unexplained bone pain
- unexplained bruising.

If the blood film or full blood count indicates leukaemia then an urgent referral should be made. [C(DS)]

10 The presence of either of the following signs in a child or young person requires immediate referral:

- unexplained petechiae
- hepatosplenomegaly. C

Lymphomas

Hodgkin's lymphoma presents typically with non tender cervical and/or supraclavicular lymphadenopathy. Lymphadenopathy can also present at other sites. The natural history is long (months). Only a minority of patients have systemic symptoms (itching, night sweats, fever).

Non Hodgkin's lymphoma typically shows a more rapid progression of symptoms, and may present with lymphadenopathy, breathlessness, SVC obstruction, abdominal distension.

11 Lymphadenopathy is more frequently benign in younger children but urgent referral is advised if one or more of the following characteristics are present, particularly if there is no evidence of local infection:

- lymph nodes are non-tender, firm or hard
- lymph nodes are greater than 2 cm in size
- lymph nodes are progressively enlarging
- other features of general ill-health, fever or weight loss
- the axillary nodes are involved (in the absence of local infection or dermatitis)
- the supraclavicular nodes are involved. C

12 The presence of hepatosplenomegaly requires immediate referral. C

13 Shortness of breath is a symptom that can indicate chest involvement but may be confused with other conditions such as asthma. Shortness of breath in association with the above signs (recommendation 1.14.11), particularly if not responding to bronchodilators, is an indication for urgent referral. C

14 A child or young person with a mediastinal or hilar mass on chest X-ray should be referred immediately. C

Brain & CNS Tumours

<u>Children 2 years and older and young people</u>

15 Persistent headache in a child or young person requires a neurological examination by the primary healthcare professional. An urgent referral should be made if the primary healthcare professional is unable to undertake an adequate examination. D

16 Headache and vomiting that cause early morning waking or occur on waking are classical signs of raised intracranial pressure, and an immediate referral should be made. C

17 The presence of any of the following neurological symptoms and signs should prompt urgent or immediate referral:

- new onset seizures
- cranial nerve abnormalities
- visual disturbances
- gait abnormalities
- motor or sensory signs
- unexplained deteriorating school performance or developmental milestones
- unexplained behavioural and/or mood changes. D

18 A child or young person with a reduced level of consciousness requires emergency admission. C

Children < 2 years

19 In children aged younger than 2 years, any of the following symptoms may suggest a CNS tumour, and referral (as indicated below) is required.
- Immediate referral:
  - new onset seizures
  - bulging fontanelle
  - extensor attacks
  - persistent vomiting.
- Urgent referral:
  - abnormal increase in head size
  - arrest or regression of motor development
  - altered behaviour
  - abnormal eye movements
  - lack of visual following
  - poor feeding/failure to thrive.
- Urgency contingent on other factors:
  - squint. C

Neuroblastoma (all ages)
The majority of children with neuroblastoma have symptoms of metastatic disease which may be general in nature (malaise, pallor, bone pain, irritability, fever or respiratory symptoms), and may resemble those of acute leukaemia.

20 The presence of the following symptoms and signs requires investigation with FBC:
- persistent or unexplained bone pain (and X–ray)
- pallor
- fatigue
- unexplained irritability
- unexplained fever
- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- unexplained bruising .[C(DS)]

21 Other symptoms which should raise concern about neuroblastoma and prompt urgent referral include:
- proptosis
- unexplained back pain
- leg weakness
- unexplained urinary retention. C

22 In children or young people with symptoms that could be explained by neuroblastoma, an abdominal examination (and/or urgent abdominal ultrasound) should be undertaken, and a chest X-ray and full blood count considered. If any mass is identified, an urgent referral should be made. [C(DS)]

23 Infants aged younger than 1 year may have localised abdominal or thoracic masses, and in infants younger than 6 months of age, there may also be rapidly progressive intra-abdominal disease. Some babies may present with skin nodules. If any such mass is identified, an immediate referral should be made. C

Wilms' tumour (all ages)

24 Wilms' tumour most commonly presents with a painless abdominal mass. Persistent or progressive abdominal distension should prompt abdominal examination, and if a mass is found an immediate referral be made. If the child Or young person is uncooperative and abdominal examination is not possible, referral for an urgent abdominal ultrasound should be considered. C

25 Haematuria in a child or young person, although a rarer presentation of a Wilms' tumour, merits urgent referral.C

Soft tissue sarcoma (all ages)

26 A soft tissue sarcoma should be suspected and an urgent referral should be made for a child or young person with an unexplained mass at almost any site that has one or more of the following features. The mass is:
- deep to the fascia
- non-tender
- progressively enlarging
- associated with a regional lymph node that is enlarging
- >2 cm in diameter in size. C

27 A soft tissue mass in an unusual location may give rise to misleading local and persistent unexplained symptoms and signs, and the possibility of sarcoma should be considered. These symptoms and signs include:
- head and neck sarcomas:
  - proptosis
  - persistent unexplained unilateral nasal obstruction with or without discharge and/or bleeding
  - aural polyps/discharge
- genitourinary tract:
  - urinary retention
  - scrotal swelling
  - bloodstained vaginal discharge. C

Bone sarcomas (osteosarcoma and Ewing's sarcoma) (all ages)

28 Limbs are the most common site for bone tumours, especially around the knee in the case of osteosarcoma. Persistent localised bone pain and/or swelling requires an X-ray. If a bone tumour is suspected, an urgent referral should be made. C

29 History of an injury should not be assumed to exclude the possibility of a bone sarcoma. C

30 Rest pain, back pain and unexplained limp may all point to a bone tumour and require discussion with a paediatrician, referral or X-ray. C

Retinoblastoma (mostly children aged under 2 years)

31 In a child with a white pupillary reflex (leukocoria) noted by the parents, identified in photographs or found on examination, an urgent referral should be made. The primary healthcare professional should pay careful attention to the report by a parent of noticing an odd appearance in their child's eye. C

32 A child with a new squint or change in visual acuity should be referred. If cancer is suspected, referral should be urgent, but otherwise referral should be non-urgent. C

33 A family history of retinoblastoma should alert the primary healthcare professional to the possibility of retinoblastoma in a child who presents with visual problems. Offspring of a parent who has had retinoblastoma, or siblings of an affected child, should undergo screening soon after birth. C

Investigations

34 When cancer is suspected in children and young people, imaging is often required. This may be best performed by a paediatrician, following urgent or immediate referral by the primary healthcare professional. D

35 The presence of any of the following symptoms and signs requires investigation with full blood count:
- pallor
- fatigue
- irritability
- unexplained fever
- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- persistent or unexplained bone pain (and X-ray)
- unexplained bruising. [C(DS)]

5 Algorithms

A series of algorithms now follow summarising the principal recommendations for each cancer site. These give guidance on how to proceed when a patient presents with symptoms suggestive of a cancer. They are intended to be used alongside the text version of the recommendations, which should be consulted for full, detailed guidance.

The definitions of unexplained or persistent presented in the guideline glossary are reproduced here for convenience:

Unexplained

When used in a recommendation, unexplained refers to a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any).

Persistent

'Persistent' as used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional. In many cases, the upper limit the professional will permit symptoms and/or signs to persist before initiating referral will be 4-6 weeks.

Referrals

Referral is to a team specialising in the management of the relevant cancer dependant on local arrangements, unless otherwise specified.

Urgency of referral

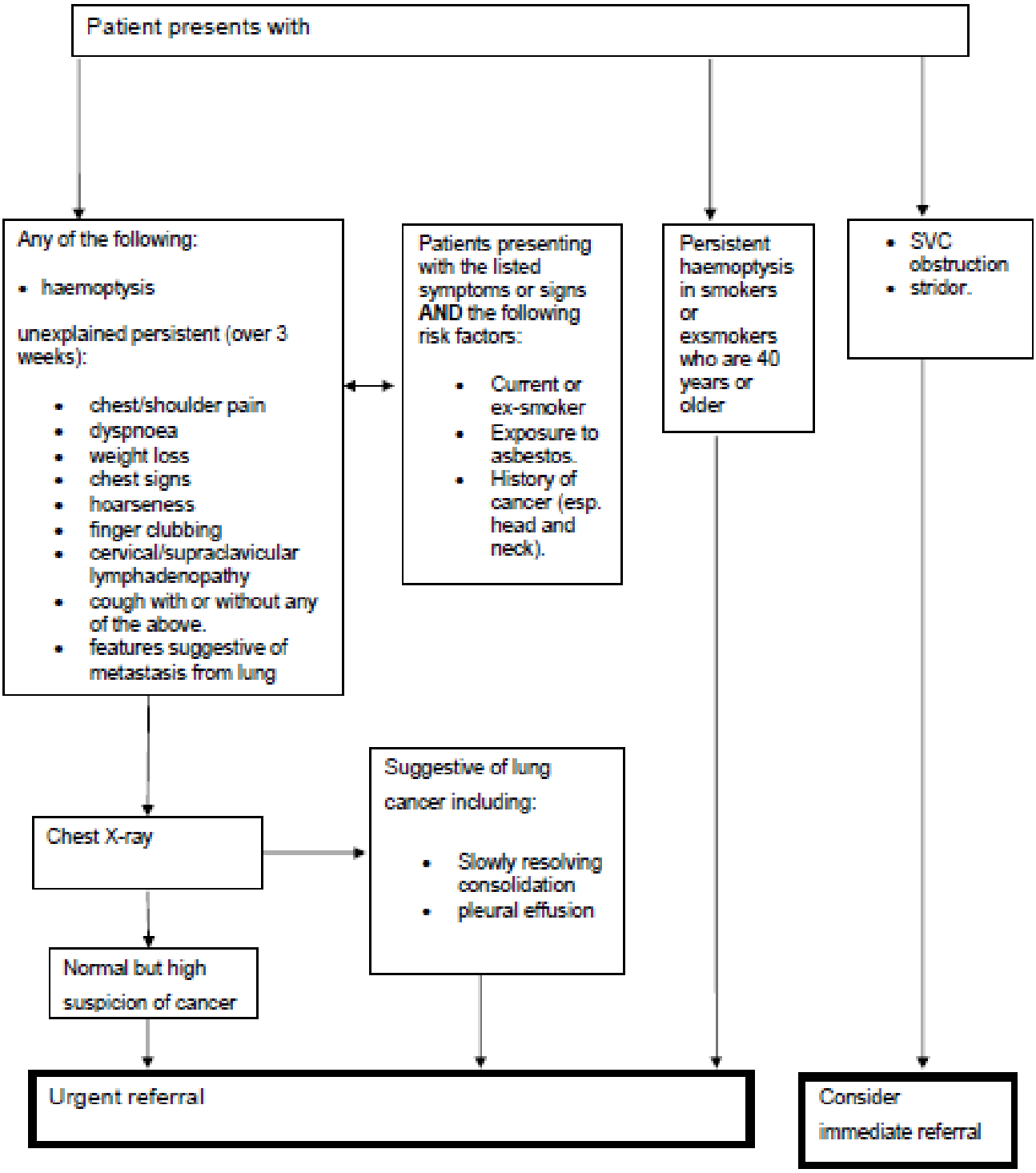
Immediate/emergency:

an acute admission or referral occurring within a few hours, or even more quickly if necessary.

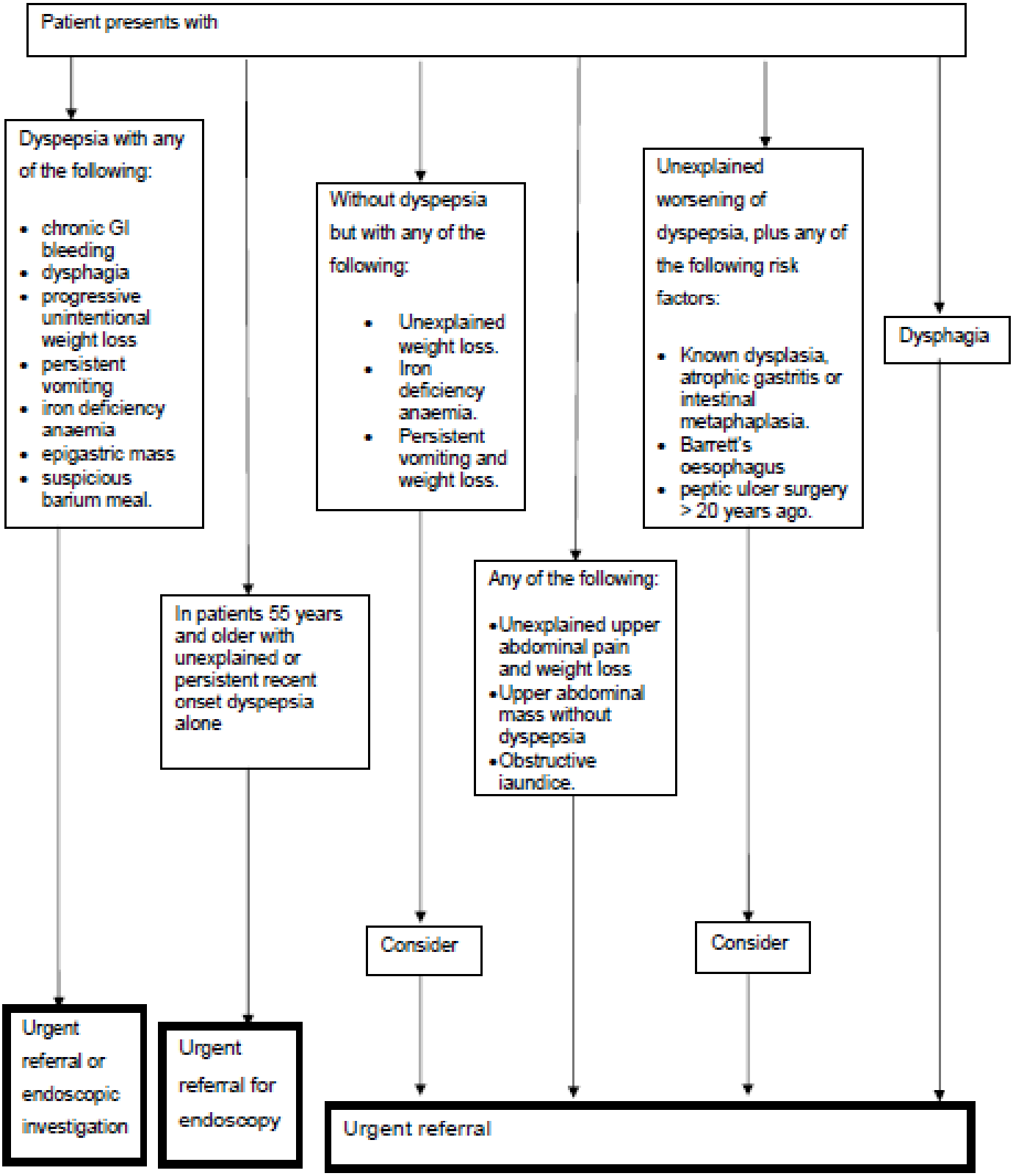
Urgent: the patient is seen within the national target for urgent referrals (currently two weeks).

Non-urgent: all other referrals.

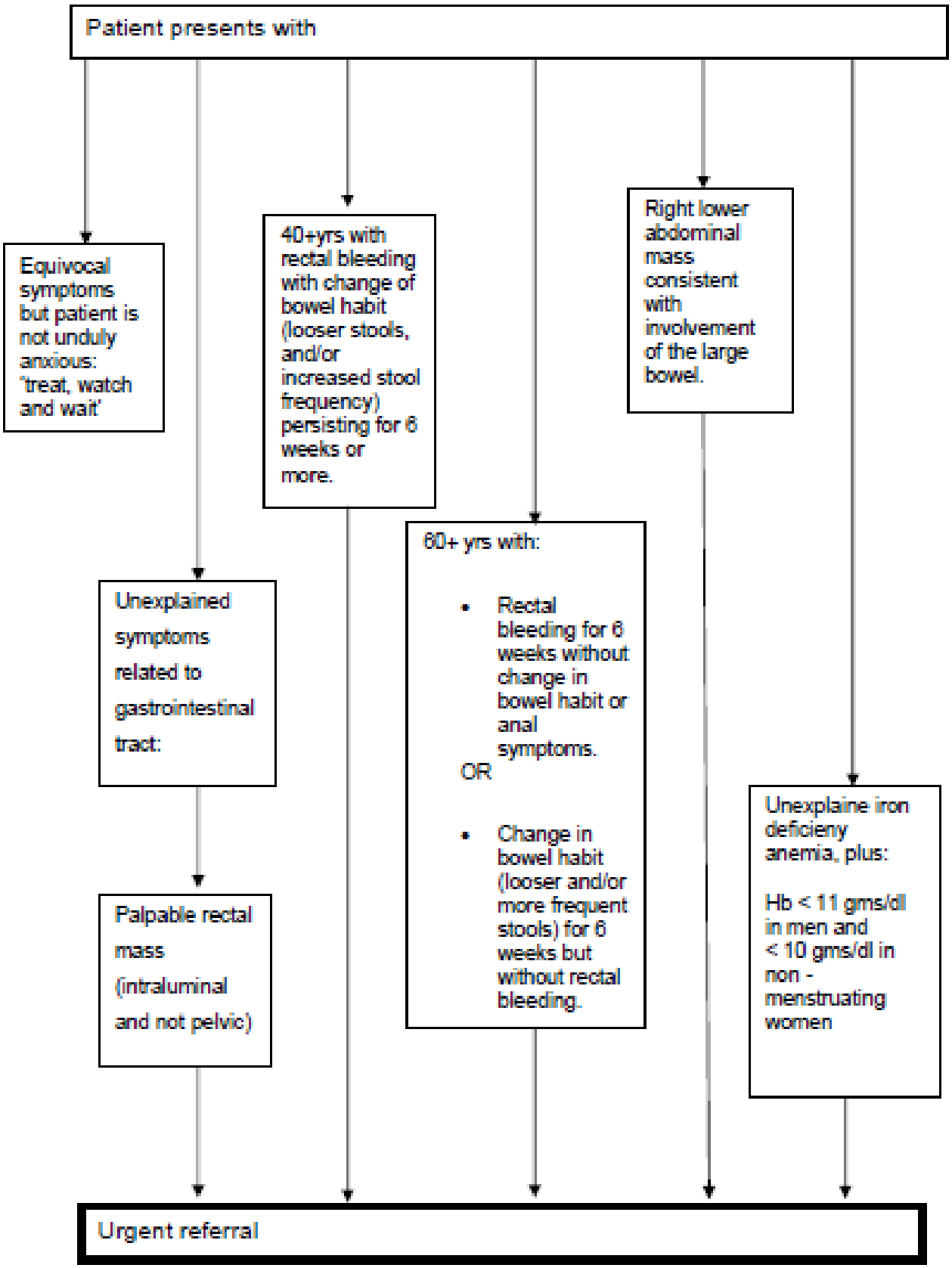
Lung cancer


Patient presents with
Any of the following:
• haemoptysis
unexplained persistent (over 3 weeks):
• chest/shoulder pain
• dyspnoea
• weight loss
• chest signs
• hoarseness
• finger clubbing
• cervical/supraclavicular lymphadenopathy
• cough with or without any of the above.
• features suggestive of metastasis from lung
Patients presenting with the listed symptoms or signs AND the following risk factors:
• Current or ex-smoker
• Exposure to asbestos.
• History of cancer (esp. head and neck).
Persistent haemoptysis in smokers or exsmokers who are 40 years or older
• SVC obstruction
• stridor.
Chest X-ray
Suggestive of lung cancer including:
• Slowly resolving consolidation
• pleural effusion
Normal but high suspicion of cancer
Urgent referral
Consider immediate referral

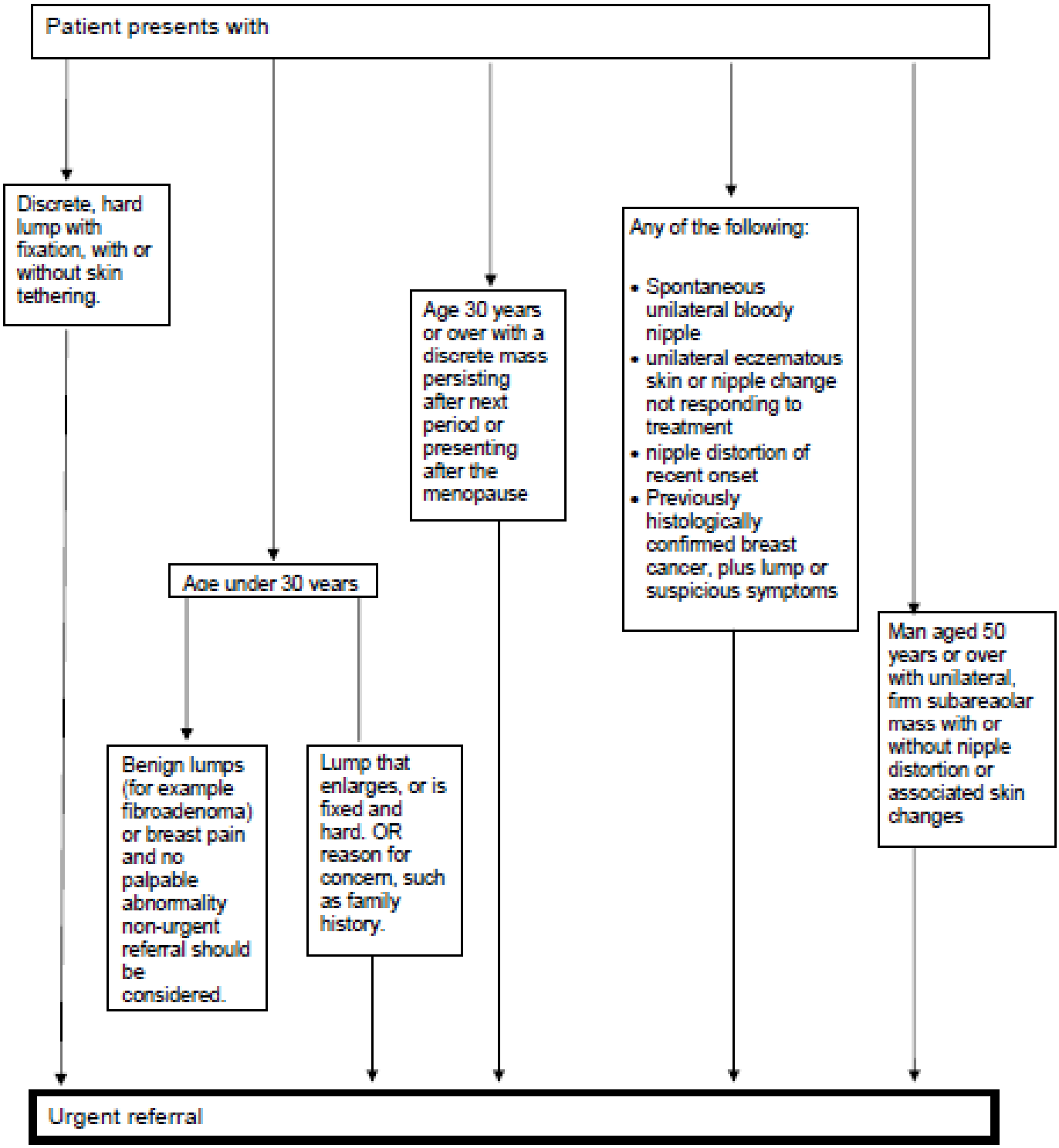
Upper gastrointestinal cancer

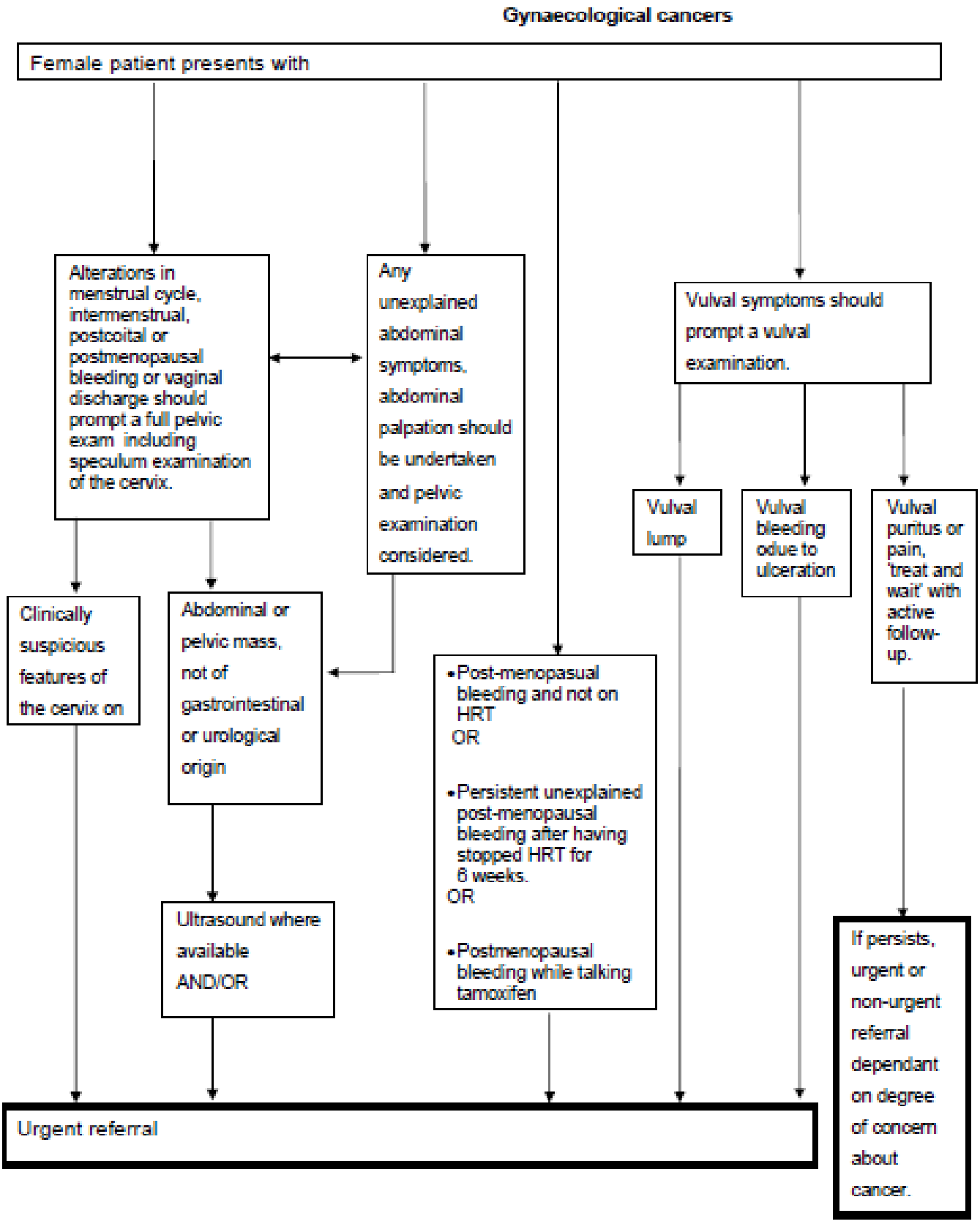


Lower gastrointestinal cancer

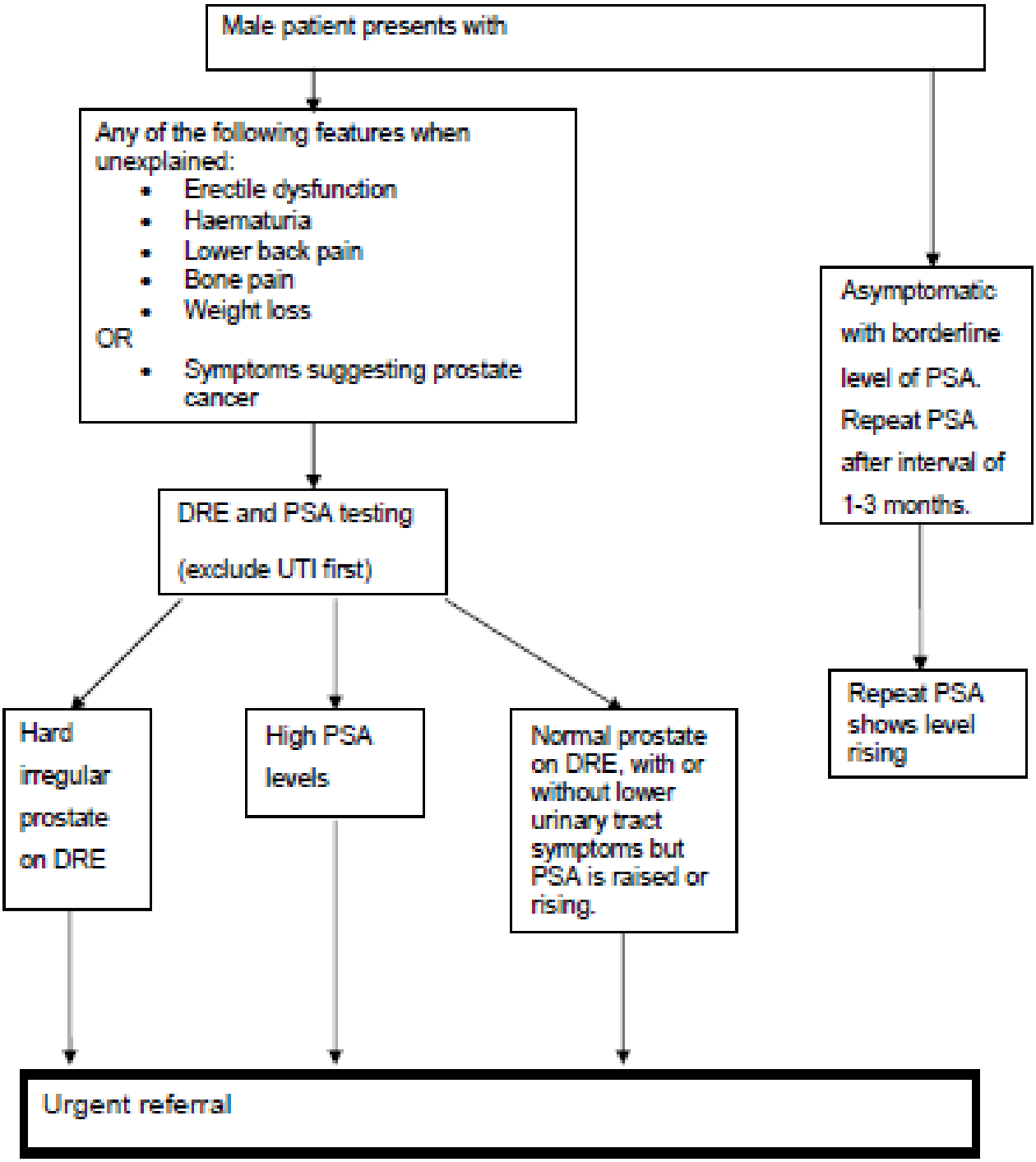


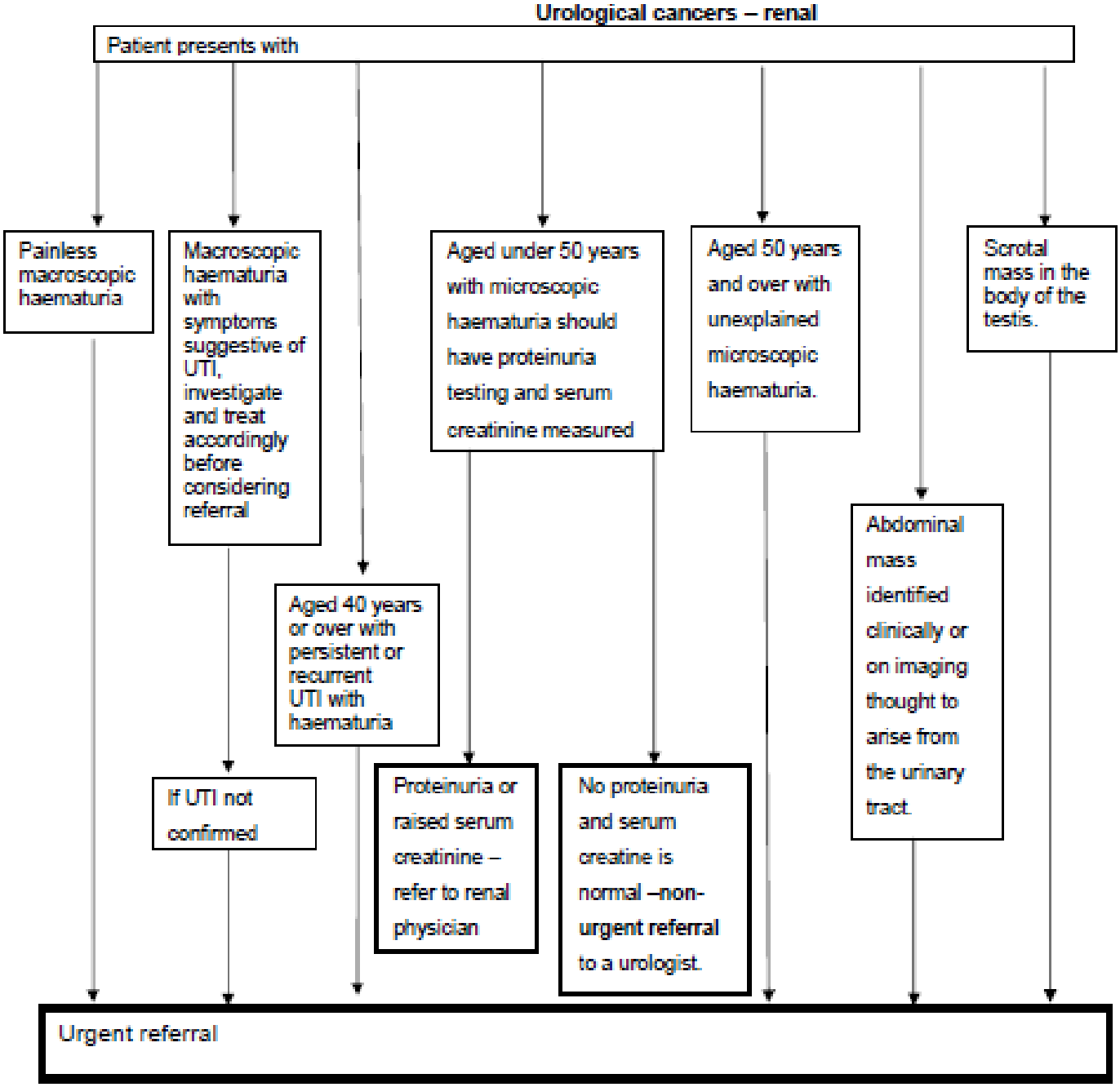
Breast cancer



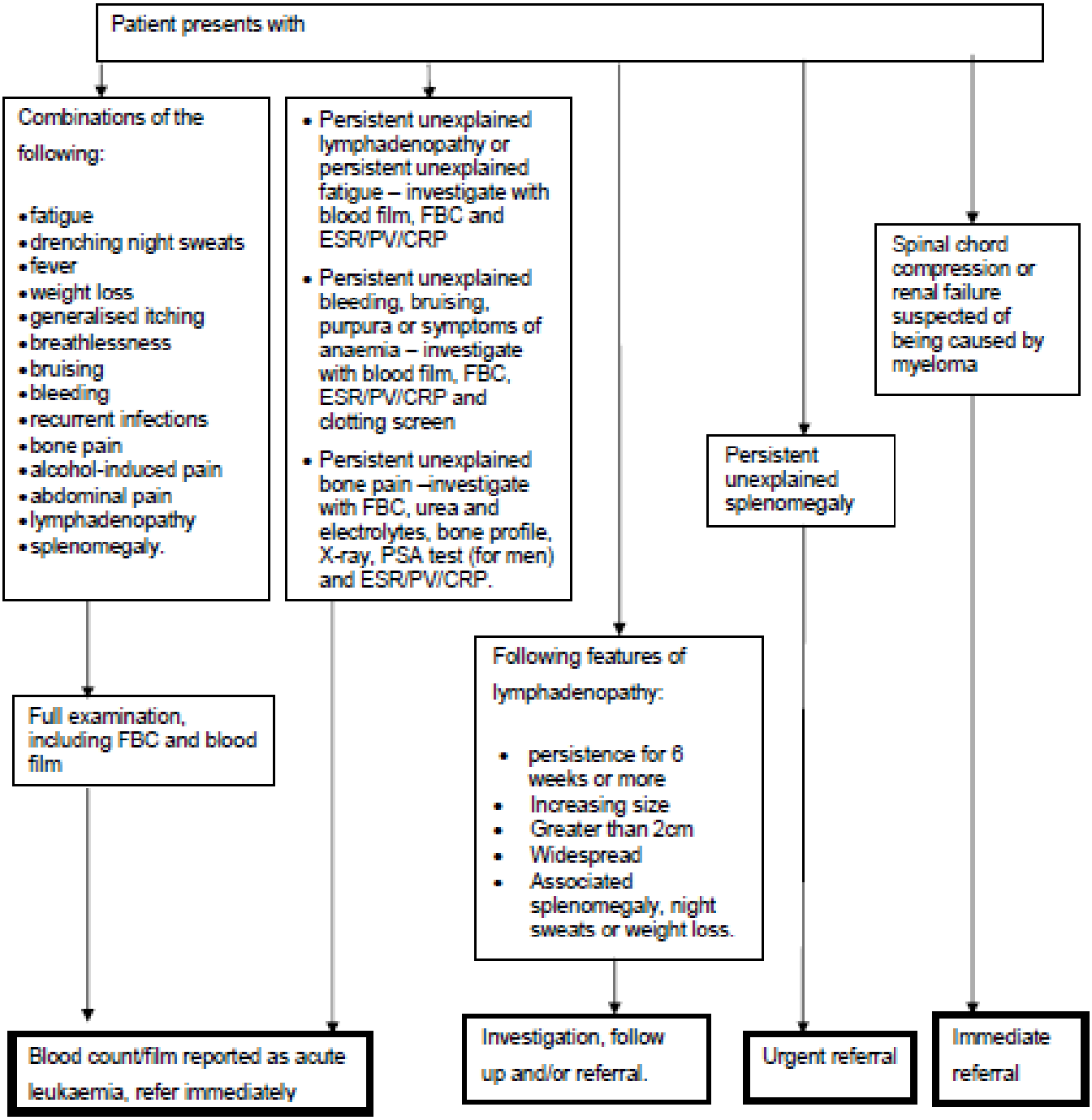

Gynaecological cancers
Female patient presents with
Alterations in menstrual cycle, intermenstrual, postcoital or postmenopausal bleeding or vaginal discharge should prompt a full pelvic exam including speculum examination of the cervix.
Any unexplained abdominal symptoms, abdominal palpation should be undertaken and pelvic examination considered.
Vulval symptoms should prompt a vulval examination.
Vulval lump
Vulval bleeding odue to ulceration
Vulval puritus or pain, 'treat and wait' with active follow-up.
Clinically suspicious features of the cervix on
Abdominal or pelvic mass, not of gastrointestinal or urological origin
•Post-menopasual bleeding and not on HRT
OR
•Persistent unexplained post-menopausal bleeding after having stopped HRT for 6 weeks.
OR
•Postmenopausal bleeding while talking tamoxifen
Ultrasound where available AND/OR
If persists, urgent or non-urgent referral dependant on degree of concern about cancer.
Urgent referral

Urological cancers –prostate

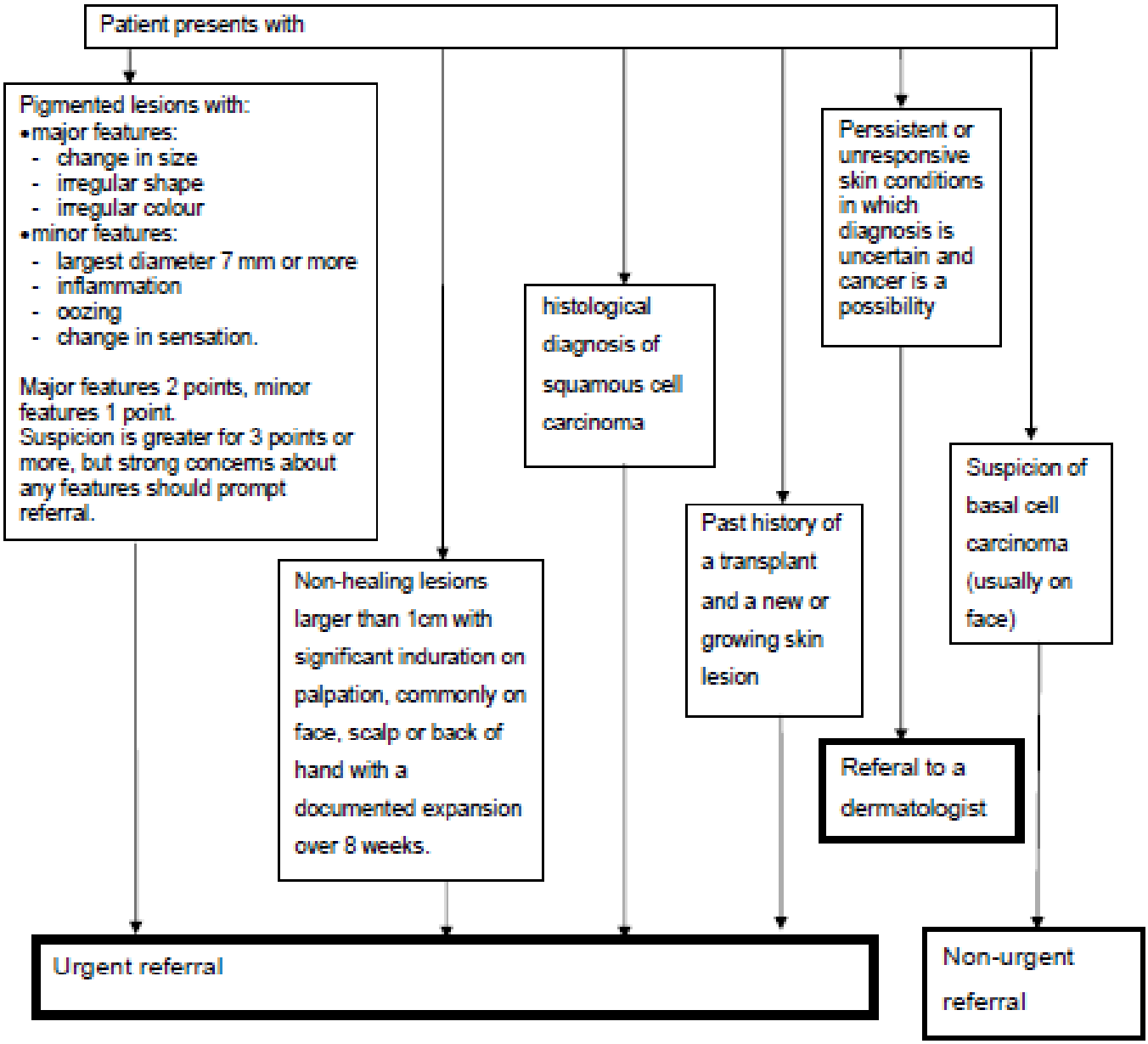



Urological cancers – renal
Patient presents with
Painless macroscopic haematuria
Macroscopic haematuria with symptoms suggestive of UTI, investigate and treat accordingly before considering referral
Aged 40 years or over with persistent or recurrent UTI with haematuria
Aged under 50 years with microscopic haematuria should have proteinuria testing and serum creatinine measured
Aged 50 years and over with unexplained microscopic haematuria.
Abdominal mass identified clinically or on imaging thought to arise from the urinary tract.
Scrotal mass in the body of the testis.
If UTI not confirmed
Proteinuria or raised serum creatinine – refer to renal physician
No proteinuria and serum creatine is normal –non-urgent referral to a urologist.
Urgent referral

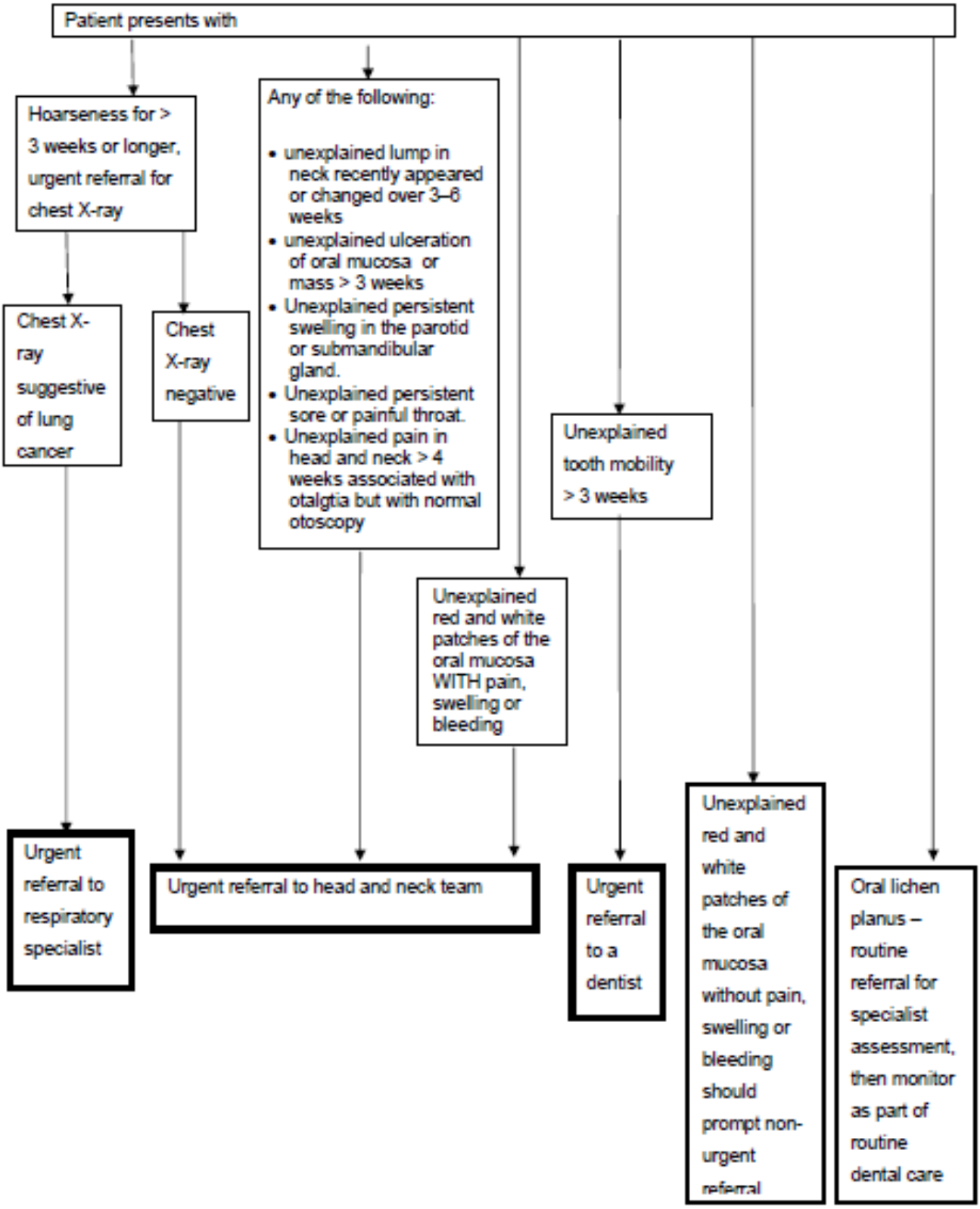
Haematological cancers

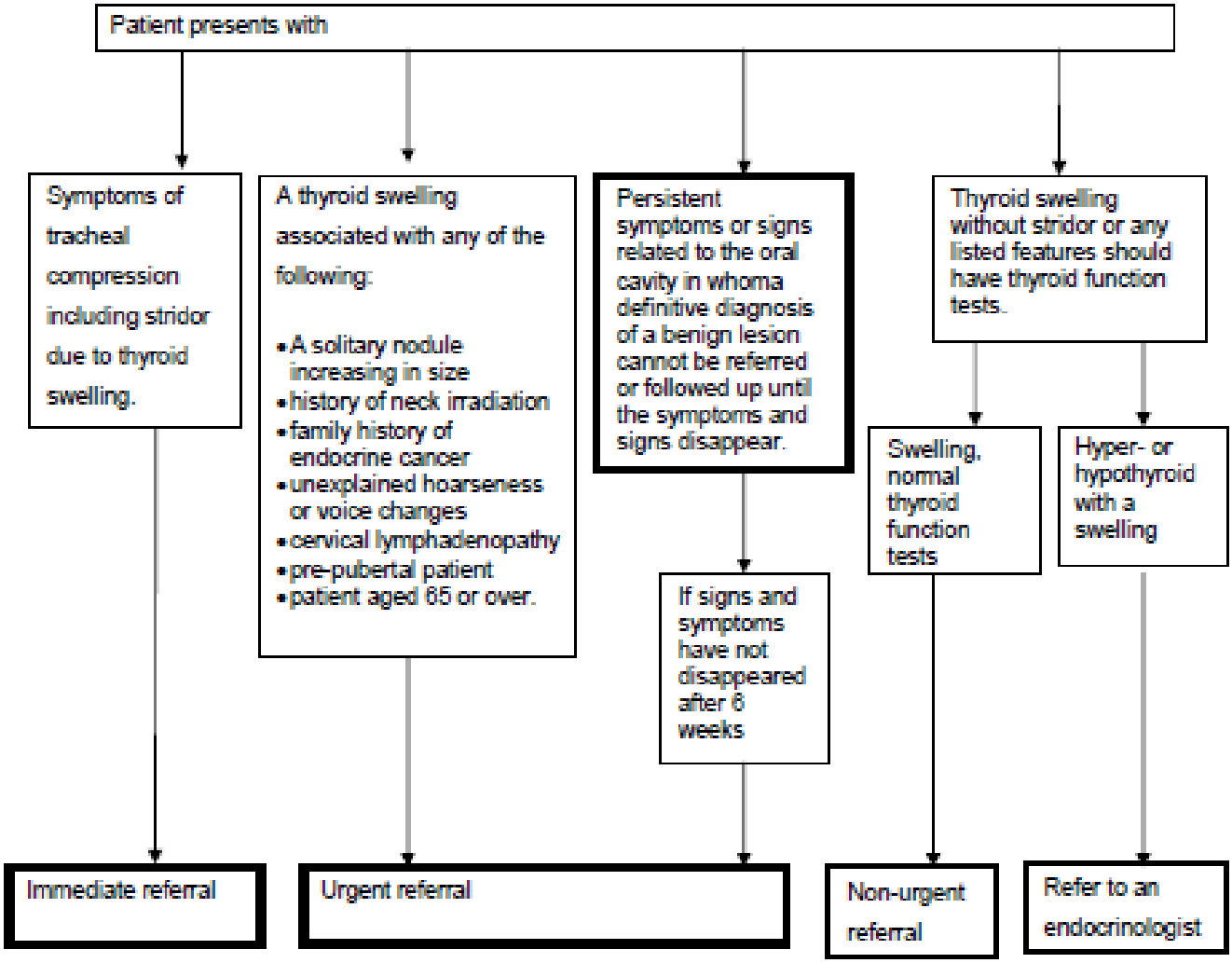


Skin cancers

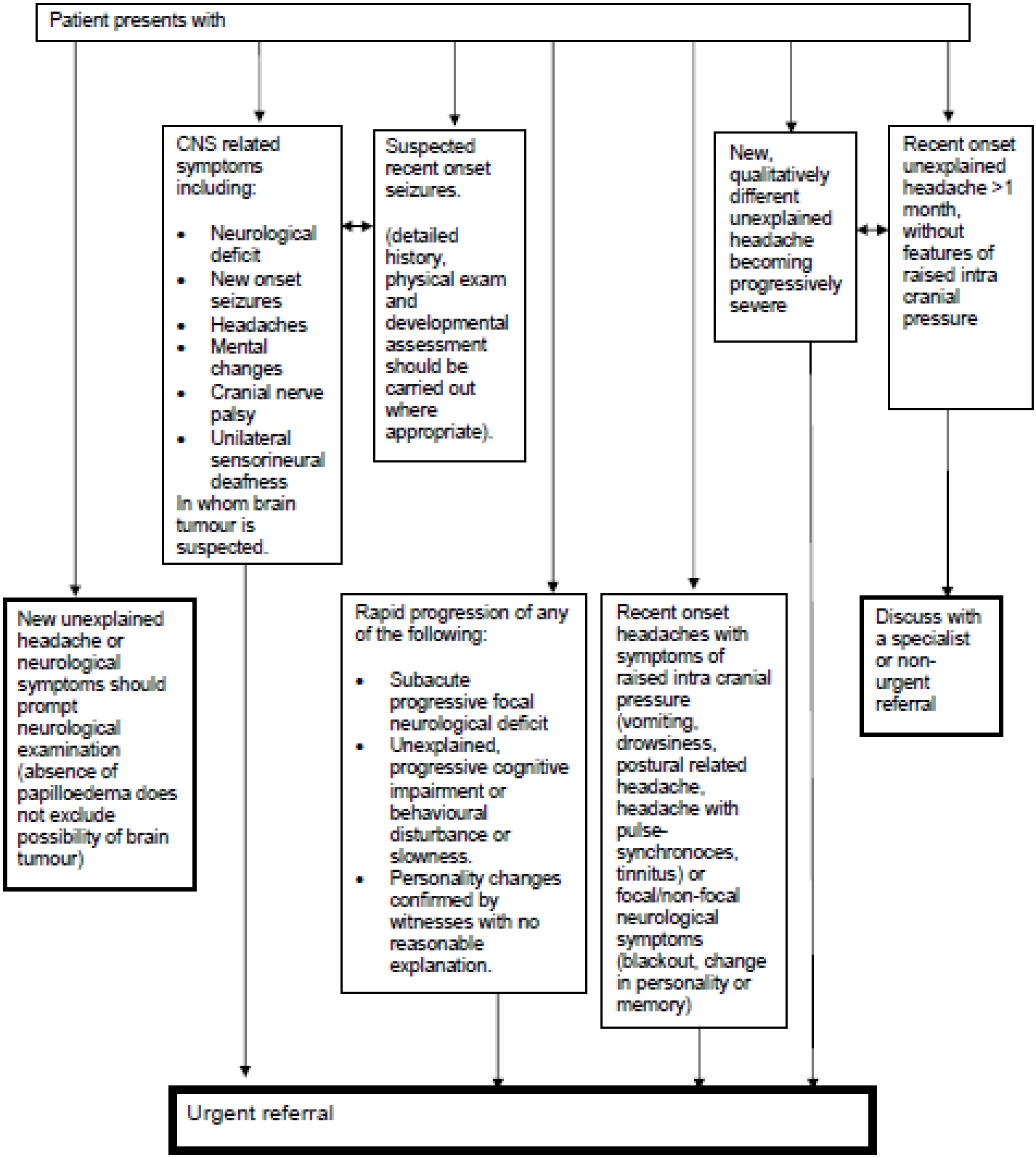


Head and neck cancers

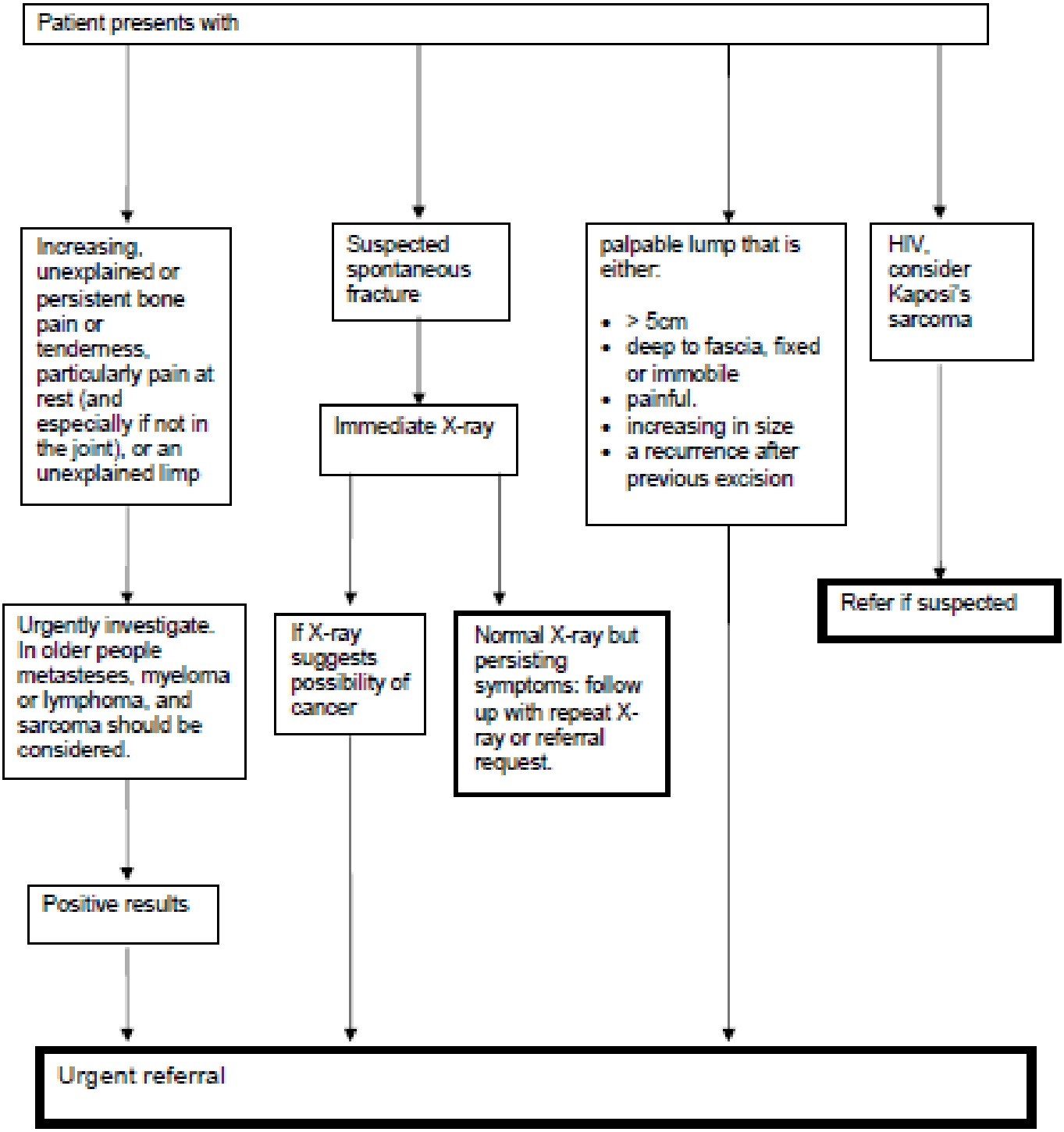



Patient presents with
Symptoms of tracheal compression including stridor due to thyroid swelling.
A thyroid swelling associated with any of the following:
• A solitary nodule increasing in size
• history of neck irradiation
• family history of endocrine cancer
• unexplained hoarseness or voice changes
• cervical lymphadenopathy
• pre-pubertal patient
• patient aged 65 or over.
Persistent symptoms or signs related to the oral cavity in whoma definitive diagnosis of a benign lesion cannot be referred or followed up until the symptoms and signs disappear.
Thyroid swelling without stridor or any listed features should have thyroid function tests.
Swelling, normal thyroid function tests
Hyper- or hypothyroid with a swelling
If signs and symptoms have not disappeared after 6 weeks
Immediate referral
Urgent referral
Non-urgent referral
Refer to an endocrinologist

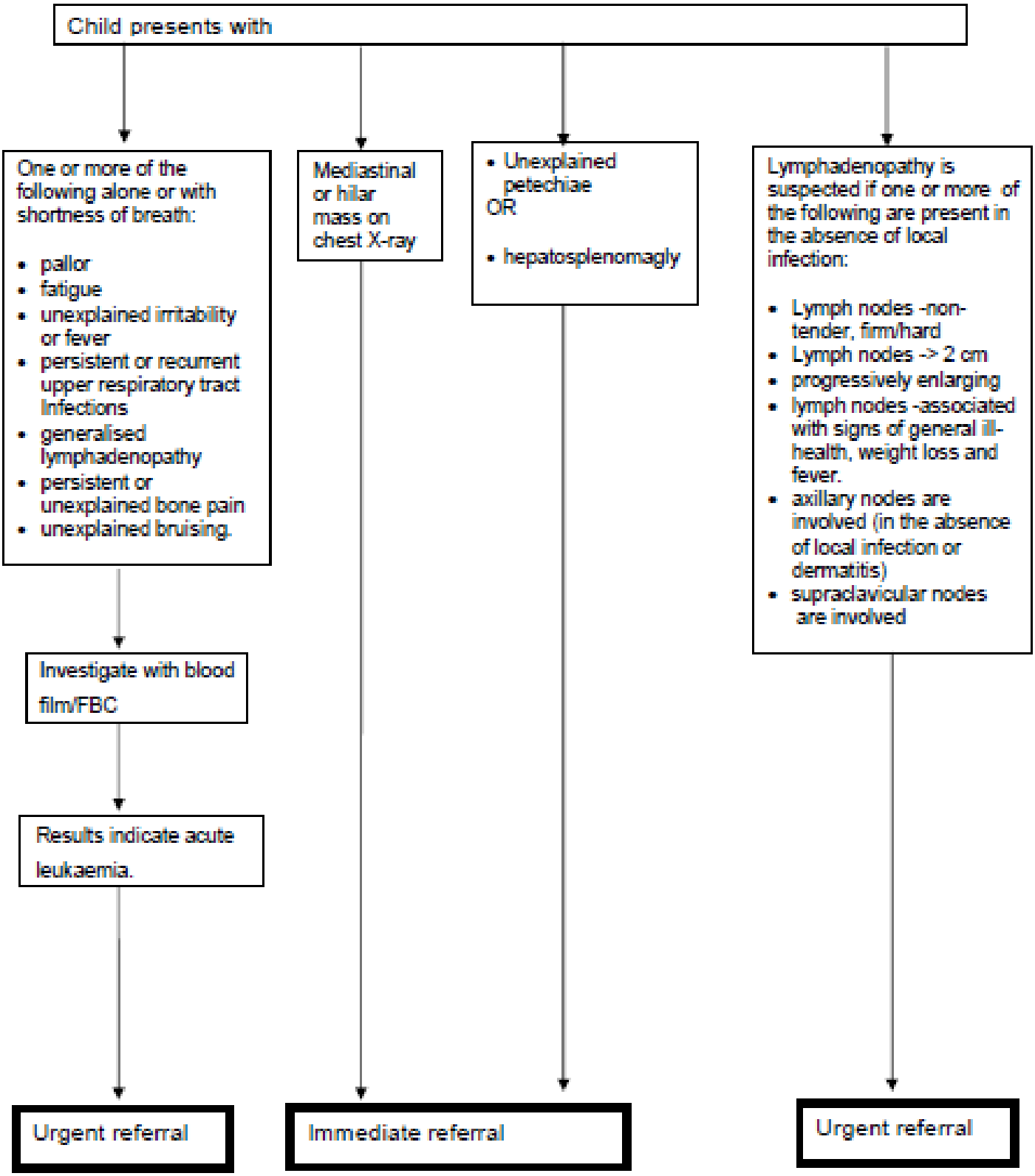
Brain and CNS cancers



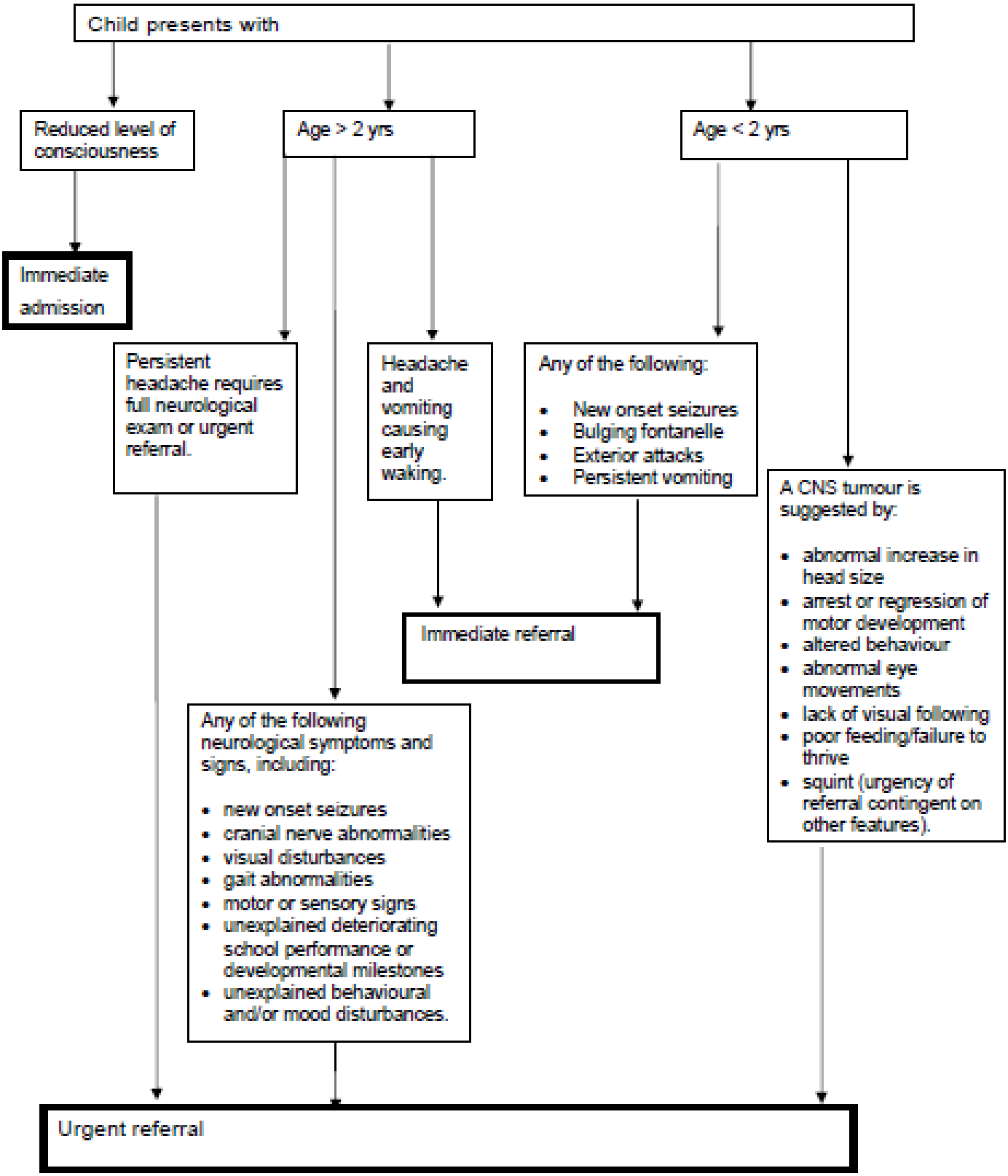
Bone cancers and soft-tissue sarcomas



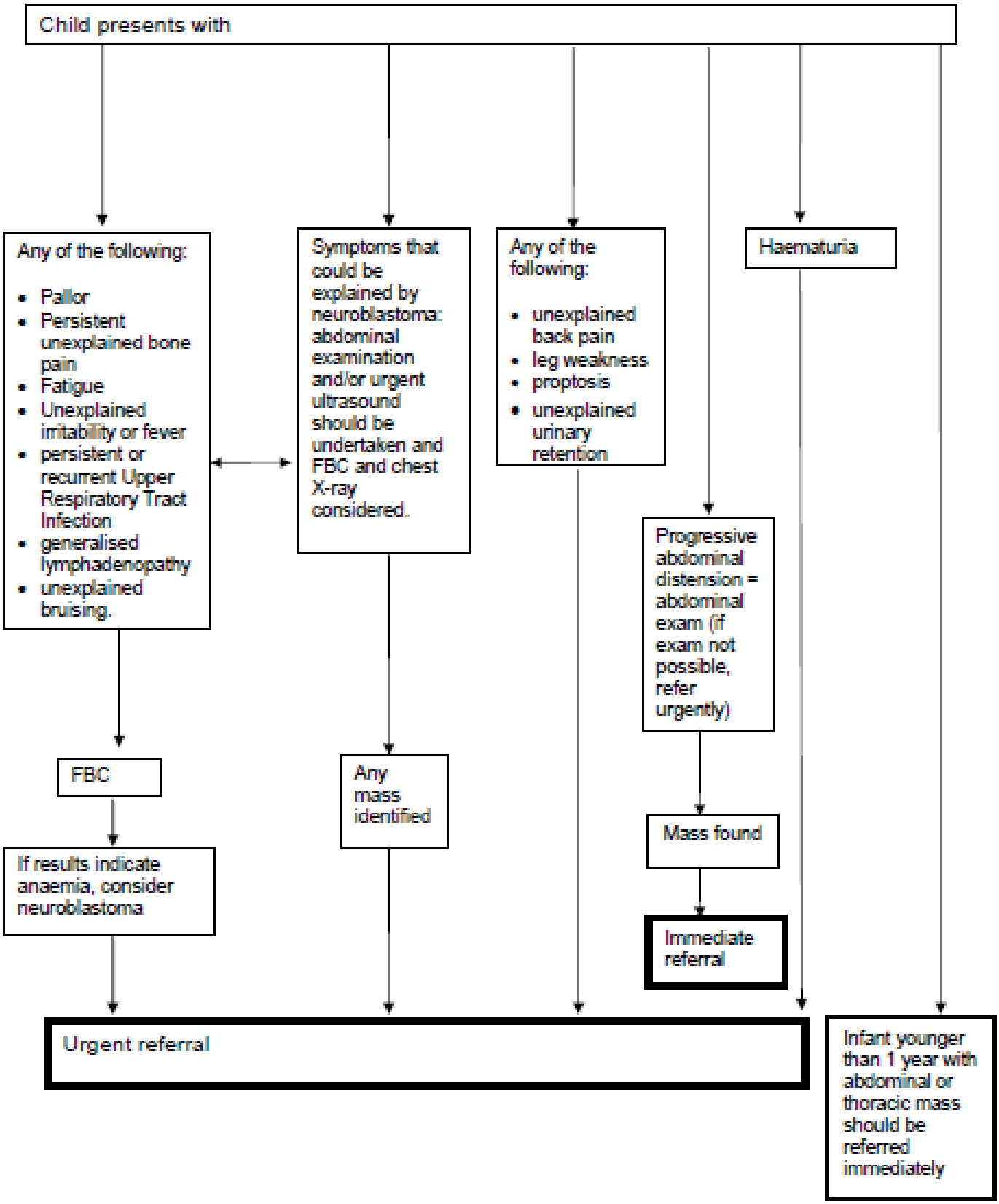
Children's cancers – leukaemia and lymphoma



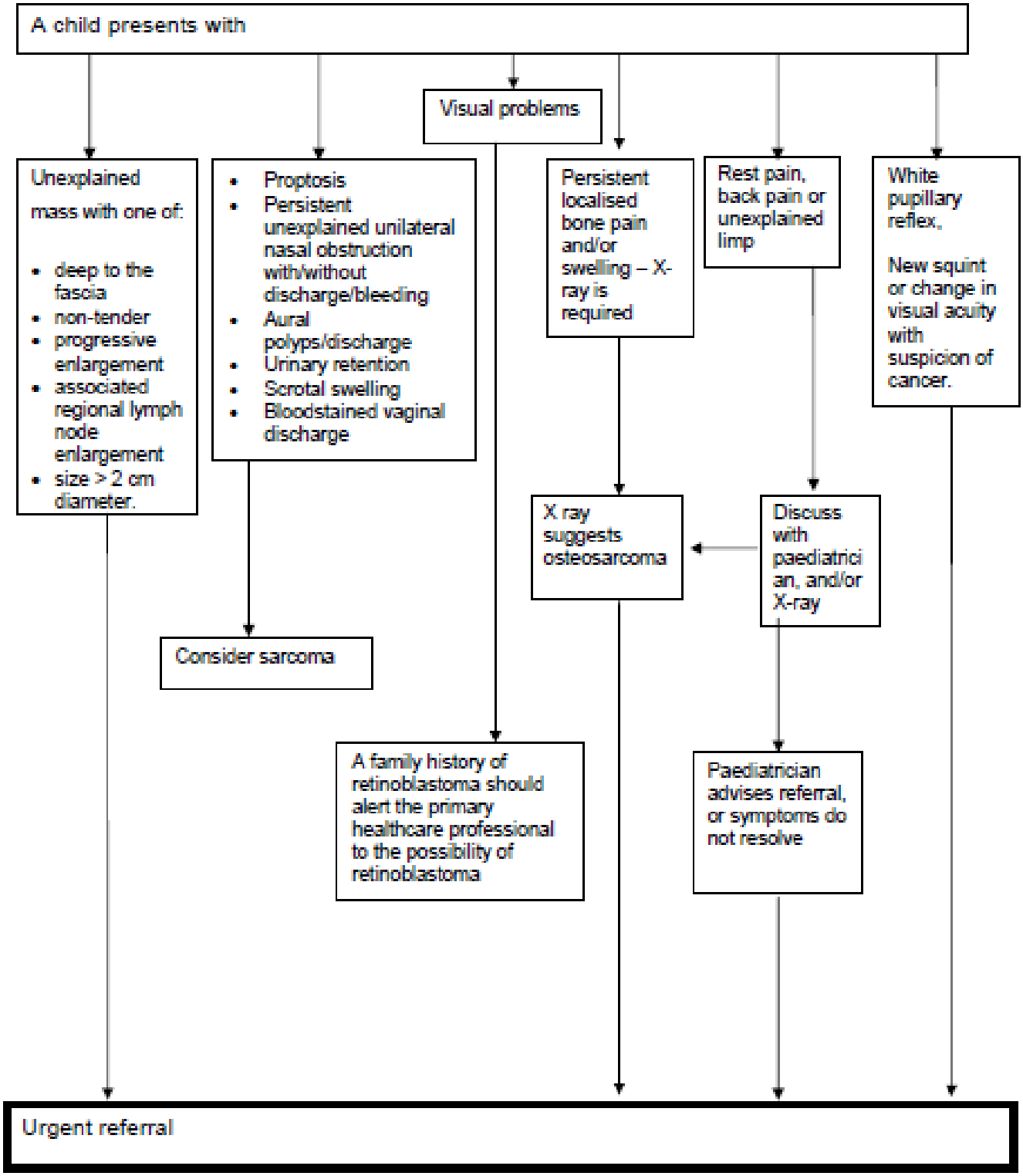
Children's cancers – brain tumours



Children's cancers – neuroblastoma and Wilm's tumour



Children's cancers –bone tumours, sarcoma and retinoblastoma



6 Audit Criteria

6.1 Audit criteria

Criterion: what should happen for a patient?

Standard: the percentage of patients who should receive the care. Exception(s): clinically acceptable circumstances that would explain why a patient doesn't receive the care described. Definition of terms: operational definitions of key terms for audit purposes.

Primary health care professionals do not refer many patients with suspected cancer in any one year. The findings of an audit limited to patients referred by one professional in one year will be at risk of misinterpretation because of the small numbers of patients involved. Therefore, the findings of the audit suggested here should be used to generate discussion and learning. The organisation of significant event audit meetings by a primary health care team would be an appropriate way to consider the findings, or delay in diagnosis in individual cases. Significant event audit across the interface with secondary care could be used to investigate the appropriateness of referrals and encourage more efficient referral practice. Many audits of cancer referrals have been undertaken in the past four years, but most have been based in secondary care and have not led to a dialogue between primary and secondary care on improving referral practice. The detection of cancer in a child would be an appropriate topic for significant event audit. In addition, primary care teams should consider the prospective collection of audit information over several years. Consideration should be given to involving patients and carers in audits. Many of the recommendations relate to information given to patients, their support and their involvement in decisions, and it would therefore be appropriate to involve them when possible in audits.

Table 6

Criterion	Standard	Exception	Definition of terms
1. Patients being referred with suspected cancer are offered a) information about the likely diagnosis, b) what to expect from the specialist service, and c) advice about seeking further help whilst awaiting the specialist consultation.	1 a) 100% 1 b) 100% 1 c) 100%	1 a) Patients who do not want information. 1 b) nil 1 c) nil	
2. Patients presenting with classical features of the cancers included in the algorithms are a) suspected of having cancer and b) initial investigation or referral is arranged at the first consultation.	2 a) 100% b) 100%	2 a) nil b) patients who refuse referral or investigation.	
c) % of patients referred as urgent who are appropriately suspected of having cancer % of patients referred non-urgently who are appropriately assessed as not	c) x% of patients referred urgently have cancer (the % is to be determined from the findings of the review of audits currently being	c) none	

having cancer 3. Patients referred for suspected cancer have had preliminary investigations undertaken in primary care as recommended in the guideline.	undertaken) d) y% (% to be determined from the findings of the review of audits currently being undertaken) 3. 100%	d) none 3. Patients who refuse investigations.	

Calculation of compliance

$$\frac{\text{Number of patients whose care is consistent with the criterion } \textit{plus} \text{ number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}} \times 100$$

7 Support and Information needs of people with suspected cancer at the time of referral

1 Patients should be able to consult a primary healthcare professional of the same sex if preferred. D

2 Primary healthcare professionals should discuss with patients (and carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations (including their potential risks and benefits), and ensure they have the time for this. D

3 When cancer is suspected in a child, the referral decision and information to be given to the child should be discussed with the parents or carers (and the patient if appropriate). D

4 Adult patients who are being referred with suspected cancer should normally be told by the primary healthcare professional that they are being referred to a cancer service, but if appropriate they should be reassured that most people referred will not have a diagnosis of cancer, and alternative diagnoses should be discussed. D

5 Primary healthcare professionals should be willing and able to give the patient information on the possible diagnosis (both benign and malignant) in accordance with the patient's wishes for information. Current advice on communicating with patients and/or their carers and breaking bad news[10] should be followed. D

6 The information given to patients, family and/or carers as appropriate by the primary healthcare professional should cover, among other issues: D

- where patients are being referred to
- how long they will have to wait for the appointment
- how to obtain further information about the type of cancer suspected or help prior to the specialist appointment
- who they will be seen by
- what to expect from the service the patient will be attending
- what type of tests will be carried out, and what will happen during diagnostic procedures
- how long it will take to get a diagnosis or test results
- whether they can take someone with them to the appointment
- other sources of support, including those for minority groups.

8 Consideration should be given by the primary healthcareprofessional to meeting the information and support needs of parents and carers. Consideration should also be given to meeting these particular needs for the people for whom they care, such as children and young people, and people with special needs (for instance, people with learning disabilities or sensory impairment). D

9 The primary healthcare professional should be aware that some patients find being referred for suspected cancer particularly difficult because of their personal circumstances, such as age, family or work responsibilities, isolation, or other health or social issues. D

10 Primary healthcare professionals should provide culturally appropriate care, recognising the potential for different cultural meanings associated with the possibility of cancer, the relative importance of family decision- making and possible unfamiliarity with the concept of support outside the family. D

11 The primary healthcare professional should be aware that men may have similar support needs to women but may be more reticent about using support services. D

13 All members of the primary healthcare team should have available to them information in a variety of formats on both local and national sources of additional support for patients who are being referred with suspected cancer. D

14 In situations where diagnosis or referral has been delayed, or there is significant compromise of the doctor/patient relationship, the primary healthcare professional should take care to assess the information and support needs of the patient, parents and carers, and make sure these needs are met. The patient should be given the opportunity to consult another primary
healthcare professional if they wish. D

15 Primary healthcare professionals should promote awareness of key presenting features of cancer when appropriate. D

7.1 Evidence Statements:

Communication between health care practitioners and patients:

7.1.1 Effective communication between health care practitioner and patient in both the history-

[10] *Improving communication between doctors and patients*. A report of the working party of the Royal College of Physicians (1997) www.rcplondon.ac.uk/pubs/brochures/pub_print_icbdp

taking part of the consultation and during discussion of the management plan positively influences health outcomes for patients. (III)

The evidence base from which these guidelines are drawn has a limited empirical and theoretical base.

Information and support needs at time of referral from primary care:

7.1.2 People want information about their suspected diagnosis and possible treatment. (III)

7.1.3 People have different preferences for information and involvement in decisions about their treatment and care at different stages in the pathway of care. (III)

7.1.4 People prefer information that is available in different formats, is specifically relevant to their condition and for which help in interpreting information is available from health care professionals. (III)

7.1.5 The pre-diagnosis stage is one of great uncertainty for the individual which could involve moving from being a person-without- cancer to a person-with-cancer: for some individuals this process can occur quickly, for others it can take a considerable amount of time. (III)

7.1.6 The pre-diagnosis stage is a time when information and support is not routinely provided (III)

7.1.7 There is a need for support at the time of referral to secondary care. Patients at the primary-secondary care interface would like access to appropriate care, orientation of care to their particular requirements, provision of information and continuity of staff and coordination and communication among professionals. Failure to provide this care can lead to patients feeling left “in limbo”. (III)

7.2 Introduction

A consistent problem during the work on the cancer referral guideline has been the lack of available evidence to answer questions of importance to the guideline development group. This has been particularly true of communication between practitioner and patient and patient support and information needs *at the time of referral from primary care*.

This section deals with communication, patient support and information needs. In view of the lack of specific evidence, this section reviews selected key important papers on communication in health care and “breaking bad news”. Reference is also made to the limited primary research in this area.

The approach has been to use selected review articles, primary papers and consensus statements. Formal systematic literature searching has been undertaken to identify relevant papers on information and support needs in primary care for specific cancer sites, and in general the studies identified have been included in the chapters dealing with each group of cancers.

7.2.1(1) General studies of health care communication between health care practitioners and patients

Guidelines

(Royal College of Physicians, 1997)(21)

The key recommendations for good communication between health care professionals and patients and carers are as follows:

- Listen to patients and respect their views and beliefs
- Give patients the information they ask for or need about their condition, its treatment and

process, in a way they can understand
- Provide the most important information first
- Explain how each piece of information will affect patients personally
- Present information in separate categories
- Make advice specific, detailed and concrete
- Use words the patient will understand; confirm understanding by questions; define unfamiliar words; write down key words; draw diagrams as appropriate
- Repeat the information using the same words each time
- Prepare material, written or taped, to back up handwritten notes
- Share information with patients' partners, close relatives or carers if they ask you to do so.
- The content, style and timing of information provision should be tailored to the needs of the individual patient.

(Masera et al, 1997)(22)

The following lists a summary of the essential points of the "Principles for Communicating the Diagnosis" in children & adolescents, as reached by general consensus by the SIOP Psychosocial Committee at their 1995
Montevideo meeting:

- Establish a protocol for communications.
- Communicate immediately at diagnosis and follow up later.
- Communicate in a private and comfortable space.
- Communicate with both parents and other family members if desired.
- Hold a separate session with the child.
- Solicit questions from parents and child.
- Communicate in ways that are sensitive to cultural differences.
- Share information about the diagnosis and the plan for cure.
- Share information on lifestyle and psychosocial issues.
- Encourage the entire family to talk together.

Local interpretation of these general guidelines is required to accommodate prevailing cultural assumptions, medical situations, family dynamics, and resources and abilities of the parents, children and staff members involved.

Secondary studies

There is research evidence that effective communication can improve health outcomes.

(Stewart, 1995)(23)

Stewart has published extensively on patient-centred medicine and the need for effective communication and sharing of decisions between practitioner and patient. Her 1995 systematic review of randomized controlled trials (RCTs) and analytic studies of physician-patient communication in which patient health was an outcome variable is widely cited.

Its key finding is that the quality of communication both in the history-taking segment of the visit and during discussion of the management plan does positively influence patient health outcomes. The outcomes affected, in descending order of frequency, are: emotional health, symptom resolution, function, physiologic measures (i.e., blood pressure and blood sugar level) and pain control.

(Davies and Higginson, 2003)(24)

This study was a systematic review of communication, information and support needs of adults with cerebral glioma. Twelve studies reported in 16 papers were identified for inclusion. The studies included qualitative and quantitative investigations, and many were limited by small sample sizes and to single specialist centres. The studies generally included patients after referral, and any views on needs and experiences at referral were retrospective.

Up to one third of patients and relatives complained that the information they received lacked coherence, and that the traditional outpatient care does not meet patients' needs for support. The proportion of patients who were aware they had a brain tumour within a few weeks of the diagnosis varied from around 50% to 95% between studies. Patients appeared to find 'telling the story of the diagnosis' a helpful step when taking part in a support group.

(Semple and McGowan, 2002)(25)

This study reviewed articles identified from MEDLINE and CINAHL 1990-2001 that reported studies of the information needs of people with head and neck cancers. The review noted two important recent trends. Health service policy changes have placed greater emphasis on patient involvement, and patients increasingly expect more and better information to enable them to understand their health. At the same time, health professionals are adopting a more open style of communication, and accept that most patients want to know their diagnosis.

The review found evidence that effective information can enable the patient to participate in decision making, or decide not to participate. Three levels of participation have been described: passive, where the doctor makes all the decisions; collaborative, where decisions are made jointly; and active, where the patient has the final say in decisions. The available evidence suggests that around 20% of patients want an active role, 28-40% a collaborative role, and 25-50% a passive role.

When patients are anxious, they do not always retain information effectively; furthermore, anxious patients are less likely to express their concerns. The provision of written information can assist in addressing these difficulties. Badly written information may convey an uncaring and unprofessional attitude.

Therefore, written information should be carefully prepared and clearly presented.

Primary studies

(Krishnasamy et al, 2001)(26)

In this study, a questionnaire was mailed to 466 patients with a diagnosis of lung cancer. The patients were attending 24 randomly selected UK hospitals. The aim of the study was to explore perceptions of healthcare need.

209 (45%) patients returned a completed questionnaire. 26% reported being unwell for a year, and 38% had been unwell for between one and two years. In describing the process of diagnosis, more than 50% reported presenting to their general practitioner within three weeks. 6% presented after two to three months of illness. When asked about their ideas about the diagnosis before consulting the general practitioner, 20% thought they had cancer, 19% a chest infection, 2% asthma, 2% COPD, 2% chronic bronchitis, 2% TB, and 16% did not know. Having seen a general practitioner, 9% waited between one and three months before being seen in a hospital, and 45% were seen within two weeks. The median time to wait for a chest x-ray was two weeks. Of those told the diagnosis by a general practitioner, most felt able to ask questions but 27% felt too upset at the time to ask questions. Patients given information by a hospital doctor were significantly more likely to perceive the information as clear. When asked about key sources of support, 65% identified the general practitioner, and 24% reported this source as being particularly helpful.

7.2.1 (2) Studies of "breaking bad news" in health care professional consultations

One way of considering communication in the consultation with individuals with suspected cancer in primary care is to focus on whether the practitioner considers the individual at 'high' or 'low' risk of having cancer. If the individual is at 'low' risk of having cancer, the consultation can be managed by explanation, reassurance and follow up as appropriate. If the individual is at 'high' risk of having cancer, however, then not only is referral indicated but the practitioner must communicate to the individual the concern that the patient may have cancer and as such is

"breaking bad news" – although it should be stressed that there will be uncertainty as to whether the "bad news" diagnosis will be confirmed.

There are published recommendations as to how practitioners should break "bad news" (see below). However, a theoretical basis for such recommendations and empirical evidence that they improve health outcomes are lacking.

Guidelines

(National Health and Medical Research Council, 2003)(27)

The Australian National Health and Medical Research Council has produced evidence-based guidelines for the psychosocial care of adults with cancer. Literature reviews were undertaken to identify relevant studies, with particular emphasis on the following cancers: colorectal, breast, prostate, melanoma, lung, gynaecological and non-Hodgkin's lymphoma. Head and neck cancers and pancreatic cancer were also included.

The guidelines noted that people who perceive they have poor support are more likely to experience greater psychological distress, and that partners and children of patients with cancer are also vulnerable to psychological distress and in need of support. The experience of the diagnosis of cancer is a stressful event that is followed by symptoms such as anxiety and depression. The experience of cancer is not a single, undifferentiated event, but people with cancer encounter a series of events which may pose different demands and difficulties. The psychosocial care of a person with cancer begins from the time of initial diagnosis i.e. when a decision on referral is made. There is a need for social and cultural sensitivity in assessment of need. Successful strategies for meeting psychosocial support needs may differ with gender.

Effective communication is central to the identification of individuals' specific needs, including for information and psychosocial support.

Potential benefits of effective communication between treatment team members and people with cancer include improvements in the patient's psychosocial adjustment, decision-making, treatment compliance and satisfaction with care (Level I evidence – obtained from a systematic review of all relevant randomised controlled trials). The way clinicians present information significantly affects people's recall of that information (Level III-2 – evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted times series with a control group). Training in communication skills can assist clinicians to improve (Level-III-I – evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)). Continuing training in the clinical setting may be beneficial given evidence that skills need to be reinforced and consolidated over time (Level IV – evidence from case studies, either post-test or pre- and post-test). Patients' psychological adjustment improves when clinicians express empathy and listen actively (Level III-3 – evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel group).

Understanding and recall can be boosted by:

- Giving clear, specific information (Level III-3)
- Explaining medical terms and avoiding medical jargon (Level III-3)
- Presenting information in terms of the specifics for each patient, rather than in a general format (Level III-3)
- Giving the most important information first (Level IV)
- Repeating and summarising important pieces of information (Level III-3)

- Actively encouraging questions (Level II – at least one properly randomised controlled trial)
- Actively checking understanding (Level III-3).

Additional strategies to increase satisfaction, recall and understanding include:

- Providing written information (Level III-3)
- Providing general information tapes (Level II)
- Taping of a consultation (Level II)

- Sending a summary letter as a follow-up to the consultation (Level II)
- Encouraging the presence of a support person (healthcare professional, family or friend) (Level II).

Secondary studies

(Ptacek and Eberhardt, 1996)(28)

This article provides a narrative review of the medical literature on the bad news process, while at the same time highlighting its limitations. It suggests a theoretical framework for considering the bad news process by discussing concepts borrowed from the stress and coping literature, and makes suggestions regarding future empirical work on breaking bad news.

"Bad news" is defined as relating to situations where there is either a feeling of no hope, a threat to a person's mental or physical well-being, a risk of upsetting an established life-style, or where a message is given which conveys to an individual fewer choices in his or her life.

The authors reviewed published work to date on "breaking bad news" and summarised recommendations that were repeatedly found in the literature. These are summarised below:

Consensus Recommendations for "Breaking Bad News"

Physical and social setting

Location

- Quiet, comfortable, private

Structure

- Convenient time, no interruptions, enough time available to ensure no rushing
- In person, face-to-face, make eye contact, sit close to patient, avoid physical barriers

People

- Support network: identify and have present at patient's request

Message

What is said

- Preparation: give a warning shot ("I'm afraid I have bad news")
- Find out what patient already knows
- Convey some measure of hope
- Acknowledge and explore patient's reaction and allow for emotions to be expressed
- Allow for questions
- Summarize the discussion: verbally and/or in written form, audiotape
- Consultation

How it is said

- Emotional manner: warmth, caring, empathy, respect
- Language: simple, careful word choice, direct, no euphemisms or technical diagnostic terminology, avoid medical jargon
- Give news at person's pace, allow them to dictate what they are told

7.2.1(3) Studies of health care communication between health care practitioners and individuals with cancer

There is an extensive literature on communication and sharing of decisions with individuals who have been diagnosed as having cancer. Much of this literature has focused on the needs of those

working in secondary care, such as oncologists and specialist nurses, who will inform individuals of the definitive diagnosis and provide continuing care and support (Fallowfield & Jenkins, 1999; Maguire, 1999) It is, however, difficult to apply this literature to individuals seen in primary care before a definitive diagnosis of cancer has been made.

Secondary studies

(The University of York NHS Centre for Reviews and Dissemination, 2000)(29)

This review focused on the communication, information giving and sharing of decisions between health professionals and people with cancer. It does not address issues of communication between patients suspected of having cancer. It draws on evidence from systematic reviews produced by the cochrane consumers and communication group, other systematic reviews and from guidance produced by the national cancer guidance steering group.

The review defines patient-centred care as:

- The use of active listening skills by health care professionals
- Encouraging patients to express their agendas
- Attempting to understand patients' points of view and their expectations
- Working with patients in the management of their illness.

The review summarised the evidence in relation to the following key components of patient-centred care: communicating with patients, informing patients and involving patients in decision-making.

The following recommendations were made:

1. NHS policy initiatives should take into account differences in peoples' preferences for information and involvement in decisions about their treatment and care.
2. Health care professionals need to know how to elicit patients' needs and readiness for information as well as their desire for involvement in decision making. Appropriate communication skills training addressing such issues should be considered and be appropriately evaluated. Key issues include: placing a higher priority on patient information; understanding patients' needs and helping people to access and understand relevant and appropriate information.
3. Personalised or tailored information is an option. Recordings or summaries of key consultations may benefit adults with cancer, without causing additional anxiety. Health professionals could consider giving either written summaries or audio-tapes of consultations to people who have expressed a preference for them.
4. People with cancer should be given the opportunity for involvement in decisions about their treatment and care. However, individual preferences for different levels of involvement need to be respected.
5. Time pressures are likely to be a barrier in implementing initiatives like shared decision-making programmes.

7.2.1(4) Studies of communication and sharing decisions with individuals with suspected cancer in primary care

Some papers specific to certain cancer groups have been summarised in later chapters of the guideline. There is limited primary research on communication and sharing decisions with individuals with suspected cancer in primary care.

7.2.1(5) Studies of the information needs of individuals with cancer

There is an extensive literature on the information needs of individuals who have been diagnosed as having cancer. Much of this literature has focused on the needs of those working in secondary care, such as oncologists and specialist nurses, who will inform individuals of the definitive diagnosis and provide continuing care and support. It is, however, difficult to apply this literature

to individuals seen in primary care before a definitive diagnosis of cancer has been made.

Secondary studies

(The University of York NHS Centre for Reviews and Dissemination, 2000)(29)

This review is cited in the previous section.

Patients cannot show informed preferences about their care, or choose to be involved in shared decision-making unless they have access to sufficient and appropriate information. The review highlighted the fact that while a majority of patients with cancer prefer to be given as much information as possible about their illness, research reporting the experiences of patients with cancer suggests that information is often not available. The following relevant recommendations were made:

NHS policy initiatives should take into account differences in peoples' preferences for information and involvement in decisions about their treatment and care.

Personalised or tailored information is an option. Recordings or summaries of key consultations may benefit adults with cancer, without causing additional anxiety. Health professionals could consider giving either written summaries or audio-tapes of consultations to people who have expressed a preference for them.

People with cancer should be given the opportunity for involvement in decisions about their treatment and care. However, individual preferences for different levels of involvement need to be respected.

Primary studies

(Jenkins, Fallowfield and Saul, 2001)(30)

As part of a multi-centre study evaluating a communication skills training model for clinicians, the authors collected information preferences using an adaptation of Cassileth's information needs questionnaire from a heterogeneous sample of 2331 patients with cancer.

Results showed that 87% (2027) wanted all possible information, both good and bad news and 98% (2203) preferred to know whether or not their illness was cancer. Cross tabulation of responses revealed no significant differences in information preferences for tumour site or treatment aims but did show an effect of age and sex. The few 58/440 (13.2%) patients who stated that in general they preferred to leave disclosure of details up to the doctor tended to be older (more than 70 years of age) (chi square = 26.01, df = 2, $p < 0.0001$).

In comparison to men women preferred to know the specific name of the illness (chi square = 4.9, df = 1, $p < 0.02$) and what were all the possible treatments (chi square = 8.26, df = 1, $p < 0.004$).

7.2.1(6) Studies of the information needs of individuals with suspected cancer in primary care

There is limited primary research on the information needs of individuals with suspected cancer in primary care. The patient information study on the information preferences of people with cancer (LSHTM 2001) did, however, interview patients about the pre-diagnosis phase and the findings of this research are summarised below.

This research is important as it marks a first step in linking what is known about 'how people become ill' from the social sciences research literature to what happens to cancer patients before their diagnosis is established.

Primary studies

(London School of Hygiene & Tropical Medicine, 2001)(31)

The patient information study was a collaboration between the national cancer charity cancer Bacup and researchers at the London School of Hygiene and Tropical Medicine. It involved in-depth interviews, focus groups and questionnaire surveys of people diagnosed with cancer.

The in-depth interviews sought to explore why patients chose to seek or not to seek information about their condition beyond that shared by their physicians at times during their illness.

This qualitative study was based in outpatient oncology clinics at one London cancer centre. The study participants were 18 people diagnosed with cancer in the previous six months. The main outcome measures were an analysis of patients' narratives to identify key themes and categories. The key results are as follows:

While all patients wanted basic information on diagnosis and treatment, not all wanted further information at all stages of their illness.
Three arching orientations to their management of cancer limited patients' desire for and subsequent efforts to obtain further information at points on the illness journey: faith, hope & charity.

During the moments when patients did require information, there was a preference for verbal information over written, for specific information over general, and for help in interpreting information from key health professionals. When patients required information, certain barriers were sometimes found to constrain their access to information.

The pre-diagnosis stage (while patients are making first contact with health professionals, before a diagnosis is reached) is a time when information and support is not systematically or routinely provided and this period needs proper consideration.

Two key messages that emerge from the accounts that patients gave of the pre-diagnosis period were:

The incremental nature of "knowing" it is cancer.

The interviews suggested that the pre-diagnosis period is fraught with difficulty with regards to information and support and in terms of individuals' understanding of what is going on. It is a period marked by "uncertainty", which involves moving from a person-without-cancer to a person-with-cancer. Sociologists have termed this process one of "biographical reconstruction", stressing that careful thought should be given to what information and support should be offered at this stage and what should be offered when the individual has a diagnosis of cancer.

Previous research has tended to present a diagnosis of cancer as a single static event, purely in terms of the "bad news" interview and much energy has been expended on describing the best ways of conveying "bad news". There is a risk that such an approach obscures the incremental nature of communicating and understanding what is going on before and when a diagnosis is made.

Importance of early interactions: pre- and post diagnosis

These early experiences are important because they provide the foundations for later interactions after diagnosis between patients and health professionals. Further research in this area is needed to determine individuals' information preferences during this early period.

(Adlard and Hume, 2003)(32)

A questionnaire was designed to assess the cancer knowledge of members of the public attending their general practitioner in the UK. The setting for the study was an urban general practice with an inner-city main surgery (predominantly social class IV and V with a high proportion of Asian and Afro- Caribbean patients) and a busy branch surgery in an affluent area

(predominantly from the higher socio-economic groups with a substantial Jewish population). Consecutive patients aged 18 and over were asked to complete the questionnaire while waiting to see their general practitioner or practice nurse.

Questions asked patients where they would seek information about cancer, familiarity with cancer terms and organisations. Other questions were designed to assess patients' abilities to distinguish between common and less common cancers, risk factors for cancer development and symptoms of cancer.

A total of 406 questionnaires were completed and returned (204 and 202 respectively from the two surgeries). The median age of all respondents was 47 (range 17-94); 63% were women and 37% men. Seven percent had a personal history of cancer and 41% had a history of cancer in a family member or close friend in the preceding five years.

Significant deficiencies were identified in the cancer knowledge of respondents. Personal or family history of cancer, younger age and female sex were associated with improved cancer awareness.

Guidelines

(Macmillan Cancer Relief, 2003)(33)

In their resource pack for managing, selecting and producing information materials in a cancer information and support service, Macmillan Cancer Relief identify the following steps in the cancer information pathway as having potential information needs for individuals suspected as having cancer in primary care, see *Table 7.*

Table 7 cancer information pathway (Macmillan Cancer Relief, 2003)(33)

PATHWAY THROUGH SYSTEM	POTENTIAL INFORMATION NEEDS
1. Symptoms discovered	Reassurance and advice to go and seek help Information concerning the symptoms and signs of cancer
2. Goes to: General practitioner or other member of the primary health care team	Information concerning the symptoms and signs of cancer Information about tests required
3. Referred to local centre for further tests	How to get to the hospital and what to expect during investigations When and how the results will be given Psychological support for the patient and carers Sign-posting to the relevant information and support network

7.2.1(7) Studies of the support needs of individuals with cancer There is an extensive literature on the support needs of individuals who have been diagnosed as having cancer. There is also an extensive literature on the considerable psychological morbidity of individuals with a definitive diagnosis of cancer attending oncology outpatient clinics. For example, it has been reported that 15%-40% of cancer patients develop clinical anxiety and/or depression (Sheard and Maguire, 1999)(34).

It is, however, difficult to apply this literature to individuals seen in primary care before a definitive diagnosis of cancer has been made.

7.2.1(8) Studies of the support needs of individuals being referred from primary care to secondary care

Research has been carried out on the support needs of individuals across the primary-secondary care interface. For example, a patient career diary (Baker et al, 1998)(35) – a generic self-report questionnaire – has been developed to obtain patients' views of services across health-care settings.

Primary studies

(Preston, 1999)(36)

As part of the development work for the patient career diary the researchers conducted a study to discover the views of patients about their experiences across the interface between primary and secondary health care, including referral from general practitioners, outpatient and inpatient care, discharge, and aftercare.

It was a qualitative study involving individual and focus group interviews of patients and interviews of carers. The subjects were 33 patients who had attended at least one outpatient appointment or had been an inpatient between two and four months previously, and eight carers of patients with chronic conditions. The setting was three acute hospitals and one community health service in Leicestershire.

Common themes in the views of patients and carers towards their experiences of care were identified and five themes emerged. The first four themes were: "getting in" (access to appropriate care), "fitting in" (orientation of care to the patient's requirements), "knowing what's going on" (provision of information), and "continuity" (continuity of staff and coordination and communication among professionals).

The fifth theme was "limbo" (difficulty in making progress through the system). The main features that characterised the feeling of "limbo" were:
An indefinite period of waiting

Uncertainty about what to expect or what would happen next

A feeling of being unimportant and insignificant; and

A feeling of powerlessness and loss of control over what was happening.

The theme of "limbo" was influenced by failures in care in relation to the other four themes.

(Nielsen et al, 2003)(37)

This study was a randomised controlled trial of a shared care programme for patients newly referred with cancer from primary to secondary care. The study was undertaken in a hospital oncology department in Denmark, and the intervention involved (1) knowledge transfer, in which communication from hospital to general practitioner included extensive information about the patients' social and psychological as well as physical problems, plus general information about treatment of common side-effects; (2) names and telephone numbers of doctors and nurses responsible for the patient were provided; (3) patients were advised to contact their general practitioner when encountering problems, and were told that the general practitioner would receive an information package.

127 patients with cancer were randomised to the control group and 121 to the intervention group. Patients' evaluations (which included use of sections of the patient career diary) of the cooperation between primary and secondary care improved in the intervention group. Men and younger patients (18-49) felt they received more care from the general practitioner and were left less 'in limbo'. Young patients in the intervention group rated the general practitioners' knowledge of disease and treatment significantly higher, although there were no differences in quality of life between the study groups.

This study was restricted to patients with cancer, and commenced after first outpatient consultation, and therefore the findings cannot be applied directly to patients with suspected but not confirmed cancer at the stage of referral.

8 The Diagnostic Process

1 Diagnosis of any cancer on clinical grounds alone can be difficult. Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them. D

2 Cancers usually present with symptoms commonly associated with benign conditions. The primary healthcare professional should be ready to review the initial diagnosis in patients in whom common symptoms do not resolve as expected. D

3 Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients thought not to have cancer fail to recover as expected. In such circumstances, the primary healthcare professional should systematically review the patient's history and examination, and refer urgently if cancer is a possibility. D

4 Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are usually the best observers of their children, and should listen carefully to their concerns. Primary healthcare professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected. D

13 A patient who presents with symptoms suggestive of cancer should be referred by the primary healthcare professional to a team specializing in the management of the particular type of cancer, depending on local arrangements. D

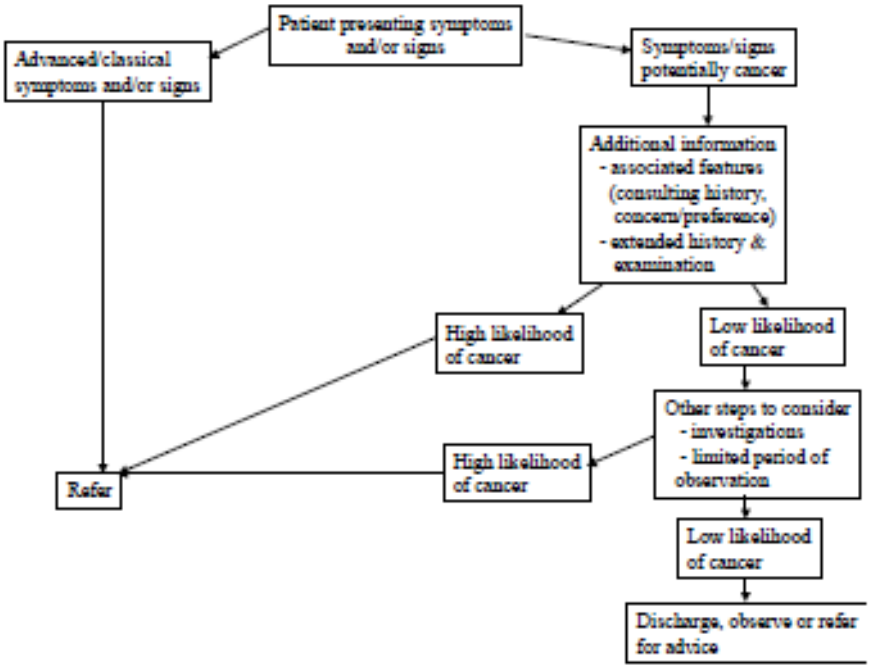
14 In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary, but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made. D

8.1 Introduction

This chapter considers the process by which primary healthcare professionals come to suspect that a patient has cancer. There is very little evidence about the diagnostic process in primary care directly relevant to cancer. This chapter therefore outlines theoretical models dealing with diagnosis and presents an illustrative example of the assessment of patients presenting with fatigue. It concludes with a review of trials of interventions to improve primary health care professionals' ability to detect cancer.

8.1.1 Models of the diagnostic process

Figure 2: The care pathway



One of the challenges of the NICE referral guideline for suspected cancer is to address the difficulties primary care professionals face when deciding whether or not a particular patient has symptoms and/or signs that support referral. Dealing with cancer symptoms and signs by twelve anatomical sites may best reflect the approach of the secondary care specialist. The primary care professional, however, must consider a wide range of differential diagnoses when faced with a patient who presents with a symptom that is non-specific but which may indicate serious underlying pathology (e.g., weight loss, abdominal pain). In some cases, reaching a suspicion of cancer is relatively straight forward, particularly when the symptoms and/or signs are advanced, or the features are classical (the so-called 'barn door' diagnosis – see *Figure 2*). In these cases, the professional is generally performing pattern recognition.(38) In many other cases, however, the symptoms and/or signs are non-specific at the time of presentation to the primary care professional. The diagnostic challenge in these circumstances can be considerable.

Only a small number of patients in primary care present with new cancers. The number of unrestricted general practitioners in England and Wales in 2000 was 29,479.(39) This figure excludes general practitioner registrars, assistants and other restricted general practitioners. In 2000, approximately 82% (24,173) of unrestricted general practitioners worked full time and 18% (5306) part time. Assuming that part time work equates on average to 60% time, the total number of full time equivalent unrestricted general practitioners is 27,357. If part time work equates on average to less than 60%, the total number of full time equivalent general practitioners will be a little lower that 27,357.

Based on these figures, *Table 8* shows the average number of numbers of new cases of the more commonly occurring cancers diagnosed each year for the years 1998-2000, and the numbers of cases expected per full time equivalent general practitioner and number of years needed for a general to have one new case in his or her patients. It should be noted that patients with cancer may first present to services other than general practice. For example, some cases of breast cancer will be identified during screening, and other cancers may be first detected by hospital services. Consequently, the total number of new cases detected by the general practitioner will be less than shown in the table. It is clear, nonetheless, that the detection of a patient with cancer is an uncommon event in primary care populations, with around 7.5 new cases per year per full time equivalent general practitioner. The infallible identification of these few patients from among the 7,000 or so consultations provided by each full time general practitioner per year (i.e. around one new case of cancer per 1,000 consultations) is a considerable challenge.

Table 8 Numbers of cases of new cancers among the patients of a typical full time general practitioner in the year 2000.(40)

	Registrations of newly diagnosed cancers 1998-2000 three year average England and Wales	Cases per full time equivalent GP per year	Mean number of years needed for a GP to see one case
Breast	35739	1.3	0.8
Lung	33855	1.2	0.8
Colorectal	30636	1.1	0.9
Prostate	22665	0.8	1.3
Bladder	10986	0.4	2.5
Non-Hodgkin's lymphoma	7924	0.3	3.3
Stomach	8622	0.3	3.3
Oesophagus	6309	0.2	5
Leukaemias	5996	0.2	5
Ovary	5924	0.2	5
Pancreas	5798	0.2	5
Melanoma	5549	0.2	5
Uterus	4792	0.2	5
Kidney	4718	0.2	5
Lip, mouth and pharynx	4228	0.2	5
Brain	3806	0.1	10
Multiple myeloma	3236	0.1	10
Cervix	2729	0.1	10
Testis	1704	0.06	17
Larynx	1544	0.06	17
Hodgkin's disease	1271	0.05	20
Total		7.47	

A key feature, therefore, of the diagnostic process for general practitioners is that the incidence of cancer in primary care is low, but that symptoms and signs that may indicate the presence of cancer (e.g., headache, low back pain) are not. One influential approach to this problem is the Bayesian approach to the diagnostic process.(41) A full review of this approach is outside the scope of the guideline but key principles are summarised in *Table 9*. It must be emphasised that the prevalence of disease has a strong effect in the usefulness of a 'test' (specific symptom/sign or investigation). The positive predictive value (probability that disease is present if the patient has symptom, sign or a positive test result) is markedly affected by the prevalence of the disease. If the prevalence is low (as in cancer in primary care), the positive predictive value of the 'test' is low and the negative predictive value (probability that disease is absent if the patient does *not* have symptom, sign or a positive test result) is high.

Table 9 Key points for using diagnostic tests in decision making(41)

- The selection and interpretation of diagnostic tests is a sequential process with the goal of reducing uncertainty about a patient's diagnosis.
- A test cannot be interpreted properly without considering what the probability of disease was before the diagnostic test or procedure result was obtained.
- Diagnostic tests help revise the probability of disease, and testing is generally continued until either the threshold for treating or not treating the patient is reached.
- When the pretest probability of disease is high, a positive result tends to confirm the presence of disease, but an unexpectedly negative result is often not sufficiently convincing to rule out disease.
- When the pretest likelihood of disease is low, a normal result tends to adequately exclude the presence of disease, but an unexpectedly postive result is often not sufficiently convincing to confirm the presence of disease.
- The approach of using a single diagnostic test to diagnose a single disease may be generalised to the use of multiple tests and the diagnosis of multiple diseases in a single patient.

Interest has recently grown in the causes and prevention of medical errors, and delayed diagnosis can be regarded as one category of medical error. Errors have been classified into three groups, knowledge-based (the result of forming the wrong intention or making the wrong plan due to inadequate knowledge or experience); rule-based (failure to apply a rule designed to avoid error or to apply a badly designed rule); and skill-based (an action that was not intended, due to absent-mindedness and failure to monitor actions).(42) The evidence about symptoms and signs presented in the guideline could reduce diagnostic knowledge-based errors (i.e. faulty pattern recognition). However, primary care professionals also need to use skills other than pattern recognition when the presenting features are complex.
One way of dealing with this difficulty is for the guideline to develop algorithms for common symptoms that, in certain situations, may indicate the likelihood of cancer (e.g., headache, dysphagia, weight loss). This would represent the creation of a set of rules for these difficult situations. However, the creation of algorithms for the assessment of common symptoms would be outside the agreed scope of the guideline and would also require extensive additional evidence reviews. Nevertheless, an example dealing with the symptom of tiredness has been included to illustrate the process.

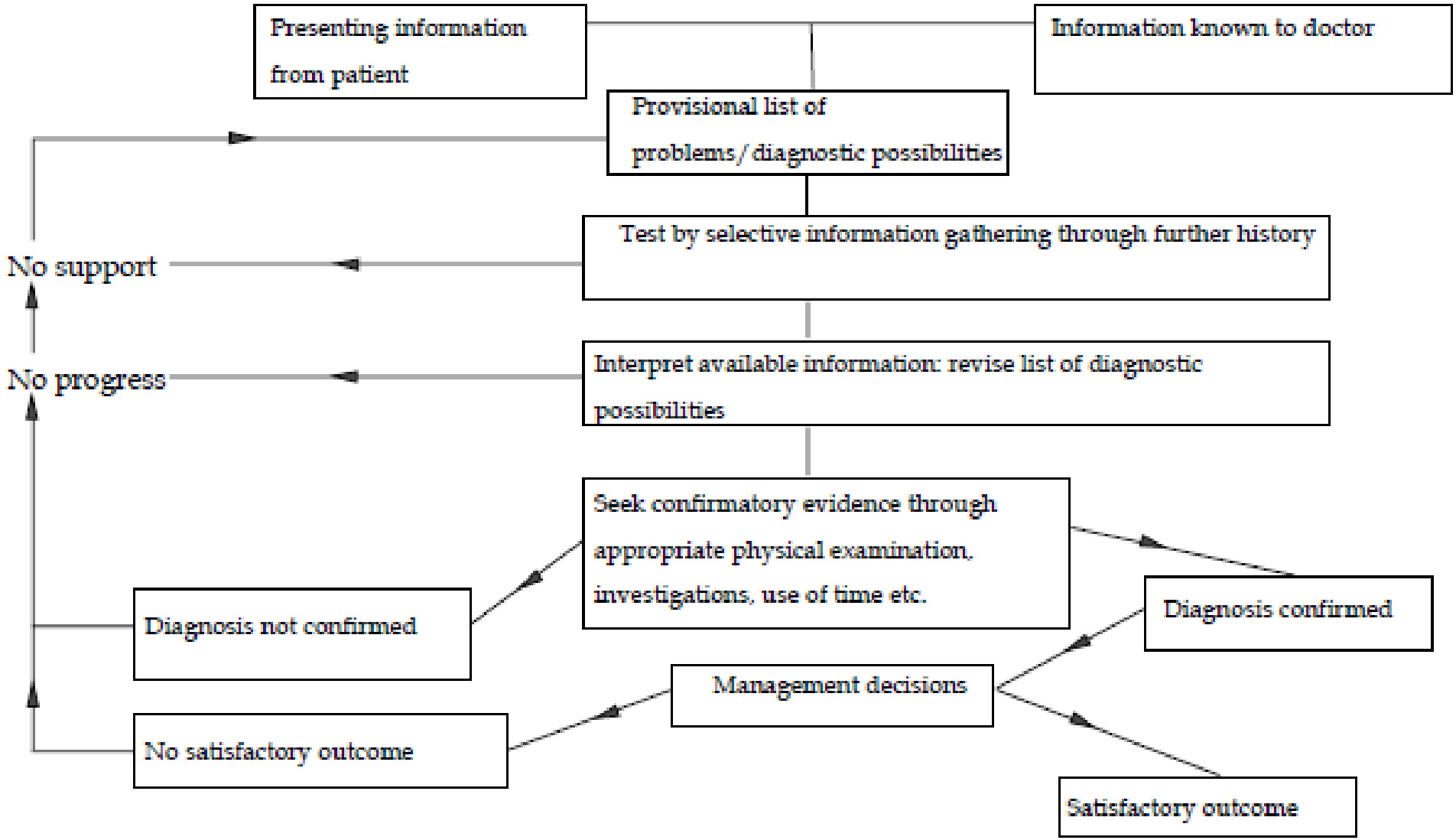
Various approaches to understanding the process by which clinicians reach a diagnosis have been proposed. The literature on the main types of approach (scheme-inductive reasoning, pattern recognition and hypothetico-deductive reasoning)(43) is extensive and a review of these is outside the scope of the guideline. The following comment by Norman & Eva is highly relevant to the current debate as to which of the three strategies is most effective:

"*To assume that any one problem-solving strategy will be shown to be consistently superior to any other amounts to a belief in a massively simplified world. It is far more likely that experts and novices will adopt a combination of strategies dependent on the problem posed, the stage they are at in finding the solution and their particular knowledge relevant to that problem*". (p. 677)

In this chapter the hypothetico-deductive method(44) (educated guessing and testing) is used to illustrate the diagnostic process. This method of multiple hypotheses-guided, problem oriented enquiry has been shown to be used by both general practitioners and hospital doctors.(45). *Figure* 3 offers a simplified representation of the stages involved in this process. It is accepted that this is only one of a number of models of problem solving and that it may be used by established practitioners when faced with problems outside their usual area of expertise.

The primary health care professional will draw on accumulated knowledge of the patient, personal experience of patient care, and assessment of the patient's reasons for consulting, in addition to items of clinical information obtained from direct questions or volunteered by the patient, in coming to a view about the significance of the presenting history and examination findings. A process of discussion with the patient then takes place as a prelude to making a decision on what action is required.

Figure 3 The hypothetico-deductive pathway(46)



8.2 An Example: Tiredness/fatigue.

Key clinical question:

How can primary care professionals distinguish tiredness or fatigue due to cancer from tiredness or fatigue caused by other conditions?

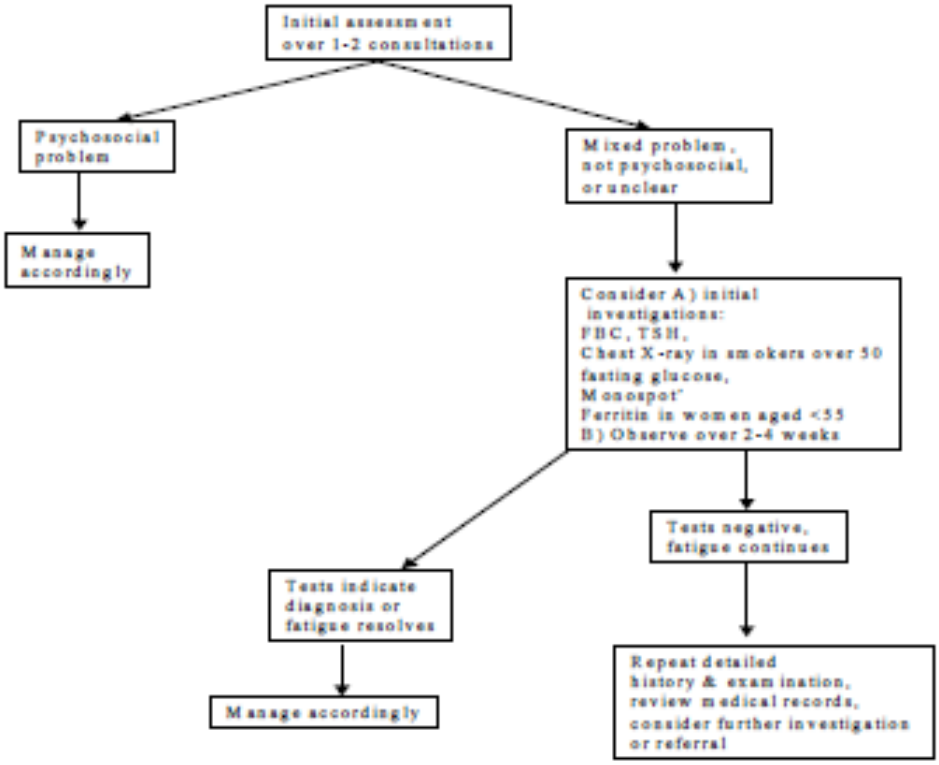
Evidence question:

In patients who present to primary care professionals complaining of tiredness or fatigue, what features are associated with cancer and which are not?

We have excluded studies of chronic fatigue syndrome (including a guideline on cancer-related fatigue(47) and an authoritative review(48) and studies of tiredness or fatigue in people after a diagnosis of cancer.

Fatigue, asthenia, weakness, exhaustion, malaise and tiredness are used more or less interchangeably, but only fatigue and asthenia are defined in the Medical Subject Heading Index.(49) Fatigue is defined as a 'state of weariness following a period of exertion, mental or physical, characterized by a reduced capacity for work and reduced efficiency to respond to stimuli'. Asthenia is defined as a 'clinical sign or symptom manifested as disability or lack of strength and energy'. Despite these definitions, fatigue appears to be the preferred term in the literature. The definitional problems are exacerbated by uncertainty about the definitions and aetiologies of chronic fatigue syndrome and neurasthenia. In the following paper, the focus is on patients newly presenting to primary care complaining of tiredness or fatigue, adopting the definition of asthenia quoted above. *Figure* 4 presents an algorithm.

Figure 4 Provisional algorithm for primary care assessment of tiredness/fatigue.



Secondary studies

(Valdini, 1985)(50)

This early review addressed the issue of fatigue of unknown aetiology. After an extensive literature search, five studies were included, representing a total of 940 patients who had been attending a variety of primary care providers, including solo practice, group practice and family practice centres, as well as one outpatient department. The earliest study had been reported in 1944 (the outpatient study), and the most recent in 1983. Age and sex distributions of the entire patient populations were not reported in the original studies. In addition to the problem of comparing five populations from different settings, the studies had not used a standard definition of fatigue, nor had they employed a standard method of investigation.

In over 50% of the 940 cases, the cause was thought to be psychological. The physical diagnoses are shown in *Table 10*.

Table 10 Physical diagnoses(50)

Cause of fatigue	No. of patients
Infection	117
Cardiovascular	58

Endocrine	57
Medications	25
Haematological	23
Neurological	15
Nutritional	9
Renal	8
Cancer	7
Gastrointestinal	6
Connective tissue disease	1
Allergy	2
Total	345

Of the 117 infections, 42 were influenza-like illnesses, 32 mononucleosis, 16 respiratory infections, and many others in much smaller numbers. The review did not present information about features associated with a diagnosis of cancer in people presenting with fatigue. The review recommended enquiry about nutrition and medications as part of the history, and checking for symptoms and signs of infection. An evaluation for depression, anxiety and stress was also recommended, as were basic investigations in patients in whom the diagnosis could not be established on the basis of history and examination, although no evidence was provided about the practical value of these tests (blood count, thyroid function tests, fasting blood sugar, urinalysis, stool for occult blood, pregnancy test in women of child bearing age, monospot in younger patients, and a chest x-ray in the elderly).

(Ebell, 2001)(51)

This review was a brief report providing an evidence-based answer to the question: what is a reasonable initial approach to the patient with fatigue? The article was published in the Journal of Family Practice, and the advice was therefore intended for family physicians. The review drew on a review of four primary studies involving patients presenting in primary care, only one of which had been included in the Valdini (1985)(50) review, although all had been undertaken from 1980 or later, and one was unpublished. The proportions of patients reported as having a psychological cause for tiredness were 55%, 50%, 50% and 20% in the four studies; physiological diagnoses were reported in 30%, 50%, 22% and 50% respectively. The second study did not report a category of 'undiagnosed', but in the other three studies, 15%, 28% and 30% were reported as undiagnosed. The review recommended screening patients for depression, and use of directed laboratory evaluation depending on the findings of history and examination, although the approach to investigation should be more aggressive in patients of 65 or older.

(Godwin et al, 1999)(52)

These guidelines were developed to provide physicians with an approach that was, as much as possible, based on evidence so that time and cost were minimized and detection and management of the causes of fatigue was optimised. The guideline group met by email; Medline was searched for relevant articles 1966 to 1997 using 'fatigue' as a Mesh heading and as a text word. Articles about chronic fatigue syndrome were excluded. The search identified 80 potential articles, but when the inclusion and exclusion criteria were applied, 12 remained. Three further articles were identified from the references lists of the included articles. No randomized

trials, cohort studies or case-control studies were identified. Articles reporting studies in primary care were given more weight than articles undertaken in secondary care settings.

The guidelines recommended that adults presenting with fatigue of less than six months duration should be assessed for psychosocial causes and should have a focused history and physical examination to determine whether further investigations should be done. The elderly require special consideration. Table 11 presents the guideline recommendations.

Table 11 Guideline recommendations(52)

Investigation	Always perform?	Perform only in these situations
Appropriate assessment for presence of anxiety or depression	Yes	
Appropriate assessment of current life stresses and past trauma and abuse	Yes	
Focused history and physical examination with special emphasis on medications, existing chronic illnesses, and presence of infection, particularly viral	Yes (to determine whether lab investigations are necessary)	
Haemoglobin test	No	Presence of pallor, tachycardia, dyspnoea, or other symptom suggesting anaemia Dietary of family history suggesting risk of anaemia Patient older than 65*
White blood cell count	No	Fever or other evidence of infection Weight loss, lymphadenopathy Patient older than 65*

Investigation	Always perform?	Perform only in these situations
ESR**	No	Evidence of inflammatory arthritis Concern about occult malignancy Patient older than 65*
Electrolyte assessment	No	Patient taking medication known to affect electrolyte balance (eg. Diuretics, steroids) Indication of a medical condition causing electrolyte imbalance (Cushing's disease, Addison's disease, parathyroidism)
Renal function tests**	No	Patient taking medication known to affect renal function Symptoms or signs possibly associated with renal disease (elevated blood pressure, oedema, generalised pruritis)
Glucose test (urinalysis only for investigating polydypsia and polyure)	No	History of gestational diabetes Known diagnosis of diabetes mellitus Symptoms of polydypsia and polyurea Unexplained peripheral neuropathy Patient older than 65*
TSH a	No	Presence of goitre History of thyroiditis Symptoms and signs suggesting hypothyroidism (dry hair and skin, change in bowel habit, change in menses) Patient older than 65*
Chest X-ray**	No	Smoker with cough or haemoptysis (especially if older than 50) History of exposure to asbestos or other pulmonary occupational hazard Exposure to tuberculosis

Investigation	Always perform?	Perform only in these situations
Other investigations**	No	As indicated by history and physical Weight loss and changes in bowel habit should prompt gastrointestinal investigation*

*The elderly were not well represented in the literature. The group's consensus, after consultation with experts in care of the elderly, is that they are more likely to have physical causes of fatigue, especially if the symptom is new. The guideline group recommended lowering the threshold for investigation in this group.
**Recommended by group consensus only; no evidence available in literature.

(VHA/DoD guideline: chronic pain and fatigue, 2001)(17)

These guidelines were developed to assist primary care clinicians in all aspects of care of patients with the medically unexplained symptoms of chronic pain and fatigue. Bibliographic databases were searched for publications 1997-2000, and some journals were hand searched. Identified evidence was assessed for quality. The guideline recommendations are summarised in *Table 12*.

Table 12 Guideline recommendations(53)

• Establish that the patient has medically unexplained symptoms (MUS)
• Obtain a thorough medical history, physical examination, and medical record review • Minimize low yield diagnostic testing • Identify treatable cause (conditions) for the patient's symptoms • Determine if the patient can be classified as chronic multi-symptom illness (CMI) (i.e. has two or more symptom clusters: pain, fatigue, cognitive dysfunction or sleep disturbance) • Negotiate treatment options and establish collaboration with the patient • Provide appropriate patient and family education • Maximize the use of non-pharmacologic therapies: graded aerobic exercise with close monitoring; cognitive behavioural therapy. • Empower patients to take an active role in their recovery.

Primary studies

The studies reported here exclude those that were included in the Ebell (2001)(51) and Valdini (1985)(50) reviews.

(Pawlikowska et al, 1994)(54)

A fatigue questionnaire plus the GHQ-12 was completed by 15,283 adults aged 18-45 registered with six general practices in the UK. The questionnaire had been mailed to a total of 31,651 people, giving a response rate of 48.3%. Non- responders were more likely to be men (53%) and slightly younger than responders (30.8 years vs. 32.4 years for responders, P<0.001).

5799 (38%) of responders had a fatigue score above the cut off for substantial fatigue, and 5621 (36.7%) scored above the cut off for psychological disorder in the GHQ-12. Scores for the GHQ-12 and the fatigue questionnaire were moderately correlated (0.62). Age was only weakly correlated with fatigue and general health scores. The mean fatigue score in men was 24.1, and in women 25.2 (P<0.0001). Stratifying by psychological distress did not remove the excess of fatigue in women. 40.1% attributed fatigue to psychosocial issues (work, family, lifestyle), and 16.7% to psychological factors (anxiety, depression); 14.7% gave physical reasons (e.g. surgery, anaemia).

(Ridsdale et al, 1993)(55)

The findings of this study were not summarised in the Ebell (2001)(51) review. It was undertaken in four UK general practices, and included patients aged 26 and over complaining of fatigue or being 'tired all the time'. Patients completed a questionnaire at enrolment and another after six months, the questionnaires also being administered to an age and sex matched control identified from the practice register. All patients also underwent a follow up examination two weeks after the first consultation.

220 patients were included, 56 (25%) males and 164 (75%) women. 34 (16%) had been tired/fatigued for between two weeks and one month, 66 (32%) one to three months, 34 (16%) for four to six months, and 74 (36%) longer than six months. 69 (33%) had one or more abnormal result on laboratory tests, and the doctors judged the result as clinically important in 19 of 210 (9%) patients. The clinical diagnoses were anaemia (eight), hypothyroidism (three), infection (three), glandular fever (three), diabetes (one), and carcinomatosis (one). A history of psychological disturbance was positively associated with the duration of fatigue.

(Kroenke et al, 1988)(56)

This study was also not included in the Ebell (2001)(51) review. It was undertaken in an army primary care centre in the USA. Attending patients were asked to complete a screening questionnaire to identify those who reported fatigue as a major problem (excluding those with fatigue of less than 30 days duration, those under the care of a psychiatrist, and those with diagnosed major illnesses, including cancer). A detailed assessment was undertaken of each of patient reporting fatigue, including examination, laboratory tests and psychometric and functional status questionnaires, plus one year follow up.

Of the 102 patients identified, 66% were women, and the mean age was 57 years. Fatigued patients had a higher ESR than the controls, but otherwise there were no differences in laboratory test results. A new diagnosis of diabetes was made in four patients, and anaemia in one. Four patients had faecal occult blood, but none had cancer. Fatigued patients were much more likely than controls to have psychometric test scores indicative of depression or anxiety. During follow up for one year, no patients died, cancer developed in 2 (2%) of the fatigued patients and one (4%) of the 26 controls.

(Fuhrer and Wessely, 1995)(57)

This study involved 367 French general practitioners identifying 3784 patients aged 18-64 who had fatigue, either as a presenting symptom, a diagnosis, or a persistent problem

during the week 12-19 November 1984. 2324 (61%) were women. Data were collected about the general practitioners' diagnoses and management, and patient information through a questionnaire. Although women were more likely to report fatigue than men, they were only slightly more likely to initiate a consultation for this problem.

Those aged 55-64 were less likely to present with fatigue than younger patients. The study presented information about the association between selected diagnoses and fatigue, but the diagnosis of cancer was not included. Depression and psychological problems were diagnosed in 50% of patients.

(Skapinakis et al, 2003a)(58)

In this WHO collaborative study, 25,916 patients attending primary care providers in 14 countries completed the GHQ-12, and those scoring above a certain threshold completed a more detailed instrument. The sample included 5438 people (62% women), 58% older than 35 years. One practice from the UK took part, and in this practice two (0.2%) of 428 attendees gave fatigue as the presenting complaint, although 115 (15.1%) had 'substantial unexplained fatigue' (i.e. they reported fatigue in response to direct questioning, for example 'In the past month, have you felt tired all the time?). In the entire sample, 6.3% gave fatigue as the presenting complaint, and 8.0% had 'substantial unexplained fatigue'. Fatigue as a presenting complaint was more common in low income countries, but substantial unexplained fatigue was more common in high income countries. Unexplained fatigue persisted in one-fifth to one-third at 12 months follow up, depending on the definition of fatigue.

(Skapinakis et al 2003b)(59)

This research group also reported on differences in the definition of fatigue between countries and the impact this has on the numbers of cases identified.(60) Widening the definition resulted in more prevalence but less overlap with psychiatric disorders.

(Verdon et al, 2003)(61)

This study was a randomised controlled trial of iron supplementation in non- anaemic women presenting with fatigue in primary care. In 366 women, fatigue was the main reason for consulting. 222 were excluded because of psychiatric disorders, physical disorders, refusals or other reasons. 144 were enrolled in the study, and 136 (94%) completed. 75 were randomised to receive iron, and 69 placebo. The level of fatigue after one month decreased in the iron group by 29%, compared with 13% in the placebo group (P=0.004). Subgroup analysis showed that only women with ferritin concentrations < or = 50 micrograms/litre improved with oral iron supplementation.

(Cathebras et al, 1992)(62)

In this study, 686 patients attending two Canadian family medicine centres completed a symptom report questionnaire. 93 (13.6%) reported fatigue, and was a major reason for the consultation in 46 (6.7%). 17.2% of patients with fatigue had major depression in the past month (8.8% among non-fatigued), and 45.2% had had a diagnosis of major depression at some time in the past (28.2% among non-fatigued). Between one third and one half of patients were no longer fatigued at 12 month follow up.

(De Rijk et al, 2000)(63)

Patients attending a women's general health care practice aged over 16 years were invited to complete questionnaires about fatigue. 152 women completed at least one questionnaire (mean age 34.8 years). 74% of respondents had suffered some fatigue in the past two weeks, but only 19 (12.3%) intended to consult because of this. 24 of 107 (22%) actually discussed fatigue during their consultation, although only 11.2% had intended to do so. Caring for young children and having a job were associated with increased likelihood of discussing fatigue.

(Hall et al, 1994)(64)

197 patients were identified in a US practice through a computer register of encounters and among people consulting. Cluster analysis was used to identify features associated with an 'organic' diagnosis and anxiety, depression, and mixed anxiety/depression groups. The assignment to groups was undertaken by the study authors based on review of the primary cause of fatigue, according to the diagnoses of the primary care physician.

The features classified as marital problems, decreased libido, nausea/vomiting, taking care of a sick relative, dizziness, bereavement, dissatisfaction at work/school, dieting, hectic life style, boredom, change in bowel habit, arthralgia, palpitations, memory loss, confusion, night sweats, irritability and increased appetite, did not occur more often among the organic group than in the other three clusters. The proportion of males, married patients and white patients in the organic group was higher than in the other clusters.

(Shahar and Lederer, 1990)(65)

A retrospective chart review was undertaken of the records of 508 patients aged

18 or over at one rural family practice in Israel, to extract information in the previous ten years of symptoms of asthenia (fatigue, lassitude, weakness). Asthenic complaints were recorded in the charts of 164 patients (32%); peak prevalence occurred in the third decade and in the summer months (June to September). The female:male ratio was 1.7:1. In nearly 50% of encounters, the physician did not reach a diagnosis. 64% had only one or two episodes, 27% had recurrent episodes, and 9% had persistent asthenic complaints but no evidence of the chronic fatigue syndrome. In the episodic group, 29% were diagnosed as intercurrent infection. 9% as psychiatric disorders, 5% anaemia, 2% pregnancy, 7% others, and 48% undetermined. In the recurrent group, the diagnoses were intercurrent infection 18%, psychiatric disorders 16%, pregnancy 7%, anaemia 2%, undetermined 57%.

8.3 Interventions to improve the ability of primary healthcare professionals to suspect cancer

Key Clinical Question:

How can the primary healthcare professionals be helped to refer patients with suspected cancer at an early stage?

Evidence Question:

What interventions can help primary healthcare professionals reduce delay in identifying patients with suspected cancer without leading to the referral of many patients who do not have cancer?

Evidence statements:

There are few studies of the effectiveness of interventions to improve healthcare professionals' identification and referral of suspected cancers. The majority of relevant studies involve educational interventions to improve identification of skin cancers. The findings of these studies are inconsistent, but tend to indicate that educational interventions can improve the identification of skin cancers (II).

In undertaking this review we sought systematic reviews of relevant interventions to improve primary care professional's identification or referral of patients who may have cancer. For inclusion, studies had to involve health professionals in their work settings. Studies employing simulations, for example use of dummies to develop examination skills, were excluded. Studies of interventions to improve adherence to cancer screening guidance or of use of investigations not directly related to identification of suspected cancer were also excluded.

For inclusion, the studies had to be randomised trials involving primary health care professionals and testing interventions designed to improve identification or referral of patients with suspected cancer.

No systematic review dealing specifically with the identification or referral of suspected cancer was identified. Consequently, we have included findings from an overview of reviews of interventions to promote the implementation of research findings. Five randomised trials were identified for inclusion.

Secondary studies

(Bero et al, 1998)(66)

Systematic reviews of interventions to improve professional practice published between 1966 and 1995 were sought through bibliographic searches of several databases. Eighteen reviews met the inclusion criteria.

In general, the passive dissemination of information was found to be ineffective. The use of computerised decision support has led to improvements in clinical management but not diagnosis. Patient mediated interventions appeared to improve preventive health care, and educational outreach improved prescribing behaviour. The use of several interventions in combination was more effective than the use of single interventions alone. The findings are summarised in *Table 13*.

Table 13 Interventions to promote behavioural change among health professionals(66)

Consistently effective interventions ƒ Educational outreach visits (for prescribing in North America) ƒ Reminders (manual or computerised) ƒ Multifaceted interventions (a combination that includes two or more of the following: audit and feedback, reminders, local consensus processes, or marketing) ƒ Interactive educational meetings (participation of healthcare providers in workshops that include discussion or practice)
Interventions of variable effectiveness ƒ Audit and feedback (or any summary of clinical performance) ƒ The use of local opinion leaders (practitioners identified by their colleagues as influential) ƒ Local consensus processes (inclusion of participating practitioners in discussions to ensure that they agree that the chosen clinical problem is important and the approach to managing the problem is appropriate) ƒ Patient mediated interventions (any intervention aimed at changing the performance of healthcare providers for which specific information was sought from or given to patients)
Interventions that have little or no effect ƒ Educational materials (distribution of recommendations for clinical care, including clinical practice guidelines, audiovisual materials and electronic publications) ƒ Didactic educational meetings (such as lectures)

(Grimshaw et al, 2001)(67)

This was another overview of systematic reviews of interventions to change provider behaviour. Forty-one reviews were identified for inclusion, and in general the findings of Bero et al (1998)(66) was substantiated. However, only one review of interventions targeted at referral was identified, and only one review of interventions targeted at investigations. Neither of these reviews were judged to have included adequate numbers of studies of sufficient quality to enable firm conclusions to be drawn about the effect of interventions to change these aspects of provider behaviour.

(Grimshaw et al, 2004)(68)

This study is the most recent systematic review of the effectiveness of methods of disseminating and implementing guidelines. It involved searches of various databases (Medline, Healthstar, Embase, Sigle) and the specialised register of the Cochrane Effective

Practice and Organisation of Care (EPOC) group. The review included randomised controlled trials, controlled clinical trials, controlled before and after studies, and interrupted time series. Participants were medically qualified healthcare professionals, and the outcomes of guideline dissemination and implementation strategies of interest were objective measures of provider behaviour and/or patient outcome.

A total of 235 studies were identified for inclusion. The key findings of the review were that:

- Reminders were the most frequently evaluated and are potentially effective;
- Educational outreach was the next most commonly evaluated intervention, and it may result in modest improvements in the process of care, although it can require significant resources;
- Evidence about the effectiveness of audit and feedback and patient directed interventions was less robust. Audit and feedback appears to result in modest effects, and patient mediated interventions in moderate effects.

The review identified very few studies of interventions to improve the identification and referral of patients with suspected cancer in primary care, although there were several studies of interventions to improve adherence to preventive measures such as cervical screening and mammography. In view of the small number of relevant studies and the narrow range of cancers addressed, conclusions about the effectiveness of interventions to improve identification and referral of suspected cancer cannot be drawn.

(Grimshaw, 1998)(69)

This was a review of randomised controlled trials of interventions to improve general practitioner out-patient referrals. It was included in a PhD dissertation. Only four studies met the inclusion criteria. The included RCTs addressed referral in the following contexts: 1). Referrals for investigation of upper gastrointestinal symptoms; 2) referrals to psychiatrists or community psychiatric nurses of patients with long term mental illness; 3) referral of patients with orthopaedic problems to orthopaedic surgeons; and 4) the total number of all referrals from participating general practices. No study was specifically concerned with referral of patients with suspected cancer. Only one of the studies (number 3) was considered unequivocally positive, the intervention consisting of a joint consultation involving the specialist and general practitioner with the patient in place of referral. The other studies had negative or ambiguous findings.

(Solomon et al, 1998)(70)

This was a systematic review of RCTs of interventions to change physician investigation behaviour. The investigations were not restricted to those used in suspected cancer, and the physicians in the included studies were from both primary and secondary care. Forty-nine studies were identified for inclusion.

The review reported that methods to develop consensus among physicians had relatively limited impact. Audit with feedback was variably successful, but more successful when combined with an educational intervention. Continuous quality improvement programmes appeared to be relatively effective, and administrative interventions (restricting investigation privileges, for example) could be, but were not always highly effective.

Primary studies

Randomised trials of interventions to improve diagnostic ability of primary care professionals to manage familial breast and ovarian cancers

(Watson et al, 2002)(71)

This cluster randomised controlled trial of educational interventions on general practitioner management of familial breast and ovarian cancer involved 688 general practitioners in 170 UK practices. Group A were provided with an information pack and in-practice educational session, group B were mailed an information pack, and group C received no intervention at all. All general practitioner referral letters between March 1999 and December 2000 were

audited and referrals classified as appropriate or inappropriate.

The appropriateness of referrals improved among general practitioners who either received the guidelines alone (68.7% of referrals appropriate), or with an educational session (75.0% appropriate). In the group that did not receive the guideline or any other intervention, only 52.6% of referrals were judged appropriate.

Randomised trials of interventions to improve diagnostic ability of primary care professionals to identify skin cancers

(Del Mar et al,1995)(72)

Australian general practitioners were offered an algorithm and the use of an instant developing camera in a trial to test whether this intervention would reduce the number of benign melanocytic lesions excised from the skin. Doctors in the city randomised to receive the intervention were offered a protocol to assist in the management of any melanocytic lesion for which a diagnosis of malignancy was entertained. Over 50 doctors, mostly in general practice, were selected in each of two Australian cities. The cities were chosen on the basis of their similarity; both being in relatively isolated tropical areas and near the coast, and with populations of around 55 000 and 65 000 people working in industries with substantial agricultural and tourist components.

The cities were sufficiently far apart so that intervention in one was unlikely to affect clinical behaviour in the other. The city that received the active intervention was chosen at random. The control group city included 45 general practitioners, seven surgeons and one dermatologist. The intervention group comprised 48 general practitioners and four surgeons. During the study, nine new doctors entered and two left the control community, and seven new doctors entered and five left the intervention community. All new incoming doctors agreed to take part except for one general practitioner in the intervention city.

A copy of the histology report of every melanocytic skin lesion that practitioners excised over the next two years was reviewed. Reports from the previous six months were collected as a baseline to check that the excision rates of benign and malignant melanocytic lesions were comparable between the two cities. In the six months before the introduction of the intervention a total of 1358 melanocytic lesions were reported by the pathology laboratories: 752 (55%) from the control community and 606 (45%) from the intervention community.

More than a hundred practitioners in total participated in the study but no power calculation was given. During the 24 months after the intervention was introduced a total of 4465 lesions were excised in the two study cities, of which 1995 (45%) were excised in the intervention city, the same proportion as at baseline.

There was no significant difference in the percentages of benign lesions reported in the intervention and control cities before the algorithm and camera were used (93.6% and 94.0% respectively) but there was a significant difference afterwards (88.8% and 93.8%, $P < 0.001$). There was no difference in the percentage of invasive melanomas excised per month in the intervention city (3.4%) compared with control city (3.4%). Offering doctors a diagnostic algorithm and providing them with a camera reduced the relative proportion of benign naevi they removed.

(English, 2003)(73)

This Australian randomised control trial was undertaken to determine whether the use of a camera and algorithm aided the diagnosis of pigmented skin lesions by reducing the ratio of benign lesions to melanomas in general practice. The trial built upon the earlier randomised control trial conducted by Del Mar et al (1995)(72) in which participants were randomised by town rather than practice.

Intervention practices were given an algorithm and instant camera to assist with the diagnosis of pigmented skin lesions. All practices were given national guidelines on managing melanoma. 488 practices were invited to take part and 223 participated. Computer

generated randomisation was undertaken which stratified by practice size. Doctors randomised to the intervention group were trained to use an algorithm and instant camera. After randomisation, participants and research assistants who visited practices were not blinded to assignment. All coding of outcome data was done blind to assignment.

1221 general practitioners were identified of whom 468 participated in the trial. Similar numbers of general practitioners in the two groups left their practices during the trial. Only 302 (65%) general practitioners completed a questionnaire at the end of the study on how they had managed their last three patients with pigmented lesions. All pathology reports on excisions of pigmented skin lesions from November 1998 to August 2000 were obtained.

From the results of the earlier trial by Del Mar et al (1995)(72), it was calculated that nine months of follow up were needed to achieve 80% power. During the two periods, the participants excised 8563 pigmented skin lesions:
295 (3%) melanomas (180 invasive and 115 in situ), 529 (6%) dysplastic naevi, 5065 (59%) other naevi and 2674 (31%) seborrhoeic keratoses. At baseline the ratios of benign to malignant lesions were lower in the intervention than the control group. During the trial period the ratios were higher in the intervention group (19:1 vs. 17:1 without seborrhoeic keratoses and 29:1 vs. 26:1 with seborrhoeic keratoses). After adjustment for patients' age, sex and socioeconomic status, the ratio was 1.02 times higher (95% CI 0.68 to 1.51, P=0.94) in the intervention group when seborrhoeic keratoses were not included and 1.03 times higher (0.71 to 1.50, P=0.88) when seborrhoeic keratoses were included.

General practitioners in the intervention group were less likely than those in the control group to excise the most recent pigmented skin lesion they had managed (22% vs. 48%, P<0.001) and to refer the patient to a specialist. Neither group showed substantial changes in excision rates within practices between the baseline and trial periods. The overall rates showed little change in the control group, but decreased in the intervention group between periods largely because of substantial reductions in a few practices with large numbers of baseline excisions. The imbalance between practices was due to specialist general practitioners (to whom others refer patients with pigmented lesions and those who perform a substantial proportion of all excisions). Four of the total (five) were in the intervention group. When these general practitioners were excluded the number of benign lesions excised was similar.

(Raasch et al, 2000)(74)

This randomised control trial was undertaken to assess the value of an educational intervention based on audit and feedback to family physicians in Australia. Clinical performance of family physicians was judged by the ability to make a correct clinical diagnosis (i.e. the diagnosis was compatible with the histology of the excised lesion) and to provide adequate surgical treatment. There were 46 family physicians allocated to either an intervention (23) or control group (23) from a total of 91 who were initially approached but either declined to participate or failed to respond.

To ensure similarity of most characteristics, randomisation of doctors who agreed to participate was carried out using a random number table.

Practitioner characteristics for doctors in the intervention and control groups were noted such as age, sex, years in practice and number of partners, full/part time and qualifications. The intervention and control group practitioners differed only on the mean number of doctors per practice. Non- participants were likely to be older and have been in practice longer. The doctors were made aware only of the fact that a skin cancer study was taking place and were not informed whether they were in an intervention or control group.

One control group doctor recorded no data from the start, leaving 22 in this category. Two doctors from the intervention group and two from the control group dropped out during the study and were not replaced. All doctors who dropped out had moved from the city or practice. The doctors' individual skin cancer practices were compared within and between groups before and after the intervention. Data were recorded on 1) the proportion of all lesions correctly diagnosed 2) unrecorded clinical diagnosis 3) inadequate excisions and 4) certainty of diagnosis.

It was estimated that 356 patient consultations for clinically suspicious or dysplastic skin lesions would be required by the intervention and control group before and after the intervention to detect a 10% difference in the proportion of correct diagnoses with 80% power (a = 0.05).

The intervention group doctors showed improved performance in providing clinical information on pathology requests and in adequate surgical excision of skin lesions. Diagnostic performance did not improve significantly but physicians' certainty of diagnosis did. When a skin cancer was present (based on the histology of the lesion) the intervention group doctors, before receiving the intervention, had made a correct diagnosis in 72.2% (95% ci 65.8–78.6) of cases. After the intervention 77.1% (95% ci 68.7-85.5) of malignant lesions had been correctly diagnosed (P=.38). There also was no significant difference in sensitivity of diagnosis for malignant lesions between intervention and control group before or after the intervention.

Improvements in performance occurred in both study groups; the only significant benefit of the intervention was improved recording of the clinical diagnosis on pathology request forms. Two factors were identified by the authors as potentially explaining the lack of effectiveness of the intervention. The patient populations consulting the doctors in the two study groups were significantly different, and the study took place in a small community in which elimination of risk of contamination between study groups could not be achieved.

(Gerbert et al,1998)(75)

This US study sought to determine whether a brief, multicomponent educational intervention could improve the skin cancer diagnosis of primary care residents to a level equivalent to that of dermatologists. The intervention comprised an interactive seminar, which included a slide show lecture, videotape and demonstrations on how to conduct a total body skin examination. This randomised control trial was suited to assessing the effects of an educational intervention with pre-test and post test measurements of residents' ability to diagnose and make evaluation plans for lesions indicative of skin cancer. The pre-tests and post-tests consisted of lesions shown on slides, computer images, and patients.

26 primary care residents were assigned to a control group and 26 to an intervention group, and 13 dermatologists completed a pre-test and post-test. There were no significant differences between control and intervention primary care residents on the demographic and dermatology experience variables or pre-test overall diagnosis and overall evaluation planning scores.

Of the 62 primary care residents who completed the pre-test, ten were unable to attend the post-test (five from the control group and five from the intervention group). There were no statistically significant differences in age, gender, dermatology experience, or pre-test scores between those primary care residents who completed the post-test and those who did not. Control and intervention groups of primary care residents and dermatologists were assessed for their ability to diagnose and make evaluation plans for six categories of skin lesions including three types of skin cancer – malignant melanoma, squamous and basal cell carcinoma and three of their noncancerous differential diagnoses, actinic keratosis, seborrheic keratosis and nevus.

The control group, the intervention group and the dermatologists all demonstrated improved performance over time, with the intervention group experiencing the largest gains. The intervention group showed significantly greater improvement than the control group in overall diagnosis and diagnosis of malignant melanoma and seborrheic keratosis. Intervention group primary care residents performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of basal cell carcinoma. The control group performed as well as the dermatologists on three of the six skin cancer diagnosis and evaluation planning scores. The dermatologists had significantly higher scores than the control group in 11 of the 14 diagnoses and evaluation planning categories.

The intervention group showed greater improvement than the control group across all six diagnostic categories (a gain of 13 percentage points vs. 5, P<0.05) and in evaluation planning for malignant melanoma (a gain of 46 percentage points vs. 36, P<0.05) and

squamous cell carcinoma (a gain of 42 percentage points vs. 21, P<0.01). The intervention group performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of basal cell carcinoma.

Some caution is required in applying the findings of this study to clinical practice. The sample of primary care residents was relatively small and lacked variation. The pre-test may have been more difficult than the post-test, as suggested by the higher scores of all three groups of subjects at the post test. Routine clinical practice is likely to differ from the test situation used in the study.

(Gerbert et al, 2002)(76)

In this US study, primary care doctors were randomly allocated to two groups – control (N=32 doctors) or intervention (N=39 doctors) in which subjects took part in a skin cancer triage tutorial, developed from the intervention used in Gerbert et al (1998)(75). The tutorial modules were registration, pretest, pretest scores with individualised feedback, skin cancer instruction, posttest I, posttest II (eight weeks after completing the course), and exit survey. The tutorial was internet based. The change between pre- and posttest scores constituted the study outcome, the tests including the presentation of digital images of skin lesions.

Only 27 of the 39 doctors in the intervention group completed the tutorial intervention. In the control group, the scores declined from pretest to posttest. In the intervention group, scores significantly improved for overall diagnosis and evaluation planning, diagnosis of malignant melanoma and seborrheic keratosis, diagnosis and evaluation planning of basal cell carcinoma and squamous cell carcinoma, and evaluation planning for actinic keratosis. Improvement was maintained for five of the eight outcomes at posttest II (not maintained for overall diagnosis, diagnosis of basal cell carcinoma, diagnosis of seborrheic karatosis and evaluation planning for actinic keratosis).

9 Lung cancer

1 A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. D

Specific recommendations

2 An urgent referral for a chest X-ray should be made when a patient presents with:
- haemoptysis, or
- any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs:
  -chest and/or shoulder pain
  -dyspnoea
  -weight loss
  -chest signs
  -hoarseness
  -finger clubbing
  -cervical and/or supraclavicular lymphadenopathy
  -cough with or without any of the above
  -features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).

A report should be made back to the referring primary healthcare professional within 5 days of referral. D

3 An urgent referral should be made for any of the following:
- persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation). D

4 Immediate referral should be considered for the following:
- signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)

- stridor. C

Risk Factors

5 Patients in the following categories have a higher risk of developing lung cancer:
- are current or ex-smokers
- have smoking-related chronic obstructive pulmonary disease (COPD)
- have been exposed to asbestos
- have had a previous history of cancer (especially head and neck).

An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients (see 1.3.1 above) but may be considered sooner, for example if symptoms or signs have lasted for less than 3 weeks. C

Investigations

6 Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray. D

7 If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral. D

8 In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made. C

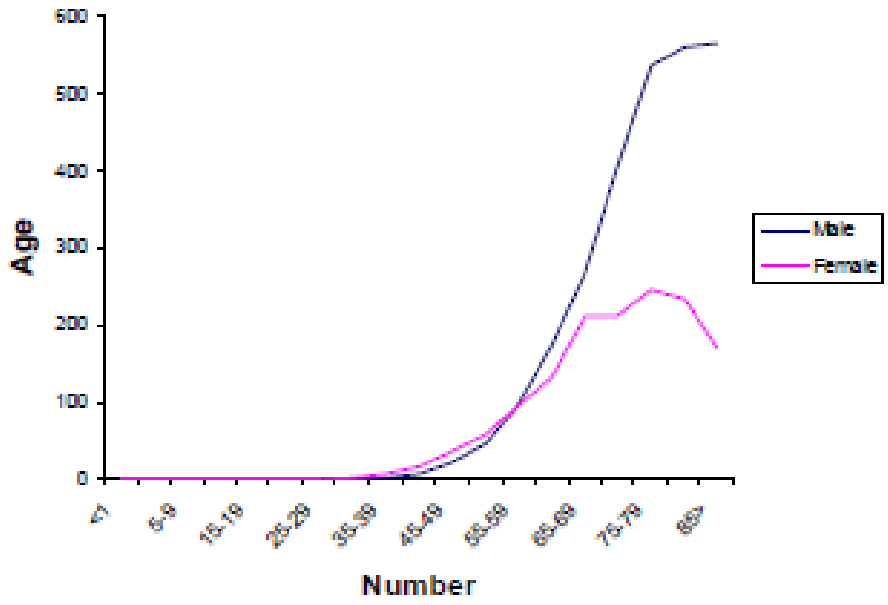
Introduction

Incidence

Lung cancer is the most common cancer in England and Wales.(77) Only 1% of cases occur before 40 years of age and 85% of cases occur in those 60 years or over. About 90% of patients are smokers or ex-smokers(2). Global incidence is generally four to six times higher in males than in females.

There were 30,485 recorded new cases of lung cancer in 2001 in England and Wales, 11,940 in females and 18,545 in males.

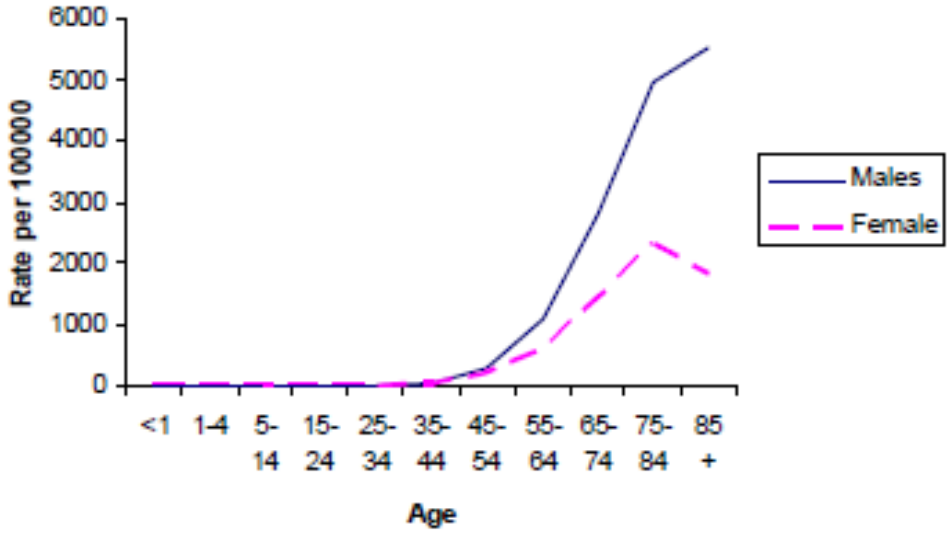
Figure 5: Newly diagnosed cases of lung cancer in 2001 in England and Wales. (77)



Mortality

Mortality figures for 2002 showed that mortality from lung cancer was low for both sexes in those aged under 40 years, but then increases sharply with registration rates decreasing in women over 75 years. The total deaths in 2002 were 17,426 in males and 11,342 in females, shown graphically in Figure 6.

Figure 6: 2002 Mortality rate for Lung, trachea and bronchial cancer in England and Wales. (78)



Audits of referral for suspected lung cancer

The systematic review of cancer waiting time audits (CRD, 2004) identified 43 audits. Fifteen audits evaluated GP conformity to the referral guidelines, the percentage of referrals being considered appropriate ranging from 78% to
100%. The proportion of patients who had been referred under the two week wait referral system who were found to have cancer ranged from 5% to 60% (14 audits). The proportion of patients with cancer who had been referred via the two week wait referral system ranged from 0% to 43% (three audits).

9.1 Symptoms and Signs

9.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of lung cancer, and which make cancer less likely as a diagnosis?

9.1.2 Evidence Question:

In people attending primary care services with lung problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

9.1.3 Evidence Statements:

The incidence is low in those aged under 50, but peaks in both males and females around 80. (III)

The incidence of lung cancer is decreasing in men but increasing in women. (III)

Common presenting symptoms include persistent or unexplained cough, haemoptysis, unexplained weight loss, dyspnoea and chest/shoulder pain. (III)

Lung cancer may present with metastases or enlarged lymph nodes. (III)

Other less common presenting features include pneumonia, clubbing and hoarseness. (III)

90% of cases of lung cancer are caused by smoking. (III) Asbestos exposure can cause mesothelioma. (III

Guidelines

The DoH Referral Guidelines for Suspected Cancer(2) listed the following as predominant symptoms at presentation: cough, dyspnoea, haemoptysis, weight loss, chest/shoulder pain and/or hoarseness.

The guidelines also noted that more than 90% of patients were symptomatic at the time of diagnosis and that chest x-ray findings were abnormal in the vast majority of symptomatic patients. However, a normal chest x-ray did not exclude a diagnosis of lung cancer.

The guidelines recommended that in most cases it was appropriate for a general practitioner to request a chest x-ray as an initial investigation, with referral to a chest physician if the chest x-ray was suggestive/suspicious of lung cancer. In a limited number of circumstances, urgent referral to a chest physician was appropriate without requesting a chest x-ray.
Sputum cytology was rarely indicated prior to referral for a specialist opinion. In most cases where lung cancer was suspected it was appropriate to arrange an urgent chest x-ray before urgent referral to a chest physician.

Urgent referral for a chest x-ray was recommended for:

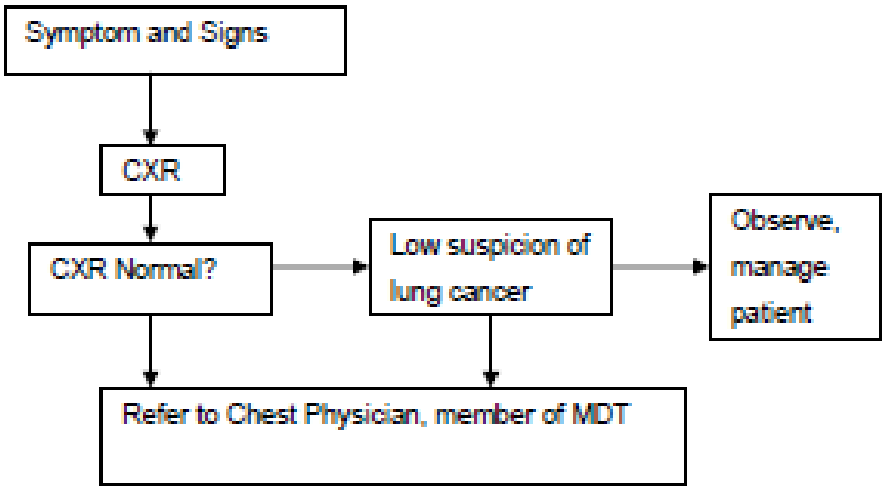
- haemoptysis
- unexplained or persistent (more than three weeks)
- cough
- chest/shoulder pain
- dyspnoea
- weight loss
- chest signs
- hoarseness
- finger clubbing
- features suggestive of metastasis from a lung cancer (eg brain, bone, liver or skin)
- persistent cervical/supraclavicular lymphadenopathy.

Urgent referral to a chest physician was recommended for any of the following:

- chest x-ray suggestive/suspicious of lung cancer (including pleural effusion and slowly resolving consolidation).
- persistent haemoptysis in smokers/ex-smokers over 40 years of age.
- signs of superior vena caval obstruction (swelling of face/neck with fixed elevation of jugular venous pressure).
- stridor (consider emergency referral).

Other relevant guidelines include those developed for NICE; the diagnosis and treatment of lung cancer(79). It included a diagnosis of lung cancer algorithm, the section relating to primary care can be seen below:

Symptom and Signs



The NICE guideline(79) recognised that the symptoms and signs of lung cancer can be difficult for the general practitioner to distinguish from those of other diseases. The main symptoms and signs at presentation identified in the guideline are displayed in the table below:

Table 14 Range of frequency of initial symptoms and signs of lung cancer(79)

Symptoms and signs	Range of frequency (%) Cough
	8-75
Weight loss	0-68
Dyspnoea	3-60
Chest pain	20-49
Haemoptysis	6-35
Bone pain	6-25
Clubbing	0-20
Fever	0-20
Weakness	0-10
SVCO	0-4
Dysphagia	0-2
Wheezing and stridor	0-2

The SIGN guideline(80) was based on a revision of its guideline published in 1998(81). It covered presentation, diagnosis, investigations and all aspects of treatment. It did not address other thoracic malignant disease such as mesothelioma (malignant pleural tumour) or secondary lung cancers.

The SIGN guidelines reported that high quality evidence on presentation and referral for lung cancer was scarce. Most of the data used were drawn from observational studies and existing recommendations on good practice. The symptoms with which lung cancer presents include cough, sputum, breathlessness and wheeze, which are also commonly experienced by cigarette smokers with chronic obstructive pulmonary disease (COPD). Non specific symptoms such as

tiredness and weight loss are also common in lung cancer. Information about the common symptoms of lung cancer were available from case series. No evidence was identified regarding the possible predictive value of combinations of symptoms.

The stated aim of the Scottish Executive Health Department's Referral Guidelines for Suspected Cancer was to facilitate appropriate referral between primary and secondary care for patients in whom a general practitioner suspected cancer. The guidelines were designed to identify patients most likely to have cancer and requiring urgent assessment by a specialist, and to assist general practitioners identify patients unlikely to have cancer. The guidelines were based on published literature and unpublished audits of symptoms in patients presenting with cancer.

Secondary studies

Liedekerken et al, 1997(82)

A literature search for papers reporting the relationship between prolonged cough (defined as being of six weeks duration or more) and lung cancer was undertaken. A MEDLINE search (1966-1995) was performed and papers were retrieved after scanning references. Sensitivity, specificity and positive and negative predictive values were recorded and studies were excluded if there were insufficient data for the calculations to be made or if patients were chosen selectively, other than by setting.

No study originating from primary care could be identified. One paper reported on the relationship between prolonged cough and lung cancer, and was based on 6027 patients in a specialised setting. It revealed a high negative (0.99) and a low positive (0.03) predictive value, a sensitivity of 0.48 and a specificity of 0.71. Little information was given as to the method by which studies were assessed other than stating that those relating to primary and secondary care were processed separately. A thorough attempt was made to identify evidence that evaluated the significance of prolonged cough in patients with lung cancer but few studies came to light.

Primary studies

Sridhar et al, 1998(83)

This prospective study sought to determine the relative frequency of clubbing in small cell lung carcinoma (SCLC) versus non-small cell lung carcinoma (NSCLC) in patients diagnosed with lung cancer. The primary data were derived from the treating cancer centre at a tertiary teaching hospital in the US. A consecutive series of 111 patients with a pathological diagnosis of lung cancer were examined for the presence or absence of digital clubbing. It was not always possible to examine patients prior to confirming the pathological diagnosis. Comparisons were made between patients with and without clubbing on the following: age, sex, substance use, tobacco, smoking history, family history of lung cancer and subtype of cancer.

Clubbing was present in 32 (29%) of the 111 patients with lung cancer. Clubbing was more common in women (40%) than in men (19%; χ^2 test P=0.011) and occurred more commonly in patients with non-small cell lung carcinoma (35%) than those with small cell lung carcinoma (4%; χ^2 test P=0.0036).

Table 15 Small cell versus non-small cell lung carcinoma.(83)

	Small Cell Carcinoma	Non-small Cell Carcinoma
Total	23	88
Men	14	45
Women	9	43
Clubbing		
Yes	1	31

No	22	57

Nine women had small cell lung carcinoma, of whom one had clubbing. None of the 14 men with small cell lung carcinoma had clubbing. No other factors such as the subtype of non-small cell lung carcinoma, age of the patient, family history of lung or other cancers and tobacco smoking were related to clubbing.

Sarlani et al, 2003(84)

Facial pain as a presenting symptom of non-metastatic lung cancer was evaluated in thirty-two patients (one case report and 31 cases identified from the dental literature since 1983). This series comprised 12 males (37.5%) and 20 females (62.5%). The mean age at presentation was 54 years (range 34 to 78). The vast majority of the patients were smokers or former smokers. The facial pain preceded the diagnosis of lung cancer by a mean of nine months (range 1-48). Facial pain related to non-metastatic lung cancer was almost invariably unilateral, always ipsilateral to the tumour. Eighteen of the 32 cases (56.3%) involved right-sided pain and 12 (37.5%) left-sided pain. The pain most commonly affected the ear, the jaws and the temporal region. Pain in or around the ear was present in 20 of the 32 cases (62.5%) and jaw pain in 14 cases (43.8%).

Pain was commonly misdiagnosed as atypical facial pain, dental pain or pain associated with temporamandibular disorders (TMD) or trigeminal neuralgia.

Herth et al, 2001(85)

This UK study was a case series of lung cancer in patients with haemoptysis. A retrospective review of the records of 722 patients was undertaken at a tertiary referral centre for pulmonary diseases between January 1990 and December 1993. A source and aetiology for the bleeding was identified in 587 patients (81%) at the initial evaluation. In the remaining 135 patients (19%) no aetiology for the bleeding could be determined and this group was targeted for further follow-up. However, for 20 patients, follow-up data could not be obtained. Eighty-one patients (60%) were smokers, 16 (12%) had a history of chronic obstructive pulmonary disease (COPD) and ten (7%) had a history of tuberculosis.

Of the 115 patients followed-up, lung cancer developed in seven (6%). All seven patients developed lung cancer within the first three years after the initial workup. Their mean age was 49.7 years (range 43 to 61 years). Lung cancer developed in these seven patients despite negative bronchoscopy and normal chest radiographic findings at initial presentation. Endobronchial and transbronchial biopsies were performed when indicated and all specimens were routinely examined for cytology and microbiology. Using the cohort study analysis for unpaired differences, a 10% probability was found for lung cancer developing after haemoptysis of unknown origin if the patient was a current smoker and > 40 years old.

(Koyi et al, 2002)(86)

All patients referred to a specialised centre between January 1997 and December 1999 were investigated in this prospective Swedish study. General practitioners were encouraged to refer all suspected cases of lung carcinoma including those with a very poor prognosis as early as possible. It was intended to reach a definite diagnosis with a biopsy and/or cytology investigation, although this was not possible in 50 of the 364 patients (13.7%). Diagnosis for these patients was instead based on x-ray findings, clinical data and symptoms. Compared to other Swedish studies, the more comprehensive approach to data collection resulted in a sample of older age groups. This affected the distribution of cancer types with more squamous cell carcinomas and fewer adenocarcinomas.

Table 16 First symptoms of lung cancer and the symptoms that prompted a visit to the doctor.(86)

Symptom	First symptom N (%)	Reason to visit doctor, N (%)
Cough	86 (24.9)	81 (23.5)
Dyspnea	52 (15.1)	59 (17.1)
Fatigue	49 (14.2)	29 (8.4)
Pain in thorax	17 (4.9)	18 (5.2)
Back pain	13 (3.8)	11 (3.2)
Haemoptysis	11 (3.2)	17 (5.1)
Cough and fever	9 (2.6)	9 (2.6)
Abdominal pain	8 (2.3)	11 (3.2)
Fever	7 (2.0)	7 (2.0)
Neurological symptoms	8 (2.3)	12 (3.5)
Hoarseness	7 (2.0)	8 (2.3)
Others	39 (11.4)	55 (15.7)
Total	306 (88.7)	317 (91.8)

(Melling et al 2002)(87)

The proportion of patients referred according to lung cancer guidelines was analysed in a case series of 400 patients randomly selected from the former Yorkshire Cancer Registry database in 1993 to assess how different pathways resulted in varying management. The sample was stratified by three age groups (<65, 65-75, >75). Those with missing case notes or receiving private treatment or extra-regional care were excluded. General practitioner and hospital case notes were traced for 362 out of 400 patients (90.5%). The 'with chest x-ray diagnosis' group consisted of patients who presented to their general practitioner with a respiratory related complaint. Less than half of lung cancer patients (173, 47.8%) presented to hospital with a chest x-ray diagnosis of lung cancer. A total of 148 patients in the 'without chest x-ray diagnosis group' were referred to hospital because of their symptoms but with no prior chest x-ray. Forty-one (11.3%) presented as self referrals to A&E and the remainder were referred without a diagnosis of lung cancer by other routes, mainly via general practitioners.

Table 17 shows that 80% of the 'with diagnosis group' presented to their general practitioner with mainly lung related symptoms (cough, chest pain or infection, haemoptysis or dyspnoea) compared to 69 (46.6%, CI: 38.4%, 55.0%) of those without a diagnosis. Patients who did not present initially with a lung cancer diagnosis were less likely to receive specialist care (62%: 96%) or have histological confirmation (57.1%: 80.3%) or receive surgery or radical radiotherapy (6.9%: 13.9%). Surgery, chemotherapy and palliative radiotherapy were all used most frequently in the 'with chest x-ray diagnosis group', but the difference was only significant for surgery (P=0.035). It was concluded that patients presenting to hospital without a suspicious chest x-ray were less likely to have specialist care, histological confirmation of their cancer and had lower rates of active treatment.

Table 17 Presenting symptoms with and without diagnosis.(87)

	Principal presenting symptom†					
	With diagnosis		Without diagnosis		Acute	
Symptoms	n	%	n	%	n	%
Cough	57	32.9	16	10.8	1	2.4
Chest pain	26	15.0	16	10.8	3	7.3
Chest infection	26	15.0	14	9.5	1	2.4
Shortness of breath	22	12.7	24	16.2	8	19.5
Haemoptysis	18	10.4	7	4.7	3	7.3
Weight loss	12	6.9	14	9.5	0	0
Other pain	7	4.0	23	15.5	6	14.6
Other (non respiratory)	17	9.8	44	29.7	19	46.3

†Some patients had more than one principal presenting symptom

(Mansson et al, 2001)(88)

In this case series, information on diagnostic activities was collected from the records of patients whose differential diagnoses included colorectal, breast, lung or prostate cancer. Data collection took place in four primary healthcare centres in Sweden from different periods between 1992 and 1997 and involved a sample of 6812 patients ≥30 years of age.

Pulmonary diagnostic codes comprised the greatest part of the study (9422 codes corresponding to 65%). Most of these codes were assumed to be accounted for by infectious diseases in the upper airways. C-reactive protein tests were taken 865 times and nasopharyngeal cultures 580 times. Blood haemoglobin and ESR were tested 822 and 579 times respectively. Chest x- rays were performed 643 times. The yield of malignancy following chest x-ray was low, 0.4%.

Table 18 Number of selected diagnostic codes according to classification of diseases in the primary health care from the Swedish Board of Social Welfare 1987 with a possible association with pulmonary cancer.(88)

Diagnostic codes with pulmonary cancer as a differential diagnosis (n=9422)					
Shortness of breath (786A)	415	Upper airway disease (460)	3340	Epiglottis, larynx, lung and bronchus (162)	21
Cough (786C)	420	Inflammation in the epiglottis, larynx and trachea (464)	114		
Haemoptysis (786D)	9	Bronchitis (acute and chronic) (466, 491)	2426		
		Pneumonia (486)	619		
		Emphysema (492)	94		
		Asthma (493)	1714		
		Pleuritis (511)	82		
		Other diseases in the respiratory organ (519R)	168		

(Interdisciplinary Group for Cancer Care Evaluation G.I.V.I.O, 1989)(89)

The quality of diagnostic and therapeutic care was examined in a case series of 380 patients with lung cancer seen in 20 Italian general hospitals between January and June 1987. A maximum of 30 patients was accepted from each of the participating hospitals. A total of 380 cases with median age 63 years (range 37-86) entered the study. Histologic and cytologic findings were available for 363 cases. Eighty-seven percent were males. Symptoms most frequently reported at presentation were cough in 175 (46%), shortness of breath in 86 (23%), chest pain in 87 (23%), haemoptysis in 75 (20%) and fever in 52 (14%). Lung cancer appeared to be a chance diagnosis in 48 (13%) patients who did not have any specific symptom and whose disease was found on routine chest x-ray. Finally, 26 (9%) patients had symptoms due to distant metastases at diagnosis, whilst no information was available in six cases.

(Mansson et al, 1994)(90)

The records of a sample of 40 (26 men and 13 women) subjects with lung cancer reported to the Swedish Cancer Registry 1980-1984 were examined using hospital records in this case series, with special reference to the general practitioners' role. The mean and median ages at the time of the diagnosis was 69 and the range was 43-85 years. The initial symptoms were cough followed by dyspnoea, chest pain, fever, weight loss and tiredness. Other presenting symptoms were oedema, haemoptysis, facial pain, pricking sensations in the throat, stuffed nose, dizziness, frequent colds and tumour outside the throat. Symptoms included palpable lymph nodes (two patients), dyspnoea, liver enlargement, cachexia, tendency to fall and an episode of unconsciousness. No abnormal signs were found on physical examination in ten patients (26%).

Table 19 Initial symptoms in patients with pulmonary cancer.(90)

Symptom	Number	%
Cough	13	33
Dyspnoea	7	18

Chest pain	6	15
Fever	4	10
Weight loss	4	10
Tiredness	4	10
Other symptoms	12	31
Health control	4	10

(Sridhar et al, 1990)(83)

The hospital charts of a case series of 127 patients with adenosquamous lung carcinoma identified between 1975 and1988 were reviewed. Men constituted 72% and 90% were smokers. Nearly two-thirds of the patients were between 50 and 70 years of age. The symptoms in order of decreasing frequency were cough, weight loss, expectoration, anorexia, chest pain, dyspnoea, weakness, haemoptysis, pneumonia, fever, nausea, vomiting, dizziness and chills. Most patients had multiple symptoms. Haemoptysis was a more common presenting symptom in men than in women (P=0.05). Weight loss was more frequent in men than in women but this difference was not significant.

Table 20 Symptoms in the 127 patients with adenosquamous lung carcinoma(83)

	Present		Absent		Not documented	
Symptoms	n	%	n	%	n	%
Cough	68	54	18	14	42	32
Weight loss	54	43	25	20	48	38
Expectoration	49	39	17	13	61	48
Anorexia	45	35	10	8	72	57
Chest pain	41	32	29	23	57	45
Dyspnea	38	30	17	13	72	57
Weakness	38	30	3	2	86	68
Haemoptysis	30	24	37	29	60	47
Pneumonia	16	13	4	3	107	84
Fever	16	13	46	36	65	51
Nausea	13	10	18	14	96	76
Vomiting	9	7	11	9	107	84
Dizziness	8	6	6	5	113	89
Chills	6	5	42	33	79	62

Risk Factors

Secondary studies

Ruano-Ravina et al, 2003(91)

In this systematic review, studies were identified through a search of MEDLINE and EMBASE for relevant studies published from 1985 onwards. Editorials, commentaries and studies involving less than 50 cases were excluded. The risk of developing smoking-related lung cancer was found to depend on several factors including duration of habit (number of cigarettes per day), age at initiation and type of tobacco. Passive smoking was considered a risk factor for lung cancer (RR reported to be approximately 1.5) although exposure was very difficult to measure. Many occupational groups including construction labourers, carpenters, and wood or timber workers were identified as at risk. Individuals in contact with dust or microscopic particles (asbestos, wood dust, silica) were at higher risk of developing lung cancer despite the effects of environmental pollution being difficult to assess. Ecological studies lacked information on certain confounders such as tobacco use.

Survival was rated as being better in women than men, and slight ethnic differences were observed, with higher mortality rates among African- Americans. Certain diseases increased the risk of developing lung cancer, in particular tuberculosis, chronic obstructive pulmonary disease and silicosis. Family history of lung cancer was associated with increased risk. In one study, women reporting a family history of lung cancer had a 1.9 fold risk (95% CI 0.7-5.6) of developing lung cancer and those reporting a family history of cancer had a 1.8 fold risk of developing lung cancer (95% CI 1.0- 3.2). Lung cancer was more common in families with a record of breast and ovarian cancer.

(Alberg and Samet, 2003)(92)

This article reviewed the epidemiology of lung cancer. The authors concluded that a single etiologic agent, cigarette smoking, was by far the leading cause of lung cancer accounting for approximately 90% of cases in the United States. They also stated that the risk of lung cancer among cigarette smokers increased with the duration of smoking and the number of cigarettes smoked per day and that this observation had been made repeatedly in cohort and case-control studies.

The likelihood of developing lung cancer was reported to decrease among those who quit smoking compared to those who continue to smoke. As the period of abstinence from smoking cigarettes increased, the risk of lung cancer decreased. However, even for periods of abstinence of >40 years, the risk of lung cancer among former smokers was found to be elevated compared to never smokers. Studies showed comparable reductions in risk following smoking cessation, regardless of sex, type of tobacco smoked and histologic type of lung cancer.

Almost one quarter of lung cancer cases among never-smokers were estimated to be attributed to exposure to passive smoking. Estimates derived from case-control studies of the proportion of lung cancer that is contributed to by occupational exposures ranged widely, but most point estimates or ranges included values from 9 to 15%. The authors reported that asbestos exposure may pose a risk to building occupants and that radon was associated with lung cancer.

(Tyczynski et al, 2000)(93)

This review addressed the epidemiology of lung cancer in Europe. Tobacco smoking featured as the most prominent risk in developing lung cancer. A clear dose-response relation was reported between lung-cancer risk and the number of cigarettes smoked per day, degree of inhalation and age at initiation of smoking. A person who has smoked all their life has a lung cancer risk 20-30 times greater than a non-smoker. Lung cancer risk decreases with time since smoking cessation.

The observation that the risk of lung cancer is greater in women than in men exposed to equivalent amounts of tobacco smoke is not supported by studies which concluded that the risk is similar between the two sexes. Passive exposure to tobacco smoke also increases the risk of lung cancer and it is estimated that environmental exposure to tobacco smoke increases risk by 15-25%.

Additional risk factors include exposure to asbestos, with risk being almost two-fold among those with the longest periods of exposure. A synergistic (multiplicative) effect between asbestos

and tobacco smoking has been documented in three comprehensive reviews. Occupational exposure to carcinogens and residential exposure to radon may increase the risk of lung cancer in men who have never smoked. The combined effect of smoking and radon exposure however, is unknown.

(Macbeth et al, 1996)(94)

The risk factors associated with lung cancer have been identified as including tobacco, asbestos and radon. The influence of genetic factors and the effects of chromosomal abnormalities has also been assessed. At least thirty retrospective and eight prospective studies have established a link between cigarette smoking and lung cancer. It has been estimated that 85-90% of all lung cancers can be linked to active smoking. The use of cigarettes carries a significantly greater risk of developing lung cancer than either pipe or cigar smoking.

The age of starting cigarette smoking, the duration of smoking and the nicotine content of the cigarettes are all important factors. The risk of lung cancer at the age of 60 years is reported to be three times greater for those who started smoking between the ages of 14 and 16 years compared to those who began ten years later. It has been calculated that someone aged 35 years who smokes 25 or more cigarettes per day has a 13% chance of dying from lung cancer before the age of 75 years. Exposure to known carcinogens including asbestos, radon, chromium, nickel and inorganic arsenic compounds increases the risk of lung cancer. Even a short exposure may be sufficient to cause lung cancer, if the concentration of asbestos is high enough. Miners who are exposed to high concentrations of radon have an increased risk of lung cancer, but its role in domestic housing as a factor causing lung cancer is uncertain. Several studies have shown an increased risk in the siblings of patients who develop lung cancer.

9.2 Investigations

9.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care before referral?

9.2.2 Evidence Question:

In patients attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

9.2.3 Evidence Statements:

A chest x-ray is the principal diagnostic investigation in primary care. (III) False negative chest x-ray results do occur in lung cancer. (III)

Sputum cytology is not a discriminatory investigation in symptomatic patients. (III)

Secondary Papers

Schreiber, 2003(95)

A systematic review and meta analysis was undertaken in the USA to determine the test performance characteristics of various investigations for the diagnosis of suspected lung cancer. The investigations included sputum cytology, bronchoscopy, transthoracic needle aspirate (TTNA) or biopsy. The search covered MEDLINE, Healthstar and Cochrane Library databases from 1966 to July 2001 among other sources. Studies included in the review had to involve samples of at least 50 patients. The pooled specificity for sputum cytology from 16 studies was 0.99 and the pooled sensitivity was 0.66, but sensitivity was higher for central than for peripheral lesions (0.71 vs. 0.49 respectively).

Most of the studies on sputum cytology involved the identification of patients from cytology laboratory samples without regard to the indication for sputum cytology testing. Studies of the

accuracy of sputum cytology for the diagnosis of lung cancer were difficult to summarise due to methodological problems. The studies showed highly variable estimates of sensitivity and no clear reasons for this. Sensitivity calculations may have been affected by the different thresholds for considering cytology 'positive' with regard to the category of 'suspicious' and whether insufficient specimens were excluded or classified as negative also may have influenced the results.

Primary studies

Simpson et al, 1988(96)

The indications and diagnostic yield of general practitioner referrals for static miniature chest radiography were investigated in this study. A total of 1205 consecutive general practitioner referrals for chest radiography to the Leeds Chest Clinic were included. All films were read by chest physicians and were classed as normal, abnormal but not requiring further investigation, or abnormal requiring recall to the clinic. Patient notes were reviewed one year later to assess outcome.

Of the 1205 films, 878 (73%) were classified as normal. In 132 (11%) cases the patient was recalled. Of those patients with significant pathology 15 had pneumonia, 14 a cardiac lesion, five had active tuberculosis, three had malignant effusions, four had pulmonary metastases and one had a pneumothorax. There was a low recall rate (5%) and prevalence of significant pathology (1%) in those patients under 40 years of age. In the over 60 age group there was much higher recall rate (23%) with 13% having significant pathology.

Of the 15 patients with lung carcinoma, nine had died by one year and only three had received active treatment (two radiotherapy and one surgery). The symptoms most likely to be associated with significant pathology were cough, haemoptysis, wheeze, dyspnoea and weight loss. Non-specific symptoms of malaise, tiredness or general ill health, chest pain and hypertension were rarely associated with abnormal radiographs. The study did not identify symptoms solely predictive of carcinoma because cases of cancer were placed in a category of 'significant pathology', which also included pneumonia, cardiac lesions, active tuberculosis and pneumothorax. No pathological or histological verification of the diagnosis of cancer was reported.

(Pederson, 2003)(97)

This study prospectively assessed the diagnostic value of an elevated platelet count and other routine laboratory tests for predicting malignancy in 126 patients with radiologically suspected lung cancer. Patients were divided by pathologic diagnosis into those with benign disorders (N=65) or malignancies (N=61). Cytological examination of sputum and pleural fluid and percutaneous transthoracic needle biopsy were among the investigations performed.

All 126 consecutive subjects were admitted to the outpatient clinic with an abnormal chest x-ray. Thrombocytosis (platelet count $>400x10^{9/1}$ was present in 8% (5/65) of patients with benign disease and in 57% (35/61) of patients with malignant disease (P<0.00001).

Table 21: Diagnostic value of laboratory tests in the prediction of malignancy.(97)

	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Platelet count	0.57	0.92	0.70	0.88
Leukocyte count	0.52	0.63	0.59	0.57
Serum LDH	0.48	0.80	0.62	0.69
ESR	0.59	0.81	0.68	0.75

Haemoglobin	0.41	0.85	0.60	0.71
Platelet count combined with:				
Leukocyte count	0.59	0.98	0.73	0.95
LDH	0.54	0.94	0.75	0.87
ESR	0.67	0.98	0.83	0.95
Haemoglobin	0.48	0.98	0.76	0.94
Leukocyte count + LDH	0.62	1.00	0.79	1.00
Leukocyte count + ESR	0.65	1.00	0.83	1.00
Leukocytes + haemoglobin	0.53	1.00	0.79	1.00
LDH + ESR	0.71	1.00	0.89	1.00
LDH + haemoglobin	0.52	0.98	0.82	0.92
ESR + haemoglobin	0.59	0.98	0.84	0.93
All tests together	0.67	1.00	0.88	1.00

The prevalence of thrombocytosis in patients with primary lung cancer was 53% (27/51). Elevated platelet count was more common in advanced disease (stage III and IV). The sensitivity of thrombocytosis for predicting malignancy was 0.57 and the specificity 0.92. When elevated platelet count, serum lactate dehydrogenase and erythrocyte sedimentation rate were combined, a sensitivity of 0.71 and a specificity of 1.00 was achieved.

(Holmberg, 1993)(98)

The value of routine convalescent chest radiography was assessed retrospectively using medical records from patients with pneumonia admitted to a Swedish hospital during 1981 and 1985. All patients had pneumonia. The study included 1011 patients (544 males and 467 females, mean age 66 years, range 15-97), of whom 678 underwent chest radiography and clinical examination one to two months after the acute onset of illness. Excluded cases comprised those with incorrect diagnoses (N=59), those who had no x- ray performed (N=15), patients with severe chronic debilitating disease resulting in multiple episodes of pneumonia (N=30), age < 15 years (N=19) and various other reasons.

Thirteen of the 1011 patients with pneumonia had previously undiagnosed pulmonary carcinoma. Many of these carcinomas (8/13) were identified by an acute chest x-ray. Pulmonary carcinoma was found by the convalescent chest x-ray in 2/88 patients not feeling well and in 2/524 patients feeling well at follow-up. ESR was of no value in detecting underlying pulmonary carcinoma at follow-up in patients with pneumonia. Of the 232 inpatients (181 men and 51 females, mean age 68 years, range 38-89) with pulmonary carcinoma, 29 (12.5%) presented with an acute respiratory tract infection; most of these patients did not recover as expected and their correct diagnosis was made following a chest x-ray requested because of the persistent symptoms.

Table 22 Initial symptoms in 232 patients with pulmonary carcinoma (many patients had more than one symptom).(98)

	No of patients	Frequency (%)
Cough	92	39.7
Dyspnoea	65	28

Haemoptysis	38	16.4
General malaise	35	15.1
Acute respiratory infection	29	12.5
Routine check-up	28	12.1
Thoracic pain	25	10.8
Hoarseness	8	3.5
Neurological symptoms	5	2.2
Enlarged lymph nodes	3	1.3
Others	6	2.6

9.3 Delay and diagnostic difficulties

9.1.1 Key clinical questions:

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with symptoms/signs suggestive of lung cancer may or may not need urgent referral with suspected lung cancer?

In people attending primary care services, which psychosocial and socio-demographic factors are associated with delayed presentation of lung cancer? Which factors influence delay by patient and which delay by provider?

9.1.2 Evidence questions:

What diagnostic difficulties do primary care practitioners themselves report in determining whether a patient may or may not need urgent referral with suspected lung cancer?

In people attending primary care services, which psychosocial and socio-demographic factors are associated with delayed presentation of lung cancer? Which factors influence delay by patient and which delay by provider?

9.1.3 Evidence Statements:

Delay can occur when patients fail to recognise the significance of a symptom such as prolonged cough (III)

Presentation with non-respiratory symptoms such as shoulder pain may be associated with difficulty in diagnosis (III)

Papers covering delay or diagnostic difficulties are scarce but those with relevant findings are summarised below.

Primary studies

(Gorman et al, 2002)(99)

General practitioners in the UK were surveyed about the use of investigations prior to referral of patients with suspected lung, large bowel, non-melanoma skin and breast cancer. The study was confined to one health board in Lothian. The questionnaire was distributed in May 1997 to 134 general practices, following a pilot study in eight practices. Information was sought about referral choices, communication, quality of care, liaison between community and hospital, health promotion, treatment outcomes and palliative care. The main outcome measures were

determinants of primary care referral behaviour and clinical investigation strategies, and perceptions of quality in secondary care and health promotion services.

Seventy-nine general practices (59%) returned completed questionnaires. Most cases of suspected lung cancer, approximately half of suspected colorectal cancer cases and very few cases of suspected breast cancer were investigated in primary care before referral to hospital. It was unlikely that a practice would investigate further in primary care a woman with symptoms suggestive of breast cancer, but with lung cancer investigations prior to referral would be done in three quarters of cases and in 45% of those with colorectal cancer symptoms. Practices highlighted their wish for fast track facilities and an increase in the availability of open access investigation and diagnostic services.

(Varney et al, 1996)(100)

A three-year case series study using UK hospital data sought to identify the early symptoms of lung cancer in order to decrease delay in identification of lung cancer. Cough was the initial complaint in 117 patients. In 80% the cough was a new symptom, usually reported as dry, in 20% a previous cough had clearly changed, and 30% of all patients had quit smoking because of the cough. Most consulted their general practitioner promptly but 26 patients delayed consulting by an average of 12 months. In those who consulted promptly, there was a mean delay of seven months between reported symptoms and the first chest x-ray. Asthma treatment, antibiotics and steroids were commonly prescribed during this time.

A total of 104 patients reported shoulder or chest pain as the first complaint: the tumours were always located in the upper lobes, with pain referred to the shoulder, anterior chest wall or scapula on the affected side. Most were initially treated with nonsteroidal anti-inflammatory drugs and shoulder injections. Only 12 delayed consulting their general practitioner by an average of 3.5 months. Patients who consulted promptly had their first chest x-ray five months later on average. Sixty of these were current smokers. Additional presenting symptoms were: breathlessness (35 patients); weight loss with malaise (17 patients); haemoptysis (ten patients); and hoarseness (nine patients).

10 Upper gastrointestinal cancer

General recommendations

1 A patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specializing in the management of upper gastrointestinal cancer, depending on local arrangements. D

Specific recommendations

2 An urgent referral for endoscopy or to a specialist with expertise in upper gastrointestinal cancer should be made for patients of any age with dyspepsia[11] who present with any of the following:
- chronic gastrointestinal bleeding
- dysphagia
- progressive unintentional weight loss
- persistent vomiting
- iron deficiency anaemia
- epigastric mass
- suspicious barium meal. C

3 In patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made. D

4 In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary

[11] The definition of dyspepsia is taken from the NICE guideline on *Dyspepsia: management of dyspepsia in adults in primary care* (www.nice.org.uk/CG017). Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting.

in the absence of alarm symptoms. D

5 In patients presenting with dysphagia (interference with the swallowing mechanism that occurs within 5 seconds of having commenced the swallowing process), an urgent referral should be made. C

6 Helicobacter pylori status should not affect the decision to refer for suspected cancer. C

7 In patients without dyspepsia, but with unexplained weight loss or iron deficiency anaemia, the possibility of upper gastrointestinal cancer should be recognised and an urgent referral for further investigation considered. C

8 In patients with persistent vomiting and weight loss in the absence of dyspepsia, upper gastro-oesophageal cancer should be considered and, if appropriate, an urgent referral should be made. C

9 An urgent referral should be made for patients presenting with either:
- unexplained upper abdominal pain and weight loss, with or without back pain, or
- an upper abdominal mass without dyspepsia. C

10 In patients with obstructive jaundice an urgent referral should be made, depending on the patient's clinical state. An urgent ultrasound investigation may be considered if available. C

Risk Factors

11 In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors:
- Barrett's oesophagus
- known dysplasia, atrophic gastritis or intestinal metaplasia
- peptic ulcer surgery more than 20 years ago. C

Investigations

12 Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H2 receptor antagonists, for a minimum of 2 weeks. C

13 In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements. D

14 All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia. D

Introduction

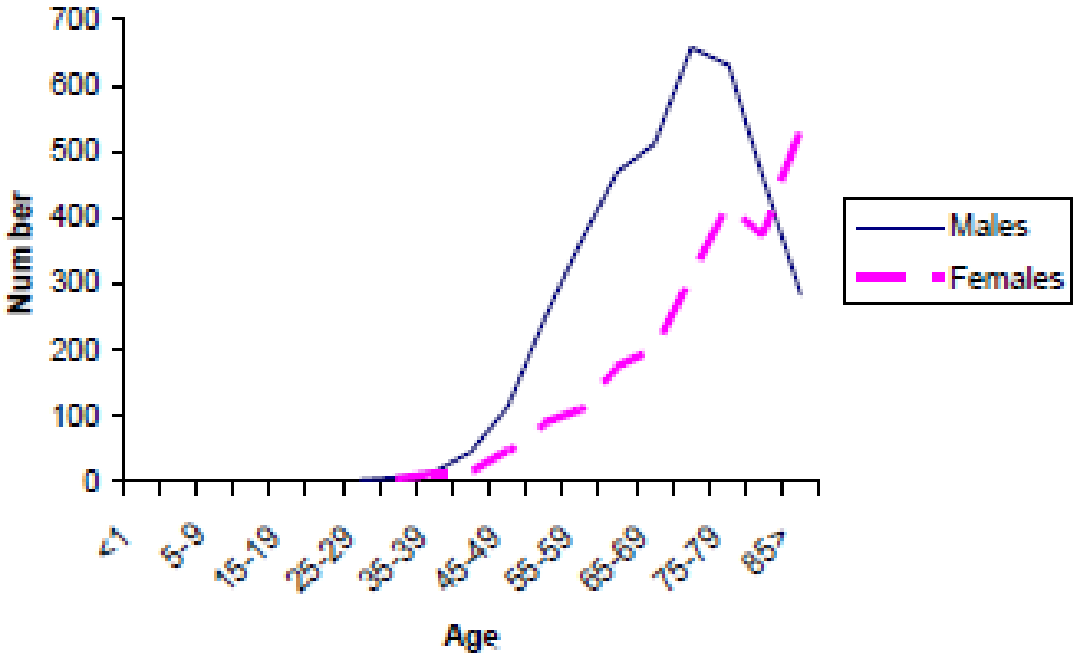
Incidence

Cancer of the oesophagus

The Office for National Statistics recorded 6,080 newly diagnosed cases of oesophageal cancer in 2001 in England and Wales, of which 3,806 were in males and 2,274 in females.

Numbers of registrations of oesophageal cancer have continued to increase over the last 20 years and the figures for 2001 are shown below.

Figure 7 2001 Newly diagnosed cases of malignant neoplasm of the oesophagus in 2001 in England and Wales. (77)

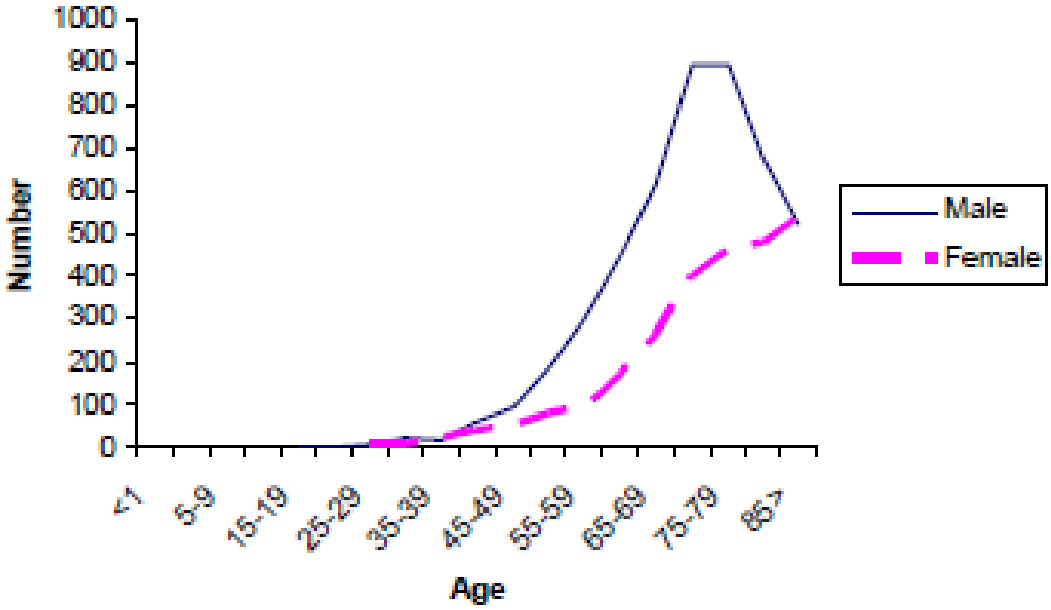


Cancer of the stomach

In 2001 there were 4,741 newly diagnosed cases of stomach cancer in males and 2,626 in females in England and Wales. Incidence recorded by the Office for National Statistics was low in both men and women in those under 50 years and increases rapidly with age peaking in those aged 85 years and over

The 2001 registrations of stomach cancer demonstrate a continuing trend of increased incidence and are shown below.

Figure 8 Newly diagnosed cases of malignant neoplasm of the stomach in 2001 in England and Wales. (77)

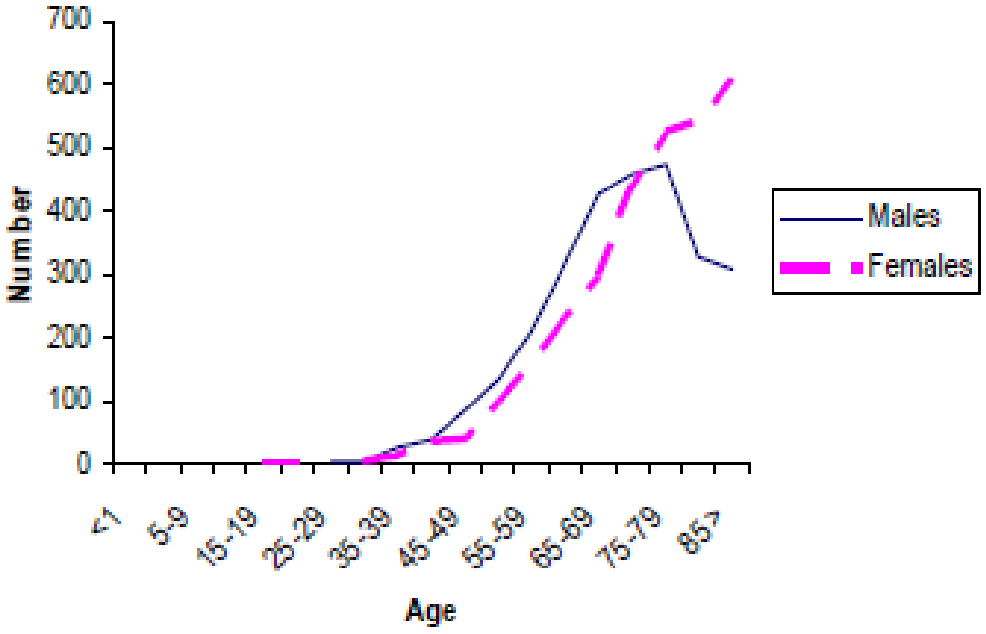


Pancreatic cancer

There were 2,807 cases of pancreatic cancer in males and 2,986 in females in 2001. Incidence indicates that it is rare in those aged under 50 years in both sexes.

2001 statistics show a similar trend but with the incidence in males over 80 years beginning to decline (Figure 9).

Figure 9 Newly diagnosed cases of pancreatic cancer in 2001 in England and Wales. (77)

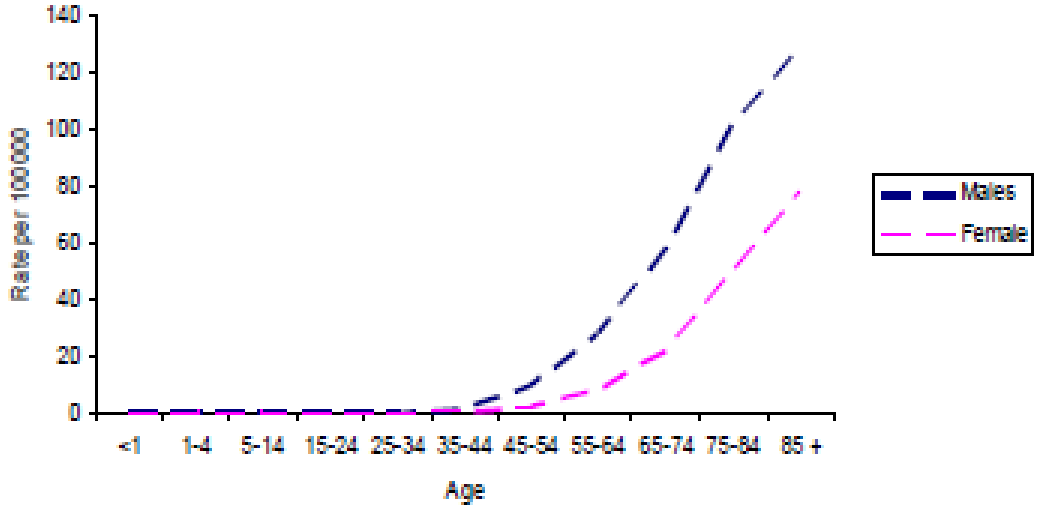


Mortality

Cancer of the oesophagus

Mortality rates from cancer of the oesophagus have been in creasing over the last 20 years. In 2002 the number of deaths from cancer of the oesophagus was 4,001 in males and 2,329 in females.

Figure 10 Mortality figures from cancer of the oesophagus for 2002 in England and Wales. (78)

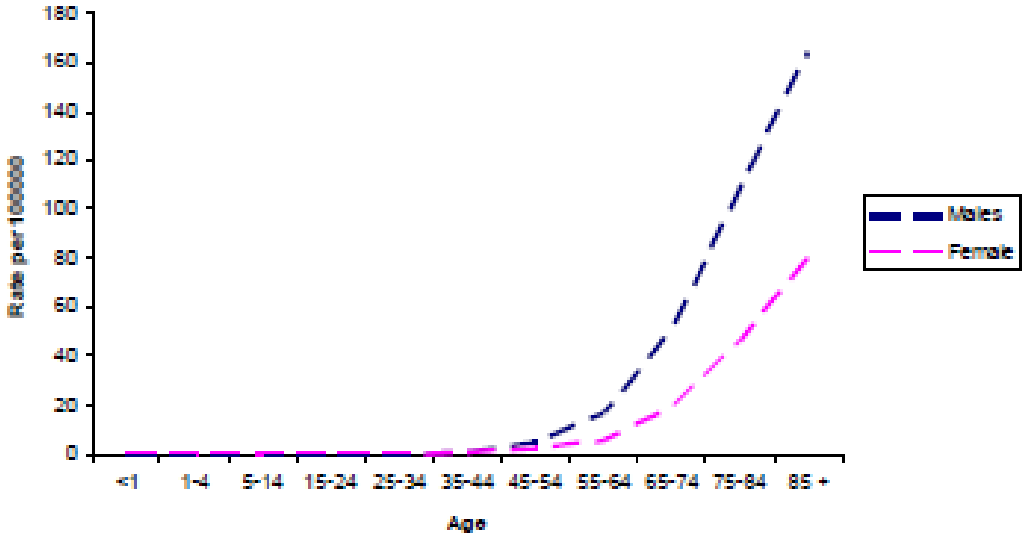


Cancer of the stomach

The 2002 mortality data for cancer of the stomach demonstrates a higher rate of mortality in

males that in females, with numbers totalling 3,211 in males and 2,105 in females. Mortality is low in those aged under 35 years and increases with age (shown in Figure 11).

Figure 11 Mortality figures from stomach cancer for 2002 in England and Wales. (78)

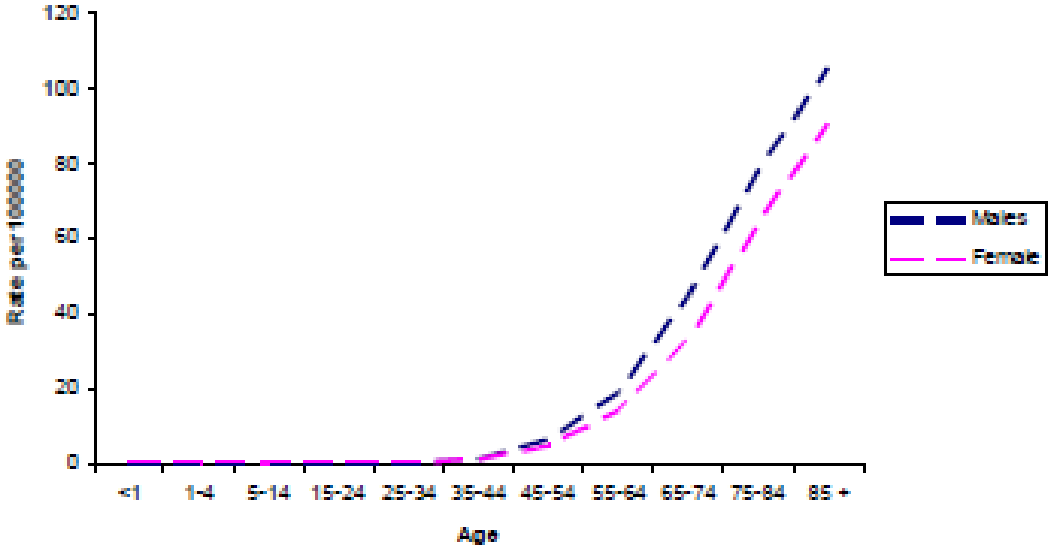


Pancreatic cancer

Trends in mortality from pancreatic cancer are similar to the incidence rates as the disease has a poor survival rate.

In 2002 the number of deaths due to cancer of the pancreas was 3,169 females and 2,952 males in England and Wales. (Shown in Figure 12)

Figure 12 Mortality figures from pancreatic cancer for 2002 in England and Wales. (78)



10.1 Symptoms and Signs

10.1.1 Key Clinical Question:

In people attending primary care services with upper gastrointestinal problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

10.1.2 Evidence Question:

In people attending primary care services with symptoms and signs that might be associated with upper gastrointestinal cancers, which symptoms and signs and other features including family history, when compared with the 'gold standard', are predictive of a diagnosis of cancer, and which symptoms and signs are not? Are any non-clinical features associated with a diagnosis of cancer?

10.1.3 Evidence Statements:

Upper gastrointestinal cancers are relatively uncommon in primary care. The typical general practitioner will encounter a case of oesophageal cancer once every five years, a case of stomach cancer once every three years, and a case of pancreatic cancer once every five years. (III)

The incidence of oesophageal, stomach and pancreatic cancers rises from around aged 50 years. (III)

Oesophageal and gastric cancer

The risk of gastric cancer is increased among smokers by a ratio of between 1.5 and 2.5. (III)

Barretts' oesophagus increases the risk of oesophageal cancer by 40-125 fold. (III)

Dyspepsia is very common, and a poor predictor of cancer. (III)

In a patient presenting with dyspespsia, weight loss (2kg or over) and dysphagia are features associated with cancer, . (III)

Other features associated with 20-30% of cases of gastric cancer include haematemesis, persistent vomiting, and anaemia, although these features may be less discriminatory than dysphagia and weight loss. (III)

Pancreatic cancer

Smoking is a risk factor for pancreatic cancer (risk ratio 1.6-3.1). (III)

The most common presenting symptom of pancreatic cancer is abdominal pain, occurring in approximately 70% of cases. (III)
Jaundice is the next most common feature, occurring in approximately 50% of cases. (III)

Non-specific symptoms and signs are common in pancreatic cancer, and include nausea and vomiting, weight loss, change in bowel habit and onset of diabetes. (III)

Guidelines

Oesophageal and gastric cancers

(NICE, 2004)(101)

Guidelines on the management of adults with dyspepsia in primary care have been published by NICE in 2004. Dyspepsia was defined as:
'*any symptom of the upper gastrointestinal tract, present for four weeks or more, including upper abdominal pain or discomfort, heartburn, acid reflux, nausea, or vomiting.'*

When referred to broadly in this way, the guideline indicated that dyspepsia occurs in 40%, leads to general practitioner consultation in 5% and referral for endoscopy in 1% of the population annually. In patients with signs or symptoms sufficiently severe to merit endoscopy, 40% have functional or non- ulcer dyspepsia, 40% have gastro-oesophageal reflux disease and 13% have some form of ulcer. Gastric and oesophageal cancers were reported as very rare, occurring in 3% of endoscopies although many cases arise from on- going hospital investigation

rather than primary care referral.

The guideline found that dyspeptic symptoms were a poor predictor of significant disease, and in primary care described symptoms were a poor predictor of underlying pathology.

(SIGN, 2003)(102)

The SIGN guidelines recommend referral for endoscopy iof patients with alarm symptoms and also those aged 55 or over with persistent or recurrent dyspepsia. The guideline found no evidence to support the mandatory use of early upper GI endoscopy to investigate patients over 55 years old who present with new onset uncomplicated dyspepsia. A non-invasive *H. pylori* test and treat policy may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia (level A recommendation). However, referral for assessment should be considered for patients over 55 years old with uncomplicated dyspepsia whose symptoms persist after initial management with the *H.pylori* test and treat strategy.

Secondary studies

(Heading et al, 1999)(103)

This was a systematic review of studies of the population prevalence of upper gastrointestinal symptoms in the UK. Studies were included if they had been published up to December 1997, if sample size and response rate were reported, if vague terms such as dyspepsia or indigestion were defined, abdominal pain or discomfort enquired about, and patients with a history or evidence of organic disease had not been excluded. Follow-up studies on groups of patients previously studied were excluded.

A total of 25 studies were identified, but 15 did not meet the defined inclusion criteria. In the ten included studies, the reported prevalence of upper abdominal symptoms (mostly upper abdominal pain or discomfort) ranged from approximately 8% to 54%, while the prevalence of heartburn ranged from 10% to 48%, and regurgitation from 9% to 45%, and 21% to 59% for both or either.

The most likely explanation for the broad range of prevalence reported in the case of upper abdominal symptoms is variation in the definition of symptoms. In the case of heartburn and regurgitation, different use of these terms by various investigators and subjects were viewed as contributing to the range of results.

Primary studies

Oesophageal and gastric cancers

(Numans et al, 2001)(104)

This was a multicentre case series study of the diagnostic features of gastro- oesophageal malignancy undertaken in the Netherlands. The subjects were 861 consecutive patients who were investigated with first time gastroscopy between 1986 and 1988. The diagnostic features were then validated in a second population (N=1153 from the same region during the next six years). These patients were referred by 150 of the original 196 general practitioners asked to participate in the first study, and the gastroscopies were performed in the same hospitals between 1988 and 1994. Univariate and multivariate analyses identified four symptoms predictive of malignancy that were then compared with the classic ‘alarm symptoms’.

During the first study period, malignancy was found in 21 patients (2.4%). The presence of weight loss, presence of dysphagia, absence of pain during the night and the absence of heartburn were predictors of malignancy. Classic symptoms were statistically significant as indicated in Table 23. The authors used the findings to assess a scoring system for symptoms that should trigger endoscopy (*Table 24*).

Table 23 Presence and absence of characteristics in patients with a diagnosis of

gastro-oesophageal malignancy. Crude odds ratio (OR), 95% confidence intervals (95% CI) and P-values for a diagnosis of malignancy by patient characteristics in the study population.(104)

Characteristic	Present	Absent	N	OR	95% CI	P
Age > 45	18	3	861	4.7	1.4-24.9	0.01
Sex (male)	13	8	861	1.3	0.5-3.6	0.76
History of dyspepsia	7	13	789	0.3	0.1-0.9	0.02
History of peptic ulcer	3	18	771	0.5	0.1-1.6	0.30
History of any UGI episode*	10	11	861	0.4	0.2-1.1	0.08
Prior barium meal	14	7	360	2.9	1.1-8.4	0.04
Use of H_2 RA	7	14	861	0.8	0.3-2.2	0.87
Smoking >5/days	13	8	813	2.4	0.9-6.8	0.08
Alcohol >4/days	2	16	782	2.0	0.2-9.1	0.57
Dysphagia	13	8	835	6.2	2.3-17.6	<0.01
Vomiting	8	13	834	1.9	0.7-5.1	0.23
Weight loss	14	7	861	6.6	2.4-19.5	<0.01
Fatigue	14	6	804	4.3	1.5-13.7	<0.01
Melaena	3	16	815	2.2	0.5-8.1	0.38
Regurgitation	12	9	786	1.9	0.7-5.1	0.23
Retrosternal pain	13	6	754	1.9	0.7-6.1	0.29
Heartburn during the night	2	18	809	0.2	0.0-0.9	0.02
Heartburn during the day	4	16	807	0.2	0.1-0.7	<0.01
Complaints while bending over	1	18	758	0.1	0.0-0.6	<0.01
Pain during the night	3	17	820	0.2	0.0-0.6	<0.01
Epigastric pain	12	6	824	0.4	0.1-1.3	0.13
Empty stomach pain	5	16	800	0.5	0.1-1.4	0.20
Bloating	14	5	823	1.2	0.4-4.4	0.92

Characteristic	Present	Absent	N	OR	95% CI	P
Nausea	11	9	817	1.2	0.4-3.3	0.88
Pain after a meal	7	11	761	0.7	0.2-2.0	0.62
Haematemesis	1	19	834	0.9	0.0-5.9	1.00
Duration > 3 months	8	12	758	0.6	0.2-1.7	0.45
Abnormal physical examination	7	12	835	0.6	0.2-1.6	0.34
Hb <7 female / <7.5 male	0	1	164	0	0.0-29.5	1.00
Hemoccult +	1	1	60	3.4	0.0-277.6	0.83

History of any upper gastrointestinal episode' means that the patient has consulted the current or any other physician with any complaint or non- malignant disease that has been diagnosed as originating from the upper gastrointestinal tract. This includes the whole range from functional dyspepsia and NUD to GORD and peptic ulcer, but it excludes malignancy in the upper abdomen. Bold case indicates classical alarm 'symptoms'. Underlined italics indicate additional features included in full statistical model (see *Table 24*).

Table 24 'Full' and 'classical' alarm symptoms models. Adjusted odds ratios (OR), 95% confidence intervals and scoring list values of patient characteristics associated with a diagnosis of malignancy in the study population (N=861).(104)

Patient characteristics	OR	95% CI	Full scoring list	OR	95% CI	Alarm scoring list
Age (yrs)	1.0	1.0-1.1	/10	1.1	1.0-1.1	/10
Sex	1.4	0.5-4.3	Male +1	2.1	0.7-6.5	Male +1
History of any UGI episode (year/n)	0.4	0.1-1.1	Yes –2	0.3	0.1-1.0	-2
Smoking (>5/day versus <5 or 0/day	2.6	0.9-8.0	Yes +2	2.8	0.9-9.0	+2
H_2-receptor antagonist (year/n)	1.4	0.4-4.3	Yes +1	0.8	0.2-2.7	-1
Weight loss (>2kg / <2kg)	4.4	1.6-12.5	Yes +4	2.8	0.9-8.6	2
Dysphagia (years/n)	6.1	2.1-17.6	Yes+4	5.2	1.8-15.5	3
Pain during the night (year/n)	0.3	0.1-1.1	Yes –3			
Heartburn during the day (year/n)	0.2	0.1-0.8	Yes -4			
Fatigue				2.1	0.7-6.9	1
Vomiting				1.4	0.4-4.5	1
Meleana				3.0	0.7-13.4	2

(Irving et al, 2002)(105)

This UK case series sought to determine the impact of the two week target for referrals for suspected cancer. A total of 90 patients with oesophago-gastric cancer treated at Cumberland Infirmary between 1999 and 2001 were included.

65 patients were diagnosed with oesophageal cancer and 25 with gastric cancer. Dysphagia was the most common presenting symptom and was experienced by 58 patients in the study (64%), being more common in patients with oesophageal rather than gastric malignancies (77% versus 32%).

(Crean et al, 1982)(106)

In this UK study, a formal decision system was developed for assessment of patients with dyspepsia. The value of symptoms in duodenal and gastric ulcer, gastric carcinoma and alcohol related dyspepsia was investigated. 1000 patients attending a dyspepsia clinic were recruited and relevant clinical information was collected in a standardised manner.

Symptom scores indicated that a brief history of dyspepsia occurring in a patient over 55 should raise the possibility of gastric cancer; when the symptoms 'daily pain or discomfort', 'early repletion' and haematesis or 'coffee ground vomit' were combined, the probability of gastric cancer was increased.

(Adachi et al, 1993)(107)

This retrospective study carried out in Japan sought to identify the most effective approaches for detecting superficial oesophageal carcinoma. Clinical histories were investigated by review of hospital charts. The method of recruiting patients was not explicitly described, and it is not clear whether the sample comprised a consecutive series. The case series provided data on the symptoms associated with early stage and more advanced oesophageal cancer.

Symptoms were more frequent and the size of lesions larger with increasing depth of invasion. A piercing sensation was present mostly in superficial oesophageal carcinoma, while pain or dysphagia were present both in advanced oesophageal cancer and submucosal carcinoma. No calculations were performed to assess the predictive values of the symptoms described.

(Ojala et al, 1982)(108)

This retrospective case series was an investigation of the presenting signs and symptoms of patients with carcinoma of the oesophagus and gastric cardia attending a university hospital in Finland over the period 1964 to1977. The study included 225 patients, 139 males, and 86 females (see *Table 25*).

Table 25 Incidence of symptoms in 225 patients with carcinoma of oesophagus or gastric cancer.(108)

Results	Upper third (N=9) N and %	Middle third (N=68) N and %	Lower third (N=61) N and %	Gastric cardia (N=81) N and %	Total N and %
Dysphagia	8 (89%)	66 97%	58 95%	77 89%	209 93%
Weight loss	5 (56%)	20 29%	32 52%	47 54%	104 46%
Vomiting	0 -	7 10%	28 46%	39 45%	74 33%
Gastric pain	0 -	7 10%	20 33%	29 33%	56 25%
Thoracic pain	1 11%	11 16%	14 23%	21 24%	47 21%
Anorexia	0	4	4	8	16

	-	6%	7%	9%	7%
Haematemesis	0	2	4	7	13
or melaena	-	3%	7%	8%	6%
Belching,	0	1	5	4	10
hiccups,	-	1%	8%	5%	4%
dyspepsia					
Pharyngeal	2	4	3	0	9
pain	22%	6%	5%	-	4%
Sensation	3	3	0	0	6
of a lump	33%	4%	-	-	3%
Anaemia	0	0	0	6	6
	-	-	-	7%	3%
Cough,	2	2	1	0	5
hoarseness	22%	3%	2%	-	2%
Others	2	8	3	7	20
	22%	12%	5%	8%	9%

Age at the time of diagnosis varied from 37-84 (mean 62.5) years. The most common symptoms were dysphagia (obstruction or pain upon swallowing and/or regurgitation) (93%), weight loss (46%), vomiting (33%), gastric cancer (25%), thoracic pain (21%), anorexia (7%) and symptoms of gastrointestinal bleeding (9%). Respiratory symptoms (cough and hoarseness) occurred principally with tumours of the upper oesophagus. Gastrointestinal bleeding and anaemia were found in tumours of the lower oesophagus and gastric cardia. Other symptoms including poor general condition, infections, backache or pain in the lower abdomen occurred in 9% of patients. Dysphagia was the chief symptom in a large percentage of patients regardless of the location of the initial symptom. All diagnoses were verified histologically either on the basis of biopsies taken at endoscopy or from specimens obtained at surgery.

The mean duration of symptoms before the establishment of the diagnosis was 4.1 months in carcinoma of the oesophagus and 4.3 months for gastric cancer (cardia).

(Fielding et al. 1980)(109)

This study reviewed patients with histologically proven adenocarcinoma of the stomach and reported the natural history and associated signs and symptoms of early gastric cancer. The study reviewed all patients notified to the Birmingham Cancer Registry during the period 1960 to1969.

A total of 13,288 cases of gastric cancer were recorded. Ninety (0.7%) were identified as having ‘early’ gastric cancer. Most of the 90 patients experienced symptoms related to the gastrointestinal tract but in contrast to patients with advanced gastric cancer only 9% had lost weight on admission. The mean age at presentation of the 90 patients was 62.3 years and the condition was most common in the fifth and sixth decades. Fifty-nine patients were men and 31 women. Forty-six patients had presented with a solitary symptom and 44 with a combination of symptoms. The most common symptom was epigastric pain (26 cases), and weight loss occurred in only 17 cases. Twenty-one patients had presenting symptoms listed as ‘other’ which included malaise, stomach troubles and general weakness. Type II and

type III lesions had been manifested predominantly by epigastric pain and type I lesions by haematemesis. No patient had physical signs of a gastric primary neoplasm. The length of history varied and in 14 cases it was a year or more.

(Scottish Audit of Gastric and Oesophageal Cancer, 2002)(110)

The audit was based on data from 3,293 patients with upper gastrointestinal tumours (1490 oesophageal, 539 oesophago-gastric junction, and 1264 gastric) diagnosed 1997-1999, and included 98% of all such tumours diagnosed in Scotland during the study period. Information was collected from hospital records and investigation reports. The median age of patients was 72 years. Patients delayed presenting to their doctors by more than 4 months in 30% of cases.

Among patients with oesophageal adenocarcinomas, 14% were previously known to have Barrett's oesophagus. Approximately one third has a history of gastro-oesophageal reflux. Risk factors associated with gastric cancer included H pylori infection, previous gastric surgery, previous peptic ulcer disease and pernicious anaemia. A previous history of an ulcer was present in 1 in 5 patients who developed gastric cancer. Endoscopy and biopsy was the primary method of diagnosis (94% of patients); 0.9% of patients had a ruptured oesophagus following endoscopy, with 27% dying from this complication.

(Crean et al, 1994)(111)

The aim of this UK study was to develop a diagnostic decision system for dyspepsia, by recording the symptoms and clinical features of the common causes of dyspepsia as well as their distribution between diseases. The study included patients (N=1540) referred to hospital, data being recorded from 1974 to 1987. The authors included 107 inpatients with 'organic disease', although the majority of subjects were outpatients seen on referral by general practitioners (N=1433). The period of follow-up was not given. Biopsy specimens were taken depending on findings but it is not clear how many samples were analysed. The study had not been included in the Talley (1998)(112) review.

For the purposes of this study dyspepsia was defined as 'any form of episodic recurrent or persistent abdominal pain or discomfort, or any other symptoms referable to the upper alimentary tract, excluding bleeding or jaundice, of duration four weeks or longer'. Of the 1540 patients at diagnosis, 3% (50) were diagnosed with gastric carcinoma.

(Gillen et al, 1999)(113)

The main aim of this study was to assess whether concern over occult malignancy was valid in UK patients aged <55 years presenting with uncomplicated dyspepsia. Patients were identified between 1989 and 1993 from the West of Scotland Cancer Registry.

A total of 169 patients aged <55 years were diagnosed with gastroesophageal malignancy over the five year period, an incidence of about one per 28,000 total population/year. Only five patients were found to have upper gastro intestinal malignancy when undergoing investigation in the absence of 'sinister' symptoms (see *Table 26*).

Table 26 Sinister symptom prevalence in gastric and oesophageal cancer patients.(113)

	Prevalence of sinister symptoms in gastric cancer patients	Prevalence of sinister symptoms in oesophageal cancer patients

Weight loss	61.8%	63.0%
Persistent vomiting	35.6%	35.6%
Dysphagia	23.7%	84.9%
Anaemia	22.4%	5.5%
Haematemesis/melaena	18.4%	2.7%
Palpable mass	9.2%	0

A total of 84 patients had gastric cancer. Their median age was 50 years (range 31-54 yr) and 65 were men. Case sheets could be retrieved for 76. Of these, 71 (93.4%) had at least one sinister symptom at the time of initial referral for investigation. The most common presenting symptoms identified for gastric and oesophageal cancer patients were weight loss, persistent vomiting, dysphagia, anaemia, haematemesis, melaena and palpable mass.

(Voutilainen et al, 2003)(114)

Voutilainen and colleagues investigated the impact of clinical symptoms and referral volume of patients with dyspepsia on the detection of gastric and duodenal lesions. Data were collected prospectively on all patients referred for upper gastrointestinal endoscopy by general practitioners in 1996. The included study population was 3378 patients; male to female ratio 1:1.3 and mean age 58 years.

Alarm symptoms were defined as anaemia, dysphagia, weight loss and/or vomiting. Of the 1104 patients referred with alarm symptoms, 12 (1%) were diagnosed with gastric cancer, compared with 0.1% for those referred with dyspepsia, 0.5% referred for failure of empirical treatment, 0% referred for reflux, and 0.3% referred for other symptoms. The authors calculated that alarm symptoms were associated with an increased risk factor of 3.6 (95% CI 2 to 10.7) for gastric cancer.

Pancreatic cancer

(Wilson et al, 2000)(115)

The objectives were to identify the symptoms experienced by patients with pancreatic cancer and the response by health professionals in providing supportive care. The study was a retrospective review of the records of patients diagnosed with pancreatic cancer (N=99).

According to the Nova Scotia Cancer Registry, approximately 541 individuals were diagnosed with cancer of the pancreas. Slightly more than half were female (N=53). The mean age of all subjects was 69 years. Most patients were married.

At the time of admission to hospital 76 patients reported pain. The abdomen was the most prevalent pain site (N=43). Other symptoms included jaundice (N=35), diarrhoea (N=27) and constipation (N=22). Once hospitalised, pain continued to be the most common symptom experienced by nearly all patients (N=91). Other symptoms included nausea, vomiting and/or anorexia, alteration in bowel habit, and symptoms affecting the skin including jaundice. During hospitalisation 83% of patients experienced one or more gastrointestinal symptoms.

(Bakkevold et al, 1992)(116)

The study was designed to compare the symptoms and signs, and delays in diagnosis of pancreatic cancer at Norwegian hospitals. Information about the sensitivities of diagnostic investigations was obtained prospectively but data on signs and symptoms were extracted from the records. 472 patients with histologically verified carcinoma of the pancreas (N=442) or the papilla of Vater (N=30) were included. Patients with endocrine tumour, cholangiocarcinoma, metastatic pancreatic tumour, cystadenocarcinoma, and histologically or cytologically unverified primary pancreatic tumour were excluded. Thirty-eight Norwegian hospitals participated in the study. The university and district hospitals diagnosed and treated 190 (40%) and 282 (60%) respectively. After preliminary investigations, the local hospitals referred their patients to larger hospitals for diagnosis and treatment.

Presenting symptoms and signs in patients with carcinoma of the pancreas or papilla of Vater were jaundice (47%), acute pancreatitis (5%), abdominal pain (72%), weight loss (58%), diabetes (8%), and other (49%). Jaundice without pain was present in 18%. The commonest nonspecific symptoms were dyspepsia (12%), diarrhoea/steatorrhoea (12%) and nausea (5%). Thromboembolism was seen in two patients (0.4%).

Jaundiced patients had less advanced tumours than non-jaundiced at staging (P=0.0000). In contrast, abdominal pain and/or weight loss predicted advanced disease (P=0.0001 and 0.004 respectively). Acute pancreatitis occurred more often in patients with tumours of the papilla of Vater (19%) than at other sites (P=0.003).

(Klamer et al, 1982)(117)

This US case series aimed to investigate epidemiologic factors, presenting symptoms, diagnostic strategies, site and extent of cancer, treatment approaches and survival data associated with pancreatic cancer. The charts of all 33 patients treated for cancer at Mount Sinai Medical Center between 1971 and 1978 were reviewed. Patients with cancers arising from periampullary and islet cell tissue were excluded. The 33 included patients had histologically confirmed duct cell carcinoma. No patient was aware of exposure to asbestos or other known carcinogens, and no patient had a previous history of pancreatitis. Fifteen gave a history of smoking, 11 of diabetes and five of alcohol abuse.

Seventeen patients were men and 16 women. The mean age was 63.3 years (range 40 to 89). Four patients were black, three of them women. The 29 white patients were nearly equally distributed by sex. All were city dwellers. Although most patients presented with more than one symptom, the most common complaint leading to hospitalisation was abdominal pain, which occurred in 23 (70%), followed by jaundice in 19 (57%), anorexia in 15 (45%), weakness in ten (30%), and nausea in eight (24%). Six patients (18%) complained of pruritis or diarrhoea. A range of diagnostic investigations were undertaken including radiography or radionuclide scanning, pancreatic scans, arteriography, ultrasound, computerised tomography and liver biopsy. Histologic confirmation was not obtained until autopsy in seven patients.

Risk Factors

Secondary studies

Oesophageal and gastric cancers

(Shaheen and Ransohoff, 2002)(118)

The evidence linking gastroesophageal reflux disease (GORD) and Barrett's oesophagus to oesophageal carcinoma was reviewed. A MEDLINE search was performed to identify all English language reports about GORD, adenocarcinoma, and Barrett's oesophagus from 1968 through 2001. Cohort studies demonstrated that symptoms of GORD occurred monthly in almost 50% of US adults and weekly in almost 20%. There were no prospective cohort studies of reflux patients to assess cancer risk. Three large case- control studies demonstrated a positive association between reflux symptoms and risk of adenocarcinoma of the oesophagus, with more prolonged and severe symptoms accentuating this risk. However, because of the low incidence of adenocarcinoma of the oesophagus and the ubiquity of reflux symptoms, the risk of cancer in any given individual with reflux symptoms was low.

Most studies on individuals with Barrett's oesophagus reported a risk ratio of cancer that was 40 to 125 times higher than that of the general population. Estimates of the absolute risk of oesophageal adenocarcinoma varied widely from 0% to almost 3% per patient year. Recent larger studies and a meta analysis suggested that a reasonable estimate was approximately 0.5% per- patient year, resulting in the risk of a patient with Barretts' esophagus developing cancer in a year as approximately one in 200.

(Tredaniel et al, 1997)(119)

A review and meta-analysis of 40 studies was undertaken to provide a quantitative estimate of the association between gastric cancer risk and tobacco smoking.

A total of 40 studies was included in the meta-analysis and 30 provided results on ever smokers; not all however, reported enough details to be included in the weighted analysis. In particular, the variance-weighted regression was restricted to the 20 studies providing risk estimates and confidence limits for men, since results for women were reported for only one study. The analysis weighted on number of cases showed a higher summary relative risk in men (1.59) than in women (1.11, P-value for difference, 0.04). All the cohort studies showed a significantly increased risk of gastric cancer of the order of 1.5 –2.5 for cigarette smokers. Evidence from case-control studies was less consistent. The results suggested a risk of stomach cancer among smokers of the order of 1.5-1.6 as compared to non-smokers.

A number of studies reported separate analyses for current and ex-smokers: the summary variance-weighted relative risk was higher in current smokers (1.47) than in ex-smokers (1.18, P value 0.27). A dose-response relationship was suggested by the analysis of studies reporting risk estimates for different levels of smoking: summary relative risks were 1.49 for smokers of up to 20 cigarettes per day and 1.67 for heavier smokers (P value, 0.43). The differences between current and ex-smokers and between light and heavy smokers persisted when the meta-analysis was stratified according to year of publication, sex, geographical region and study design.

(Wei and Saheen, 2003)(120)

Risk factors for oesophageal cancer and how these related to the increased in incidence were reviewed by Wei and Saheen. They concluded that the most suspicious aetiologic factors associated with the current increase of oesophageal cancer were obesity, the use of lower oesophageal sphincter relaxing medications, possibly decreasing *H pylori* infection, changes in the Western diet and the effects of smoking even when people have subsequently stopped. They also included increased age, male gender, white ethnicity, family history, and gastro-oesophageal reflux as risk factors but suggested that there was no evidence that any changes in these were associated with the current rise in oesophageal cancer.

Pancreatic cancer

(Lowenfels and Maisonneuve, 2002)(121)

This review of epidemiologic factors in pancreatic cancer identified the confirmed risk factors as being smoking, age and pancreatitis. Other potential risk factors were listed as being diabetes, peptic ulcer disease, gallstones, infections, salmonella, helicobacter pylori, obesity, diet, occupation, inherited and gene-environment factors. The relationship between smoking and pancreatic cancer has been studied extensively in case-control and cohort studies, the results indicating a consistent increased risk of pancreatic cancer in smokers. Most studies were reported to show a dose response, with heavy smokers having a higher risk than light smokers, and current smokers at increased risk compared with nonsmokers. The risk of pancreatic cancer was estimated to remain elevated for one to two decades after cessation of smoking.

Age was the strongest risk factor. Pancreatic cancer is extremely unusual in patients younger than age 30 and is rare before age 50. The mean age of onset was about 65. Underlying benign disease is known to increase the eventual risk of malignancy.

(Ahlgren, 1996)(122)

In this review, it was concluded that direct evidence linking specific dietary carcinogens to pancreatic cancer in humans was limited. Some studies have suggested that the risk of pancreatic cancer is increased in heavy alcohol users. However, most studies in which a relationship between alcohol and pancreatic cancer has been sought have been negative. If an association between alcohol use and pancreatic cancer does exist, it has been suggested

that the specific risk may be to the subset of alcoholics who develop chronic pancreatitis. However, studies of the chronic pancreatitis associated with alcohol consumption have not shown a major risk of pancreatic cancer. A confounding variable in some studies has been cigarette smoking, which is very frequent in heavy alcohol users, and is a known etiologic factor in pancreatic cancer. Thus, unless there is adequate control for cigarette smoking, studies of the relation between alcohol and pancreatic cancer cannot be considered reliable.

The environmental carcinogen which has been linked most closely to cancer is cigarette smoke. Considering all the evidence, cigarette smoking must be considered to be a significant risk factor for pancreatic cancer. Radiation may modestly increase the risk of pancreatic cancer, although the evidence is not conclusive. Familial clustering of pancreatic cancer has been reported, but a genuine association has thus far been established only for familial relapsing pancreatitis.

(Gold and Goldin, 1998)(123)

Incidence rates of pancreatic cancer increase steadily with age. Approximately 80% of cases fall between the age range of 60 and 80 years. Incidence and mortality rates from pancreatic cancer in blacks of both sexes are higher than in white and all other ethnic groups except Japanese. Pancreatic cancer occurs more frequently in men and higher rates have been reported among some low socioeconomic populations.

An apparent association between diabetes and pancreatic cancer has been reported although this was not a consistent finding. Diabetes and pancreatic cancer exhibited a declining sex ratio with increasing age, a phenomenon that is not observed for other digestive tract or other tobacco-related cancers. Although acute and chronic pancreatitis are related to alcoholism, the relationship of either alcoholism or chronic non-familial pancreatitis to pancreatic cancer remained unresolved.

Various studies suggested that cigarette smoking increases the risk of cancer of the pancreas. The ratios for pancreatic cancer deaths in prospective studies of current cigarette only smokers compared with non smokers range from 1.6 in British physicians to 3.1 in Swedish men and were less than two in five of the eight studies. Most studies showed increasing pancreatic cancer risk with increased amounts of cigarettes smoked. However, not all of these studies demonstrated a dose-response relationship with number of cigarettes or with duration of smoking and some studies reported no significant association.

The evidence that related alcoholism to pancreatic cancer was fairly weak and inconsistent and the data available suggested that any increased risk from alcoholism was fairly small. Data from three case control studies in Europe were pooled and no association of alcohol with pancreatic cancer was found after controlling for gender, age, smoking and socioeconomic status and no evidence of a trend existed with the amount consumed.

The role that nutrition plays was addressed in a number of reviews. The results of the descriptive studies did not support an association of dietary fat intake with pancreatic cancer. However, descriptive studies were often limited by the quality of the cancer incidence data and the quality of the data on per capita intake and were confounded by other uncontrolled variables such as other dietary intake that may be closely correlated. Four cohort studies examined the relation of diet to pancreatic cancer but were of limited value due to the small number of pancreatic cancer cases.

Several ecologic studies showed a positive correlation between age-adjusted death rates for pancreatic cancer and per capita coffee consumption, although relationships by sex and race were inconsistent. Other studies, however, reported no association. The suggestion that coffee was a significant risk factor for pancreatic cancer remained an unresolved question, and if the association did exist, it was weak. It was also reported to occur excessively among occupational workers exposed to coal gas or those employed in coke plants, metal industries and aluminium milling, but the small numbers reported in such studies should be interpreted with caution.

10.2 Investigations

10.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

10.2.2 Evidence Question:

In patients attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

10.2.3 Evidence Statements:

Oesophageal and gastric cancers

Endoscopy and biopsy detect a greater proportion of cases of gastro- oesophageal cancers than radiography. (III)

The prescribing of H2 antagonists or proton pump inhibitors to people with gastro-oesophageal cancers prior to endoscopy and biopsy increases the risk of a false-negative test result. (III)

Pancreatic cancer

In pancreatic cancer, jaundice is usually obstructive and extrahepatic. (III)

Diagnostic investigations in pancreatic cancer include abdominal ultrasound which may be arranged in primary care, and more complex secondary care investigations, for example computed tomography, endoscopic retrograde cholangiopancreatography, and other specialist procedures. (III)

Introduction

Several studies included in the section on symptoms and signs also considered aspects of investigations, in particular upper gastrointestinal endoscopy with biopsy. The evidence statements above therefore were based on the evidence presented in this section but also the evidence reported previously. The studies of pancreatic cancer reported a variety of investigations employed in secondary care, including laparotomy, ultrasonography, axial computed tomography, endoscopic retrograde cholangiopancreatography with or without cytology, percutaneous transhepatic cholangiography, fine needle aspiration cytology, and angiography (Bakkevold et al, 1992(116)).

Secondary studies

Oesophageal and gastric cancers

(Talley et al, 1998)(112)

This US review sought to determine the optimal method of investigating patients with dyspepsia. A MEDLINE and Current Contents search was performed up to April 1997 using the MeSH term 'dyspepsia'.

Endoscopy was reported as consistently providing superior diagnostic accuracy in comparison with radiography. Analysis of the results was limited to descriptions of the findings of oesophagogastroduodenoscopy in patients with dyspepsia although percentages of patients with cancer were reported. In the 36 studies of endoscopy of patients with dyspepsia, the proportion of patients found to have cancer ranged from 0% to 3.3%.

The authors concluded that endoscopy remained 'the gold standard approach because it is still the optimal means of establishing a firm diagnosis'.

Primary studies

(Voutilainen et al, 2003)(114)

Voutilainen and colleagues investigated the impact of clinical symptoms and referral volume of patients with dyspepsia on the detection of gastric and duodenal lesions. Data were collected prospectively on all patients referred for upper gastrointestinal endoscopy by general practitioners in 1996. The included study population was 3378 patients; male to female ratio 1:1.3 and mean age 58 years. Of these, 20 (0.6%) of these were diagnosed with gastric cancer, of whom 14 were referred for with dyspepsia or alarm symptoms.

(Tatsuta 1989)(124)

The accuracy of gastrofiberoscopic biopsy used in a Japanese hospital setting in the diagnosis of malignancies was evaluated by studying operative and postmortem findings. Gastrofiberscopic biopsy was performed during follow- up of all 1331 patients examined from 1968 until 1976, and the diagnosis was confirmed through histology. Biopsy materials and cytologic specimens were examined in two independent laboratories by different doctors without knowledge of the endoscopic diagnosis. Patients were referred to this hospital either because of a radiologic abnormality in the oesophagus, stomach or duodenum or because of persisting digestive complaints without radiological abnormalities and were found endoscopically to have some abnormality in the stomach.

There were 31 (3.7%) false-negative diagnoses of malignancy among 858 patients diagnosed as having benign lesions and three (0.6%) false-positive diagnoses among 473 patients diagnosed as having malignant tumours. The false-negative diagnoses were most frequent in cases of elevated types of early cancer, advanced cancer of type 4 and leiomyosarcoma, or in cases located in the posterior wall and in the antrum. The three benign lesions that were diagnosed as malignant by biopsy were all associated with active ulceration. From these findings the sensitivity and specificity of the gastrofiberscopic biopsy method for detection of gastric malignancies were calculated to be 93.8% and 99.6% respectively and the overall accuracy for all patients was 97.4%. Hence, a correct diagnosis was made in 1297 (97.4%) of 1331 patients with a satisfactory follow-up.

Related articles in health economics for endoscopy referral

Note: The following two articles consider cost-effectiveness of endoscopy in the investigation of dyspepsia, but not specifically in the investigation of suspected upper gastrointestinal cancer. Therefore, extrapolation of the findings to the costs incurred by urgent referral (as in suspected cancer) should be cautious.

(Delaney et al, 2000)(125)

The aim was to determine the cost effectiveness of initial endoscopy compared with usual management in patients with dyspepsia over age 50 years presenting to their primary care physician. 422 patients were recruited and randomly assigned to initial endoscopy or usual management. Primary outcomes were effect of treatment on dyspepsia symptoms and cost-effectiveness. Secondary outcomes were quality of life and patient satisfaction. Total costs were calculated from individual patient's use of resources with unit costs applied from national data.

In the 12 months following recruitment, 213 (84%) patients in the initial endoscopy group had an endoscopy compared with 75 (41%) of the controls. Initial endoscopy resulted in a significant improvement in symptom score (P=0·03), and quality of life pain dimension (P=0·03), and a 48% reduction in the use of proton pump inhibitors (P=0·005). The incremental cost- effectiveness ratio was £1728 (UK£) per patient symptom-free at 12 months. The incremental cost-effectiveness ratio was very sensitive to the cost of endoscopy, and could be reduced to £165 if the unit cost of this procedure fell from £246 to £100.

(Duggan,1999)(126)

A treatment algorithm for the management of upper gastrointestinal disease in general practice has been developed by an international group of general practitioners called the International Gastro Primary Care Group (IGPCG). The algorithm was evaluated to consider the overall cost per patient, showing possible savings over current practice in the UK. Adjustments to the algorithm have been proposed, usually on the basis of variations in the place and timing of Helicobacter pylori testing and eradication, with or without endoscopy.

This paper evaluated the current cost of upper gastrointestinal disease in the UK, the base IGPCG algorithm and the five major alternative scenarios. The original IGPCG algorithm was the least costly option of all those considered, with additional H. pylori testing for all patients with suspected ulcer being the second least expensive option. Routine endoscopy for all patients or for all patients aged more than 45 years were the most expensive scenarios and would require a 16 or 13-fold increase, respectively, in the provision of endoscopy services in the UK. The use of routine endoscopy for all patients aged more than 45 years who were presenting with upper gastrointestinal symptoms for the first time was a mid-priced option, but would still require a five-fold increase in the provision of endoscopy services. The modelling process highlighted the fact that early stratification of patients into diagnostic and treatment groups, on the basis of history and symptom clusters is a less costly approach than that of early routine endoscopy or H. pylori testing. If H. pylori testing is to be used routinely, then the least costly approach is to select those patients who have symptoms that are more indicative of ulcer disease.

All the scenarios considered resulted in lower drug costs than current average UK drug costs per patient per year, and in fewer prescriptions and general practitioner surgery visits per patient. There are several ways in which the management of upper gastrointestinal disease in the UK could be improved with regard to costs and resource utilisation, some of which are presented here.

Before recommending routine endoscopy, however, it would be necessary to address the issue of provision of endoscopy services, since each scenario results in increased numbers of patients receiving endoscopy.

10.3 Delay and Diagnostic Difficulties

10.3.1 Key Clinical Question:

In people attending primary care services with upper gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

10.3.2 Evidence Statements:

Presentation with ‘alarm’ symptoms such as weight loss and dysphagia was associated in some studies with reduced delay by patient and doctor (III).

Delay in diagnosis can be associated with having a normal endoscopy result in the past 12 months (III).

Clinical assessments by either general practitioner or specialist are poor predictors of gastric cancer, in comparison with endoscopy and biopsy (III).

Introduction

The fact that many studies examine factors related to the diagnosis of “early” gastric cancer (for example, cancers at an early stage) rather than early diagnosis has led to discussion amongst researchers about the benefits of prompt investigation. A large number of early cancers are clinically silent and therefore would not present for early investigation. Some of the studies exclusively examine the diagnosis of early gastric cancers, and hence observed survival may be influenced by *lead-time* biased. Most symptomatic cases appear to present as advanced disease, and there is at present no clear evidence that delay in diagnosis

influences survival.

Secondary studies

No secondary papers were identified.

Primary studies

Oesophageal and gastric cancers

(Look et al, 2003)(127)

This Singapore-based study aimed to examine the symptoms of early gastric cancer, and to document in detail the time scale of symptoms and management delays. The authors retrospectively reviewed 44 patients with early gastric cancer treated at a surgical unit.

The median duration of symptoms at the time of diagnosis was 51 days, and 36.4% of the cases had symptoms for more than six months. Epigastric pain was the main presenting complaint in 63.3% of cases, gastrointestinal haemorrhage being the mode of presentation in 27.3% of cases.

The median patient delay, defined as the period from onset of symptoms to first medical consultation, was 30 days; it was more than six months and more than 1 year for 35.9% and 25.0% of the cases, respectively. The median doctor delay, defined as the period between initial medical consultation and definite diagnosis, was 21 days; in 11.4% of cases the diagnosis was delayed at this stage by four months or more.

Patient delay of more than six months was associated with patients being aged 50 or younger (P = 0.04), and with those in whom pain (rather than bleeding or other symptom) was the main complaint (P = 0.05). Doctor delay of more than four months was more likely when there was a previously negative gastroscopy or barium meal in the last 12 months (P = 0.03). The tumour size, location or histological subtype were not associated with the duration of patient and doctor delay.

(Irving et al, 2002)(128)

This UK study aimed to determine the impact of referral guidelines for upper gastrointestinal cancers on delays in the diagnosis in a specialised oesophago-gastric cancer unit.

All patients (N=90) underwent standard history taking by the clinical nurse specialist. The details of referral, investigation and treatment were all obtained, and the dates of a number of events (first symptoms, presentation to general practitioner, general practitioner referral, endoscopy, histological diagnosis, and treatment) were recorded for each patient.

46 (51%) patients were referred before the introduction of referral guidelines, and 44 (49%) were referred after the introduction; 65 patients were diagnosed with oesophageal cancer and 25 with gastric cancer. The overall median delay from the onset of symptoms to histological diagnosis throughout the study was 15.5 weeks. This was made up of patient delay in consulting a doctor (50%), delay in general practitioner referral (33%), and delay in diagnosis (17%).

The introduction of guidelines was associated with a significant decrease in referral time from first general practitioner consultation to endoscopy (median 7.25 to three weeks, P = 0.005). Only 11% (5/44) of patients waited more than four weeks from general practitioner referral to endoscopy compared to 35% (16/46) before the guidelines were implemented (P = 0.008). No significant reduction in total delay (median 25.0 vs. 17.5 weeks, P = 0.11) or change in the stage of disease at diagnosis was identified after the introduction of the guidelines.

(Haugstvedt et al, 1991(129)

The purpose of this paper was to investigate factors influencing delay, and to evaluate the

potential consequences of treatment delay on resectability rate and postoperative morbidity and mortality in patients with stomach cancer.

The study was a sub-study of a large prospective Norwegian multi-centre trial involving 51 surgical units. Out of a total of 1165 eligible patients, the authors had data on patient delay for 939 patients, on doctor delay for 964 patients, and data for total delay for 1000 patients.

The median total delay, defined as the interval between onset of symptoms and start of treatment, was 107 days. The patient delay, defined as the interval in days between onset of symptoms and the date the patient first consulted a physician, was 42 days. The doctor delay, defined as the time interval between the first consultation and start of treatment, was 37 days.

Univariate analyses.

Patient delay was related to weight loss (increasing patient delay with greater loss of weight, P < 0.0001) and hospital level (patients referred to university hospitals had a shorter patient delay than those admitted to local or county hospitals, P=0.025). Doctor delay was longer for women than for men (P=0.013), and more advanced stages of disease were associated with a short doctor delay (P=0.004). Patients admitted to a university hospital had a longer doctor delay than those referred to country or local hospitals (P=0.008). The magnitude of weight loss did not affect the doctor delay. Women had a statistically significant longer total delay than men (P= 0.045), and the proportion of patients with a long total delay increased with increasing loss of weight (P < 0.0001).

Multivariate analyses.

Patients admitted to a university hospital had a shorter patient delay than those admitted to a local hospital (P=0.03). The patient delay was longer in those with excess weight loss (P < 0.0001). Women experienced a longer doctor delay than men (P=0.003). Total delay was associated with the disease stage (P=0.003) and weight loss (P < 0.0001). The findings, revealed by univariate analyses, that women had a longer total delay than men and that the association between disease stage and total delay was of no significance, were not confirmed in the multivariate analyses.

<u>(Suvakovic et al, 1997)(130)</u>

The aims of this UK study were to compare patients diagnosed as having gastric cancer at open access gastroscopy with patients referred through other channels (mainly outpatient clinics) to see whether open access gastroscopy did pick up more early tumours, and to analyse the effect of this on whole district figures. The study also attempted to analyse whether late stage disease was more common in patients with a longer history of symptoms prior to referral.

The authors undertook a retrospective review of patients diagnosed as having gastric cancer during a five year period (1989 to 1994). Patients had been diagnosed either at open access gastroscopy or through conventional referral channels. The retrospective analysis included presenting symptoms, general practitioner diagnosis, hospital records, operative findings, and histological findings in both groups. The primary health care records of 81 of these patients dying from gastric cancer were analysed for previous dyspeptic symptoms (e.g. excluding those leading up to referral and diagnosis), investigations, and acid suppression drug therapy. The findings were compared with 200 age and sex matched controls dying from non-malignant causes during that period.

181 cases were identified (39 cases were diagnosed following open access gastroscopy, 142 were diagnosed following clinic referral or emergency admission). The two groups were similar in terms of age and sex distribution. 21.1% of patients diagnosed through open access gastroscopy had early gastric cancer or stage I disease compared with 10.6% of patients diagnosed through conventional channels. This difference failed to reach significance (χ^2=3.149; P=0.05-0.1). The overall incidence of earlier gastric cancer remained low at 13%, with 87% of patients having greater than stage I disease.

Worrying symptoms (dysphagia, anaemia, or weight loss) were present in 85% (120 patients) of those referred to clinic compared with only 51% (20 patients) of those referred for open access gastroscopy (^{2}=17.43; P<0.001).

Gastric cancer, as specified on the referral form, was suspected in only six patients referred for open access gastroscopy despite the fact that 20 patients had one or more worrying symptoms. General practitioner diagnosis was less clear from referral letters to clinic, but from the details given gastric cancer was a possibility in at least 49 patients (^{2}=4.42; P<0.05). No differences in delay in diagnosis emerged between open access gastroscopy and clinic based referrals although not all cancers were diagnosed at the first gastroscopy (21 were not).

The primary care records of 81 patients dying from gastric cancer indicated a lifetime prevalence of dyspepsia necessitating a consultation with the general practitioner of 73%. This compares with only 22% of the 200 age and sex matched controls dying of non-malignant disease from the same practices (^{2}=56.23; P<0.001). 22 patients had no previous history of dyspepsia. Of 59 patients with a previous history of dyspepsia, 19 had not been investigated. The diagnosis was suspected in only 20 patients at the time of referral. Just under half the patients had been investigated at some time in the past (40 patients). The average time between the onset of current symptoms and diagnosis was 32 weeks, equally split between the time the patient took to consult the general practitioner and the time the general practitioner took to refer the patient to hospital.

82% of patients with a previous history of dyspepsia had received some form of symptomatic treatment prior to a gastroscopy that did not reveal malignancy even though all patients were eventually found to have gastric cancer within three years.

<u>(Martin et al, 1997)(131)</u>

The aim of this UK based study was to examine the time taken to diagnose oesophageal or gastric cancer, identify the source of delay, and assess its clinical importance.

The authors undertook a study of all new consecutive patients (N=115) presenting to a surgical unit with carcinoma of the oesophagus over 16 months, starting in January 1994. Patients were interviewed at first presentation to the department. Dates were recorded according to the patients' recollection and cross-referenced with the patients' notes. Details of the patient's first symptoms, the number of visits to the general practitioner before referral to hospital, and of any relevant drug treatment were recorded. The authors then followed the patients' subsequent clinical course.

The overall delay in weeks was recorded for each patient and divided into four periods: 1) the time from first symptoms to the patient first seeking medical advice; 2) the time from first seeking medical advice to referral for investigation; 3) the time from referral to first attendance at hospital for investigation; and, 4) the time from first attendance at hospital to establishment of a definitive histological diagnosis.

88 patients had cancer of the stomach and 27 cancer of the oesophagus. The median age of the patients when they first developed symptoms was 66 years (range 31 to 89 years). The first symptoms or signs were dyspepsia or indigestion in 19 (17%), dysphagia in 41 (24%), abdominal or chest pain in 48 (28%), nausea or vomiting in 27 (16%), heartburn in 7 (4%), weight loss in 20 (12%), early satiety in 27 (16%), and anaemia in 19 (17%). Some patients experienced more than one symptom.

The median delay from the onset of symptoms to a definitive histological diagnosis was 17.1 weeks for patients with gastric cancer and 17.3 weeks for patients with oesophageal cancer. Overall, delay in consulting a doctor accounted for 29% of the total, delay in referral 23%, delay in being seen at hospital 16%, and delay in establishing the diagnosis at the hospital 32%.

The authors found no significant relation between the nature of the first symptoms and delay

in diagnosis. Similarly no relation was found between diagnostic delay and tumour location. Use of an open access endoscopy service reduced the delay in diagnosis. Overall the median delay for the 65 patients referred directly to the open access dyspepsia clinic was 14 weeks compared with 25 weeks for the 50 who were more conventionally referred (P<0.001).

For patients with stomach cancer there was no clear relation between tumour stage and delay in diagnosis. For oesophageal cancer however, the median delay was 6.7 weeks in patients with stage I and II disease but 20.9 weeks in those with stage III and IV disease (P<0.02).

(Hallisey et al, 1990)(132)

The aim of this prospective study was to see whether investigation of dyspeptic patients aged over 40 after their first consultation with the general practitioner would increase the proportions with early and operable gastric cancers.

General practitioners in ten general practices were asked to refer all patients over 40 making their first attendance during the study period with any degree of dyspepsia. Patients were interviewed and examined by a member of the hospital team within two weeks at a dyspepsia clinic, their symptoms recorded, and endoscopy then performed within one week. 2,659 patients were seen at the dyspepsia clinics and 2,585 attended for investigation. Malignancy was detected in 115 patients (4%), of whom 57 had gastric adenocarcinoma, one had gastric lymphoma, and 15 had carcinoma of the oesophagus. All other malignancies were diagnosed after further investigations and included colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1), liver (1), and gallbladder (1), amongst others.

15 (26%) were of early gastric cancer, according to the rules of the Japanese Research Society for Stomach Cancer. High-risk lesions were identified in 19% (493) of patients, with 10 gastric cancers being identified during longer than 14-month follow up, six of which were early gastric cancers. One early case of gastric cancer was thus detected for every 177 patients examined. Neither the general practitioner nor the hospital doctor were accurate in diagnosing gastric malignancy at any stage of clinical diagnosis. For advanced lesions, the diagnostic accuracy of the macroscopic assessment of the lesion at first endoscopy was high (28 of 41 such cancers being correctly identified), whereas early lesions were reliably identified in only three of the 15 correctly diagnosed.

(Grannell et al, 2001)(133)

The study investigated public awareness of the potentially sinister significance of dysphagia. The authors conducted a community survey amongst healthy pedestrians (N=164) in a busy city centre using a questionnaire to evaluate the subjects' impression of the significance of dysphagia, and compare it with their perception of the significance of breast lump. The information sought was urgency of medical advice, options for care and the probable cause of the symptoms.

75% stated that they would visit the doctor within one week of developing dysphagia (82% of males, 68% of females). Only 17% felt that cancer was a probable explanation for dysphagia compared to 80% who felt that a breast lump could be due to cancer (P < 0.001).

Effect of acid suppression therapy on delay and diagnosis

(Bramble et al, 2000)(134)

The aim of this study was to ascertain the effect of acid suppression therapy, defined as the use of any H_2 receptor antagonist or proton pump inhibitor during the six months prior to the initial (index) gastroscopy, on the diagnostic process and findings for patients with upper gastrointestinal cancer.

The authors undertook a consecutive case study survey of the primary care records of all patients (N=133) who had died of upper gastrointestinal cancer during 1995-97 in one health

district in the UK. The records were used to ascertain factors leading to the initial hospital referral for investigation by gastroscopy, including the time elapsed to investigation, any history of prior acid suppression therapy and any subsequent association between the use of acid suppression therapy and the diagnostic process. In the analysis patients were categorised into two groups: those who had been prescribed acid suppression therapy prior to gastroscopy and those who had not. Results were compared, where applicable, using the ^{2} test with P values (5% significance, 95% confidence limits, one degree of freedom).

85 patients (64%) had gastric adenocarcinoma, 31 (23%) oesophageal adenocarcinoma, and 17 (13%) squamous cell oesophageal carcinoma. Failure to reach the diagnosis of cancer at the index gastroscopy was associated with prior acid suppression therapy. Only one of 54 patients on no treatment or antacids alone was erroneously diagnosed as suffering from benign disease, whereas 22 of 62 patients treated with acid suppression were diagnosed as suffering from benign disease (^{2} = 18.48, P < 0.00002).

Of the 62 patients with upper gastrointestinal adenocarcinoma who were on acid suppression therapy, twenty of 45 patients taking a proton pump inhibitor had a delayed diagnosis compared with two of 17 taking an H_2 receptor antagonist. Overall, 67 patients (including 62 with adenocarcinoma) from the total of 133 had been prescribed acid suppression therapy and in 22 patients (33%) the adenocarcinoma was not diagnosed at the index gastroscopy. The risk of not detecting the true nature of endoscopically observed lesions or of not seeing any pathology at all was greater in patients prescribed proton pump inhibitors (20/45, 44%) compared with H_2 receptor antagonists (2/17, 12%;
χ^2 = 4.42, P<0.05).

(Wayman et al, 2000)(135)

This small UK study reported the healing effect of proton pump inhibitors on early gastric cancer. The authors described a case series of patients (N=7) with ulcerated gastric cancers macroscopically indistinguishable as malignant gastric ulcers at initial (index) endoscopy, and who were inadvertently prescribed a short course of a proton pump inhibitor prior to a second confirmatory endoscopy.

Patients had dyspeptic symptoms and had been referred from primary care physicians for upper gastrointestinal endoscopy. Histological examination of the first endoscopic biopsy specimens of these patients had confirmed the presence of malignancy or dysplasia.

In all cases the patient became asymptomatic, the endoscopic signs seen at the first endoscopy had resolved, and the lesions could not be recognised even by an experienced endoscopist.

(Wayman et al, 1997)(136)

The aim of the study was to investigate the hypothesis that proton pump inhibitor use can delay the diagnosis of gastric cancer. Patients with gastric cancer completed a questionnaire. The time, in weeks, from onset of new gastrointestinal symptoms until first seeking medical advice was recorded, plus the time taken from first attending the general practitioner until obtaining the diagnosis. Prescription for either proton pump inhibitors or H2 antagonists prior to diagnosis was recorded.

The mean presentation delay for all patients was 16.3 weeks and was not influenced by treatment. The mean time to diagnosis in the control group (N=57) from the time of initial consultation was 4.1 weeks compared with 15.5 weeks for cases when proton pump inhibitors were prescribed before diagnosis (P=0.0002). There was no significant difference in delay if patients received H2 antagonists, the mean time to diagnosis being 5.7 weeks (P=0.12).

Pancreatic cancer

No studies on the delay or difficulties in diagnosing pancreatic cancer in primary care were identified.

11 Lower gastrointestinal cancer

General recommendations

1 A patient who presents with symptoms suggestive of colorectal or anal cancer should be referred to a team specializing in the management of lower gastrointestinal cancer, depending on local arrangements. D

2 In patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of 'treat, watch and wait' as a method of management. D

3 In patients with unexplained symptoms related to the lower gastrointestinal tract, a digital rectal examination should always be carried out, provided this is acceptable to the patient. C

Specific Recommendations

4 In patients aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, an urgent referral should be made. C

5 In patients aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms, an urgent referral should be made. C

6 In patients aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding, an urgent referral should be made. C

7 In patients presenting with a right lower abdominal mass consistent with involvement of the large bowel, an urgent referral should be made, irrespective of age. C

8 In patients presenting with a palpable rectal mass (intraluminal and not pelvic), an urgent referral should be made, irrespective of age. (A pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist.) C

9 In men of any age with unexplained[12] iron deficiency anaemia and a haemoglobin of 11 g/100 ml or below, an urgent referral should be made. C

10 In non-menstruating women with unexplained[6] iron deficiency anaemia and a haemoglobin of 10 g/100 ml or below, an urgent referral should be made. C

Risk Factors

11 In patients with ulcerative colitis or a history of ulcerative colitis, a plan for follow-up should be agreed with a specialist and offered to the patient as a normal procedure in an effort to detect colorectal cancer in this high-risk group. C

12 There is insufficient evidence to suggest that a positive family history of colorectal cancer can be used as a criterion to assist in the decision about referral of a symptomatic patient. C

Investigations

13 In patients with equivocal symptoms, a full blood count may help in identifying the possibility of colorectal cancer by demonstrating iron deficiency anaemia, which should then determine if a referral should be made and its urgency. C (DS)

14 In patients for whom the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be in

[12] 'Unexplained' in this context means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (for example, non-steroidal anti- inflammatory drug treatment or blood dyscrasia).

accordance with local arrangements. D

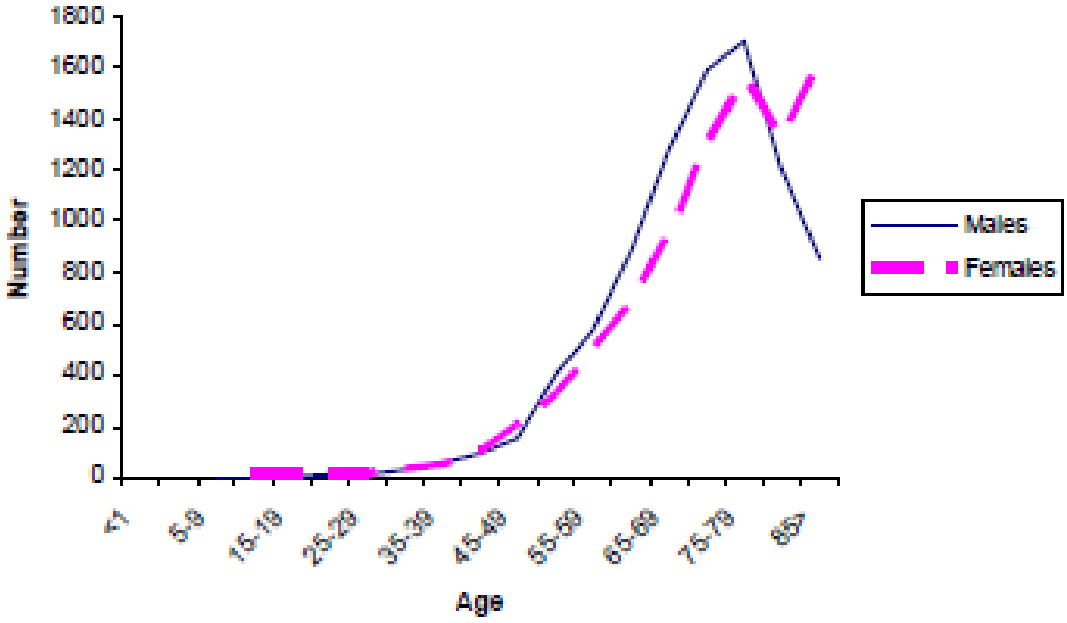
15 In patients for whom the decision to refer has been made, no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended as this may delay referral. D

Introduction

Incidence

Colorectal cancer (cancers of the colon and rectum) accounts for around 13% of all cancers in England and Wales. There were 15,535 new cases in 2001, Incidence is low in those aged 40 years and under, but increases with age in both males and females peaking in those aged 85 years and over.

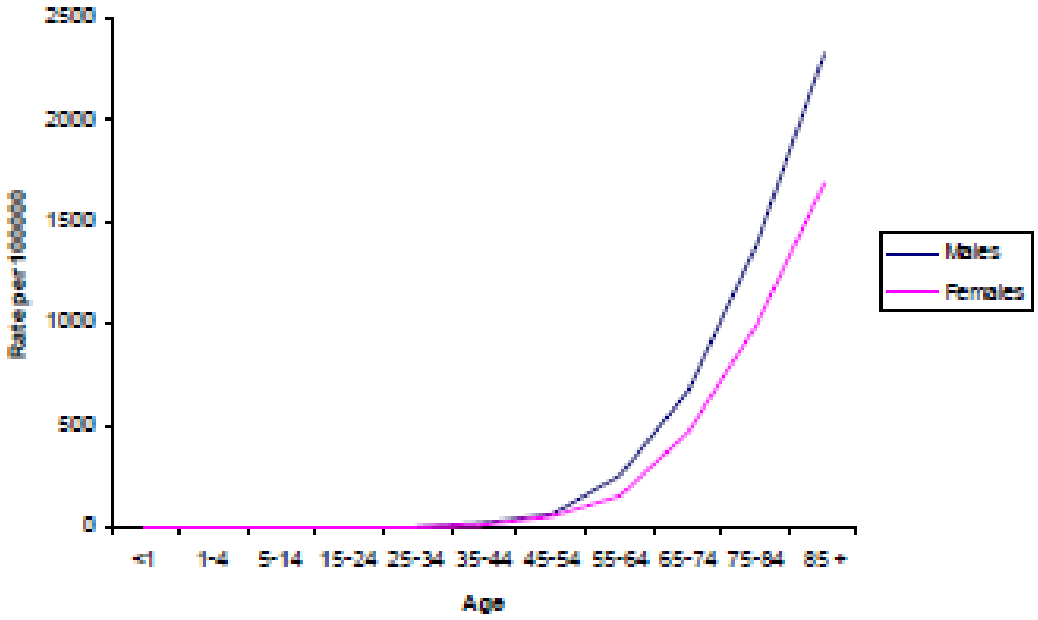
Figure 13 Newly diagnosed cases of malignant neoplasm of the colon in 2001 in England and Wales. (77)



Mortality

Mortality is low in those under 40 years in both sexes but increases steadily thereafter, peaking in those aged 85 years and over. The total mortality from colorectal cancer recorded in 2002 was 9504 of which 4,764 were in females and 4740 in males.

Figure 14 Mortality figures from cancer of the colon for 2002 in England and Wales. (78)



Audits of cancer referrals

The review of cancer referral audits(13) identified 71 audits that had evaluated referrals for lower gastrointestinal cancers. The proportion of two week wait referrals that were found to be in accordance with the guidelines ranged from 53% to 91% (25 audits). The proportion of patients found to have cancer among the two week referrals ranged from 2% to 14% (30 audits). The percentage of two week referrals that were judged by the consultant to require a two week appointment ranged from 52% to 74% (six audits). The percentage of cancer patients that were referred under the two week wait system ranged from 0% to 46% (seven audits).

11.1 Symptoms and Signs

11.1.1 Key Clinical Questions:

How common is the disease in certain population groups, such as age, sex, ethnic groups etc?

Which symptoms, signs and other features raise a suspicion of cancer, and those that make cancer less likely as a diagnosis?
Does family history discriminate patients who should be referred? What is the influence of co-morbidity on suspicion and referral?

11.1.2 Evidence Question:

In people attending primary care services with lower gastrointestinal, symptoms, which symptoms and signs and other features including family history when compared with the "gold standard" are predictive of a diagnosis of cancer; and which symptoms and signs are not?

11.1.3 Evidence Statements:

Colorectal cancer is very rare below the age of 40, and the incidence increases with increasing age thereafter. (III)

The incidence of colorectal cancer is higher in patients who have ulcerative colitis. The cumulative risk is 2.1% at 10 years, 8.5% at 20 years, and 17.8% at 30 years after diagnosis of ulcerative colitis. (III)

Among adults in the general population, rectal bleeding is relatively common (between 9% and 20% for bleeding in the past year in different studies). In most cases, cancer is not the cause (in two studies, the annual incidence was less than 1 per 1000 patients per year). (III)

Other lower gastrointestinal symptoms including change in bowel habit, abdominal pain, mucus, and tenesmus, are experienced relatively frequently by people in the community. Symptoms other than rectal bleeding tend to be more common in people aged 70 or older. (III)

Individual symptoms are poor predictors of cancer. Blood mixed with or on the stool and change in bowel habit were the most consistent predictors of cancer. (III)

Use of a combination of symptoms/signs is more sensitive and specific than single symptoms or signs. The combination of age, bleeding mixed with or on stool, change in bowel habit and raised ESR tended to be most helpful in the studies reviewed. (III)

Iron deficiency anaemia can be the presenting sign of a colorectal cancer, although this diagnosis is not the most frequent cause of anaemia (in one study, cancer accounted for 7.7% of cases of iron deficiency anaemia). (III)

Rectal examinations undertaken in general practice do not detect all cases of rectal cancer, but a suggestive finding on rectal examination is a strong predictor of cancer. (III)

The primary care studies reviewed did not consider the significance of abdominal examination to detect abdominal masses. However, some patients with right sided cancers present with a mass. (III)

The significance of a family history in patients who present with symptoms potentially due to colorectal cancer is not clear. Family history of colorectal cancer or adenomas is associated with an increased risk of cancer among healthy people. (III)

There are differences between ethnic groups in the incidence of colorectal cancer, but the relevance of this finding to the assessment of symptomatic patients in England and Wales is not clear. (III)

In comparison with other cancers, we found a relatively large number of studies of the signs and symptoms of patients presenting to general practitioners who were diagnosed with colorectal cancer. However, most of the studies included only a small number of patients with cancer, and the ascertainment of all patients with lower gastrointestinal symptoms in the presenting population was often incomplete. Furthermore, different studies concentrated on different sets of symptoms and signs. Nevertheless, despite the patchy nature of the evidence, a reasonably consistent description of the symptoms and signs can be identified. With respect to some associated risk factors, several large case control studies have been undertaken, including systematic reviews of such studies.

An economic analysis of different referral options has been undertaken, and is included in Appendix C.

Guidelines

(SIGN, 2003)(137)

This clinical guideline made the following recommendations:

- Patients over the age of 50 years with any of the following symptoms over a period of six weeks should be urgently and appropriately investigated:
- rectal bleeding with a change in bowel habit to looseness or increased frequency.
- rectal bleeding without anal symptoms
- palpable abdominal or rectal mass
- intestinal obstruction. (Grade C)
- All patients with iron-deficiency anaemia (Hb<11g/dl in men or <10g/dl in post menopausal women) without overt cause should be thoroughly investigated for

colorectal cancer. (Grade C)

- Patient groups at risk of colorectal cancer, especially those over 50 years of age, should be informed about significant symptoms and encouraged to seek medical attention early should they develop such symptoms. (Grade D)
- General practitioners should perform a thorough abdominal and rectal examination on all patients with symptoms suspicious of colorectal cancer. (Grade D)
- When a patient presents with suspicious symptoms or signs, they should be urgently investigated and referred to a surgical unit with a declared interest in colorectal cancer. (Grade D).

Secondary studies

(Fijten et al, 1994)(138)

The review was undertaken to investigate the occurrence and significance of overt blood loss per rectum. The search covered 1984 to 1991, and used Medline and the Family Medicine Literature Index (FAMLI). Nine studies were found reporting the occurrence of rectal bleeding in the general population, all concerned with adult patients, although the precise age group varied between studies. Occurrence rates varied from 2% in the last two weeks to 20% in the last year. The positive predictive value of rectal bleeding in the general population was reported in four studies, varying from 3% to 8% for prediction of adenomas and 0% to 1% for carcinomas.

The review did not identify articles on the incidence of overt rectal blood loss among patients consulting in general practice. The authors therefore reviewed data from a national registration project in Dutch general practice that recorded diagnoses, or symptoms if a diagnosis was not reached. The incidence of rectal bleeding without a specified diagnosis was 0.4 per 1000 persons per year. The incidence of bleeding associated with the diagnosis of haemorrhoids was 6.8/1000 consulting persons per year, anal fissure or perianal abscess 3.2, diverticular disease 1.6, colitis 0.8, and cancer 0 per 1000 persons per year. No epidemiologic data on the diagnostic value of rectal bleeding in patients presenting in primary care were found.

The authors of the review estimated from the findings of a single Dutch study that around 0.8 per 1000 persons per year were referred with rectal bleeding by general practitioners to specialists. They went on to estimate the predictive values of rectal bleeding for colorectal cancer from the data they had identified of less than one in 1000 in the general population, two in 100 in general practice, and up to 36 in 100 referred patients. However, these estimates involved several assumptions and they cannot be taken as precise.

(Muris et al, 1993)(139)

A Medline search was undertaken for publications between 1982 and 1991 that investigated the diagnostic value of rectal examination in patients with abdominal pain and urinary complaints. Eight studies meeting the inclusion and quality criteria were identified, but none had been undertaken in a primary care setting. All the studies were carried out in populations selected by referral, adequate gold standards, based on histological evidence. The sensitivity of rectal examination for detecting rectal carcinoma in the two relevant studies were 50% and 24%; in one of these studies the specificity had been estimated as 95%, and likelihood ratio 4.8.

(Hamilton and Sharp, 2004)(140)

Medline and Embase were searched for studies of the common symptoms of colorectal cancer. The major single predictors of cancer were found to be rectal bleeding and change in bowel habit towards looser stools or increased stool frequency. One of these symptoms plus being over 60 was a strong predictor of cancer. Other symptoms in isolation had low predictive power. The review did not find evidence to support the delay of investigation of increased stool frequency for six weeks, and recommended that in the absence of a cause for the diarrhoea, referral should be immediate. Change in bowel habit was the symptom most associated with delay in diagnosis. The review also questioned whether constipation can be regarded as a low risk. It was recommended that in people over aged 70, constipation should not be regarded as a low risk feature.

Primary studies

(Bellentani et al, 1990)(141)

This study was not included in Fijten et al's systematic review.(138) It involved 14 general practitioners in a local health care district in Italy, and the aim was to develop a scoring system for selecting patients at high risk of organic diseases of the colon. The system was intended to exclude organic disease and discriminate between irritable bowel syndrome and organic disease of the colon. Over one year, 254 (103 males and 151 females) consecutive patients who consulted one of the 14 general practitioners for chronic abdominal pain were asked to answer a guided questionnaire. An organic disease of the colon was found in the remaining 102 patients, with diverticulosis and polyps being most common (68.4%). 114 (44.9%) were referred to the gastroenterology service. In 152, (59.8%) the final diagnosis was irritable bowel syndrome, and ten patients had cancer.

Eleven items predicted the diagnosis of cancer in all ten cases. The items and the associated scoring scheme are shown below (note that the scoring system was designed to detect organic disease of the colon and not simply cancer). The mean score for patients with carcinoma was 240, range 123 – 315.

Table 27 Physical features and laboratory tests with associated scores(141)

Physical feature or laboratory test	Score
Visible distension of abdomen	-39
First degree relative with 'colitis'	-35
Feeling of distension	-34
Flatulence	-33
Irregular bowel movements	-26
ESR >17mm/hr	134
Blood in stool	112
Age >45	95
Leucocytosis > 10,000/cc	85
Fever 37-39^{0}C	74
Neoplastic disease in first-degree relative	33

The mean score among patients with inflammatory bowel disease was153 (range –26 to 332), polyps 136 (range – 60 to 374), and for diverticular disease 96 (range – 134 to 314). In predicting organic disease, the sensitivity of the scoring system was 82.4%, specificity 75.6%, and NPV 94.9%.

(Chapuis et al, 1985)(142)

A random sample of community living, well males aged over 50 years were invited to take part in a gastrointestinal survey. Each person was interviewed by a gastroenterologist and underwent flexible sigmoidoscopy. The examination was completed in 319 males (mean age 66 years). One subject had a colorectal carcinoma, and 12 had polyps of more than 10mm in diameter. Forty-four reported rectal bleeding, of whom six had small polpys, two melanosis coli, ten diverticular disease and 11 with haemorrhoids only. The patient with cancer did not report bleeding.

(Dodds et al, 1999)(143)

The sample consisted of patients with rectal bleeding referred to a specialist service in Portsmouth. Of 8438 patients, 252 had cancer. The positive predictive value (PPV) for rectal bleeding plus change in bowel habit was 1:8, for change in bowel habit alone 1:17, rectal bleeding alone 1:18, and rectal bleeding plus perianal symptoms 1:148.

(Fijten et al, 1993)(144)

The aim of the study was to determine the incidence as well as the final diagnostic outcome of rectal bleeding presenting in general practice. 83 general practitioners identified 290 patients presenting to them because of rectal bleeding over a 19 month period (study A). However, because of wide variation in incidence between general practitioners, an additional study (B) was undertaken in which ten general practitioners took additional steps to maximise the catchment rate and ensure that younger patients were not excluded.

In study A, the incidence was 2.2/1000 persons per year (range between practices 1-8). In study B, the mean consultation incidence rate was seven per 1000 people per year. A follow up period of at least one year was applied to establish the final diagnosis. Colorectal cancer was found in 3% of patients with rectal bleeding in study A, and none in study B. The figure of 3% almost certainly is an overestimation of the proportion of people who present to general practitioners with rectal bleeding who will turn out to have colorectal cancer. In about 90% of patients rectal bleeding was related to minor ailments or self-limiting disorders.

(Fijten et al, 1995)(145)

This study was a further analysis of Fitjen et al(144). The objective of the study was to determine the diagnostic value of combinations of signs, symptoms and simple laboratory test results for colorectal cancer in patients presenting with rectal bleeding to the general practitioner (83 general practitioners in the Netherlands). Age, change in bowel habit and blood mixed with or on stool independently discriminated between patients with low and high probability of colorectal cancer (see *Table 28*). The number of patients with colorectal cancer was small (N=9), but Fijten et al reported from their analysis that colorectal was highly unlikely (1% or less) in patients who did not see blood on or mixed with stool, in patients who did see blood on the toilet paper, and in patients without change in bowel habit, with pain at night, with a family history of abdominal disease or with a previous history of rectal bleeding.

Nineteen patients recorded that a first degree relative had an abdominal disease and colorectal cancer (or polyps). However, the study questionnaire did not distinguish between a family history of colorectal neoplasm and other abdominal disease. The authors concluded that the combination of age, change in bowel habit and blood seen mixed with or on stool can serve as a useful diagnostic tool for the prediction of colorectal carcinoma (and overtly bleeding polyps).

Table 28 Diagnostic values of signs and symptoms for colorectal cancer in patients with rectal bleeding (P <0.1)(145)

Signs/symptoms	N	Sensitivity %	Specificity %	PV+ %	100-PV- %	Odds ratio	P
Blood seen							
mixed with stool	14	40	95	14	1.3	5.9	*
only on stool or mixed with only	54	80	79	7	0.5	3.4	*
others or combinations	122	20	53	1	3	0.1	**
unknown	54	44	81	7	2	3.4	*
Abdominal pain	135	29	48	2	4	0.3	*
Change in bowel habit	78	88	72	9	0.5	18.4	***
Pain at night	50	0	76	0	3	0	**
Decreased appetite	42	11	84	2	4	0.7	**
Nausea	68	11	74	2	4	0.4	***
Weight loss	42	44	85	10	2	4.6	**
Family history of abdominal disease	83	0	62	0	6	0	*
Previous history of rectal bleeding	96	0	63	0	5	0	**
Pale conjunctivae	6	13	98	17	3	7	*
Perianal eczema	17	33	95	18	2	8.6	***
Rectal palpation (n=208)							
haemorrhoid	20	22	93	10	3	3.8	*
tumour	1	11	89	100	3	undefined	***

abnormal prostate	2	11	99.6	50	3	31.8	***
Proctoscopy (N=45) abnormal	30	0	30	0	13	0.2	**

N=269
Prevalence=3.3%
*0.1 > P ≥ 0.05
**0.05 > P ≥ 0.01
***P < 0.01

(Goulston et al, 1986)(146)

This article reports findings from a study also published in Mant et al(147). In this study undertaken in Canberra, Australia, 145 consecutive patients aged 40 years and over presenting to a general practitioner with rectal bleeding of less than six months were referred to a specialist for full investigation. Fifteen patients had colorectal cancers (one patient had two cancers). The general practitioners' assessment of the likelihood of cancer as the source of bleeding based on description of symptoms and clinical examination was inaccurate (PPV 20.7%). If they had followed their normal practice on referral, four of 16 cancers would have been overlooked.

(Helfand et al, 1997)(148)

Patients were recruited from those attending walk-in and general medical clinics in Palo Alto, USA. Of the 297 with visible rectal bleeding, 201 underwent double-contrast barium enema, rigid sigmoidoscopy and follow up for up to one year. Ten years later, the diagnosis was verified by review of the medical records. Thirteen (6.5%) of the 201 patients had colon cancer. Two clinical predictors had statistically significant association with cancer – age and duration of bleeding less than two months. Among the 143 patients older than 50 years, the risk of cancer was higher when bleeding had been present for less than two months (18% vs. 6%, P=0.03), but six of the cancers occurred among individuals who had experienced bleeding longer than two months.

(Mansson et al, 1999)(149)

In this retrospective study, the medical records of all subjects from one community (Kungsbacka, in Sweden, with about 46 500 inhabitants) with colorectal, pulmonary, breast or prostate cancer, reported to the Swedish Cancer Registry were reviewed to obtain information about initial symptoms, diagnostic procedures, outcome of diagnostic procedures, level of care, and doctor delay.

There were 42 patients with colorectal cancer, and the presenting symptoms are shown below:

Table 29 Presenting symptoms of patients with diagnosis of colorectal cancer(149)

	N	%
Change in bowel habit	18	43
Tiredness, dizziness etc	17	40
Blood with stool	12	29

Pain	9	21
Gas formation	4	10
Other	5	12

A palpable lesion of the rectum or the observation of a tumour on proctoscopy was a diagnostic sign in 21% of patients with colorectal cancer. However, physical symptoms were not always specified in the records. Nine patients were referred to hospital as a result of the first consultation.

Doctor delay was defined as the interval between first visit at which the symptoms and signs could be attributable to cancer and the time when the diagnosis was clinically confirmed as documented in the records. Median doctor delay for colorectal cancer was four weeks, for breast cancer two weeks, for pulmonary cancer five weeks and for prostate cancer eight weeks.

Twelve cancers were located in the rectum, twelve in the sigmoid colon, seven in the transverse colon, six in the ascending colon, and five in the caecum. Two rectal cancers were diagnosed by means of palpation and two by means of proctoscopy. The remaining rectal tumours were not found at the patient's initial visit in spite of symptoms which could have been related to the tumour.

(Mant et al, 1989)(147)(see also Goulston et al, 1986)(146)

Fifty-five general practitioners in Australia referred all patients aged 40 years and over who presented to them with rectal bleeding. A detailed history was taken followed by investigations that included colonoscopy. 145 patients were eventually fully investigated, 15 (10.3%) being found to have colorectal cancers. Few symptoms and patient characteristics were related to final diagnosis. Patients reporting blood mixed with the stool had a 21% probability of colorectal cancer, a 35% probability of cancer or polyp, and a 44% probability of bleeding coming from a colorectal rather than anal source.

(Metcalf et al, 1996)(150)

This was a prospective study of consecutive patients aged over 40 years who presented with rectal bleeding to 17 general practices in Newcastle upon Tyne. In patients in whom rectal bleeding was the primary reason for the consultation, general practitioners completed a detailed questionnaire to record the presence or absence and duration and features of bleeding, diarrhoea, mucus, change in bowel habit, abdominal pain, weight loss, meleana, and family history of bowel disease. Patients were then referred for colonoscopy. 99 patients were included in the analysis.

Eight (8.1%) patients were found to have carcinoma, 25 (25.3%) polyps, 11 (11.1%) inflammatory bowel disease, 16 (16.2%) diverticular disease, 28 (28.3%) haemorrhoids, and 11 (11.1%) no abnormality. The following symptoms were significantly more likely in cases with serious disease (carcinoma, polyps and inflammatory bowel disease): blood mixed with stool ($P<0.001$), change in bowel habit ($P<0.01$), abdominal pain ($P<0.05$).

However, the sensitivity and specificity of these symptoms were low (sensitivity 25-68%, specificity 25-53%). The high proportion of patients in this study who were found to have serious disease suggests that participating general practitioners failed to enrol all patients presenting with rectal bleeding to the study.

(Muris et al, 1993)(151)

This was a prospective, descriptive study of 578 consecutive patients with non-acute abdominal pain presenting to 11 general practices and followed for 15 months. After 15 months, three of the authors examined the medical records of all patients to collect details of outcomes and further treatment. In the younger age groups relatively more females consulted their general practitioner with abdominal complaints. Eighty percent of the 578 patients

enrolled in the study visited their general practitioner three times or less for abdominal complaints during the follow up period. The duration of pain before the patient presented for the first time varied from some days to more than one year. Eighty-three percent were managed entirely in the practice and 64% received a prescription. Only 20% were investigated in any way by the general practitioner.

No firm diagnosis was made in 47% of patients with symptoms lasting seven days or less, and in 43% of those with symptoms lasting longer than seven days. Irritable bowel syndrome accounted for 11.9% of cases, and no other condition accounted for more than 9%. Only three (0.5%) cases of malignant colorectal diseases were detected. Ninety percent of patients were not having active treatment after 15 months.

(Muris et al, 1995)(152)

This was a one-year prospective study in 80 general practices in the Netherlands. General practitioners notified patients presenting with non-acute abdominal complaints. 933 patients aged 18-75 were included in the study. Information was collected about 23 symptoms and four investigations (white blood cell count, ESR, haemoglobin, faecal occult blood). The symptoms included blood in stool, pain, change in bowel habit, weight loss, vomiting, mucus per rectum and significant past history. Five items were found to predict neoplasms: male sex (OR 2.4), greater age (OR 1.1), no specific character to pain (OR 5.7), weight loss (OR 4.4) and ESR greater than 20 mm/hour (OR 3.0).

(Norrelund and Norrelund, 1996)(153)

In the first stage of this study, 96 general practitioners in Denmark reported information about 208 patients who consulted with rectal bleeding. In the second stage, 112 general practitioners reported information about 209 patients. In the first study, 32 patients had cancer, in the second 13 had cancer. When the findings of both studies were combined, only age (OR 40-69 1.0, 70-79 5.4, 80+ 4.1) and change in bowel habit were associated with cancer (change in habit OR 1.0, no change 0.44). Caution is required in extrapolating these findings to all patients in general practice with rectal bleeding since it is likely that the study general practitioners reported only patients with symptoms they regarded as significant.

(Curless et al, 1994)(154)

The symptoms of 273 patients with colorectal cancer were compared to symptoms reported by a matched sample of 273 people in the community. The sample was divided into two groups: 'young' (under 70 years) and 'old' (70 or above). Among controls, the old group compared with the young more often reported abdominal pain (P<0.05), mucous discharge (P<0.01), faecal incontinence (P<0.05), and change in flatus production (P<0.05). There were no significant differences in regularity and frequency of bowel habit by age group. The old group tended to report the following symptoms more often: tenesmus, change in bowel habit and subjective weight loss, although the differences did not reach statistical significance. Rectal bleeding was the only symptom reported less often by old controls although this did not reach statistical significance.

Table 30 shows the odds of colorectal cancer associated with particular symptoms in the young and old samples. Since the control old patients experienced more symptoms, the odds ratios are lower in the old group. Aspects of this study are also reported in Curless et al.(155)

Table 30 Comparison of the reported frequency of gastrointestinal symptoms within the last year by colorectal cancer cases v community controls by age group ('young' <70 years; 'old' 70 years or greater). Expressed as odds ratio 7AB(154)

	'Young'			'Old'		
	Cases	**Controls**		**Cases**	**Controls**	
Symptom	(N=150)	(N=148)	OR (CI)	(N=123)	(N=125)	OR (CI)
Change in	111	0	418.4*	83	4	64.4

bowel habit			(169.2-1034.7)			(30.0-138.4)
Abdominal pain	81	6	27.9 (14.0-55.2)	59	14	7.3 (4.0-13.5)
Faecal incontinence	27	0	32.3* (8.5-121.9)	23	8	3.4 (1.5-7.6)
Tenesmus	68	7	16.7 (8.4-33.1)	30	14	2.6 (1.3-5.2)
Mucus per rectum	53	3	26.4 (11.0-63.2)	27	13	2.5 (1.2-5.0)
Rectal bleeding	93	21	9.9 (5.8-16.7)	49	13	5.8 (3.0-11.0)
Change in flatus	70	12	9.9 (5.4-18.1)	39	21	2.4 (1.3-4.3)
Anorexia	52	5	15.2 (7.0-33.0)	66	14	9.2 (5.0-16.8)
Weight loss	70	8	15.3 (7.9-29.6)	59	14	7.4 (4.0-13.7)
Bloating	68	17	6.4 3.6 – 11.2	38	28	1.5 0.9 – 2.7
Malaise	57	25	3.0 (1.8-5.1)	60	40	2.0 (1.2-3.4)

(*Estimated OR when cell = 0)

(Stellon and Kenwright, 1997)(156)

This study was undertaken in one small general practice over a period of five years. All patient aged over 50 years found to have iron deficiency anaemia were included. In addition to history and examination, patients underwent faecal occult blood testing, upper Gastro Intestinal endoscopy, flexible sigmoidoscopy and double-contrast barium enema. Patients were followed up for five years. Of the 26 patients investigated, one was found to have a tubulovillous adenoma of the rectosigmoid junction and one had caecal carcinoma.

(Trilling et al, 1991)(157)

This study was undertaken to determine how frequently patients in primary care who present with haemorrhoids also have other significant colorectal disease. Information was obtained from the clinical records of 173 patients of a family practice centre in the USA who had consulted with haemorrhoids. Only one patient had also been diagnosed as having colorectal cancer (detected by the family physician before referral). During the same period, eight colorectal cancers were detected in patients without haemorrhoidal disease. The authors concluded that haemorrhoidal disease is rarely associated with other anorectal disease. It should be noted, however, that in this US population, most patients had undergone examinations (sigmoidoscopy, proctoscopy) leading to a definite positive diagnosis of haemorrhoids.

Risk Factors

Several potential risk factors for colorectal cancer have been identified, but there is no evidence to suggest they are helpful in identifying patients who may need referral.

Secondary studies

Ulcerative colitis

(Eaden et al, 2000)(158)

This study was a meta-analysis of the risk of colorectal cancer in patients with ulcerative colitis, and involved a literature search using Medline to identify 194 studies of which 116 met the inclusion criteria. 54,478 patients in total were included in the identified studies, and these had a total of 1698 colorectal cancers. 9846 patients had total colitis, among whom 700 cancers were found.

The overall prevalence of colorectal cancers in any ulcerative colitis patient, based on 116 studies, was estimated to be 3.7% (95% CI 3.2-4.2%). For patients with total colitis (pancolitis) the overall prevalence of cancer was 5.4% (95% CI 4.4-6.5%). Colitis duration was reported in 41 of the 116 studies. From these, the overall incidence rate was 3/1000 person years duration (95% CI 2/1000 to 4/1000). The corresponding annual incidence rate in the general population given by the Office of National Statistics is 0.6 per 1000 population. 19 studies reported incidence stratified into ten year periods. For the first ten years, the incidence rate was 2/1000 person years duration, (95% CI 1/1000 – 2/1000), for the second decade 7/1000 person years duration (95% CI 4/1000 – 12/1000), and in the third decade 12/1000 person years duration (95% CI 7/1000 – 19/1000). These incidence rates correspond to cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years. Six of the 19 studies reported data for patients with total colitis. Decade specific incidence rates corresponded to a cumulative risk of 2.1% (95% CI 1.0-3.2%) at 10 years, 8.5% (95% CI 3.8-13.3%) at 20 years, and 17.8% (95% CI 8.3-27.4%) at 30 years.

The overall incidence rate for any child was 6/1000 patient year duration (95% CI 3/1000 to 13/1000).

A regression analysis was conducted using data from 21 studies to determine whether age at onset of ulcerative colitis (over 20 years) affected the log incidence rate of colorectal cancers. Overall, a negative trend emerged indicating that a younger age at onset in adults was associated with a slightly increased risk of developing cancer, but this was not statistically significant (z+ -1.61, P+0.11). A further meta regression analysis of 11 studies that reported the age at onset of ulcerative colitis together with the risk at ten yearly intervals also showed that age at onset in adults appeared to have no statistically significant bearing on cancer risk.

This was a good quality review, although some reservations about the primary studies should be noted. Many of the studies in the meta analysis were population based and their inclusion did not rely on contact with gastroenterologists. However, there was a greater likelihood that cancers were detected among those having active follow up as a majority of cases came from surveillance programmes or tertiary referral centres, and very few studies included in the meta analysis used national cancer registry data.

Table 31 Summary of estimated cancer risks(158)

	Unstratified Data			Stratified Data	
	All patients	Total UC	Children	All patients	Total UC
	(41 studies)	(26 studies)	(5 studies)	(19 studies)	(6 studies)
Cancer incidence rate	3/1000	4/1000	6/1000	2/1000	2/1000
at 10 years/1000 pyd	(2 to 4/1000)	(3 to 6/1000)	(3 to 13/1000)	(1 to 2/1000)	(1 to 4/1000)
Cumulative cancer risk (%)	3	4.4	5.5	1.6	2.1
at 10 years	(2.2-3.8)	(2.0-6.8)	(2.5-12.3)	(1.2-2)	(1.0-3.2)
Cancer incidence rate	3/1000	4/1000	6/1000	7/1000	7/1000
at 20 years/1000 pyd	(2 to 4/1000)	(3 to 6/1000)	(3 to 13/1000)	(4 to 12/1000)	(3 to 14/1000)
Cumulative cancer risk (%)	5.9	8.6	10.8	8.3	8.5
at 20 years	(4.3-7.4)	(4.0-13.3)	(4.8-23.1)	(4.8-11.7)	(3.8-13.3)
Cancer incidence rate	3/1000	4/1000	6/1000	12/1000	11/1000
at 30 years/1000 pyd	(2 to 4/1000)	(3 to 6/1000)	(3 to 13/1000)	(7 to 19/1000)	(4 to 28/1000)
Cumulative cancer risk (%)	8.7	12.7	5.7	18.4	17.8
at 30 years	(6.4-10.9)	(6.0-19.3)	(7.2-32.6)	(15.3-21.5)	(8.3-27.4)

Values are mean (95% confidence intervals)

Pyd, person years duration.

Family history – hereditary nonpolyposis colon cancer (HNPCC)

(Burke et al, 1997)(159)

Studies of cancer risk, surveillance and risk reduction in individuals genetically susceptible to colon cancer were sought through a search of MEDLINE 1990-
1995. Hereditary nonpolyposis colon cancer criteria include (1) at least three relatives with histologically verified colorectal cancer; (2) at least two successive generations should be affected; (3) in one of the relatives, colorectal cancer should have been diagnosed before age 50 years. The condition is genetically heterogeneous, and four genes are estimated to account for 73% of the families with the condition.

The risk of colorectal cancer in people with confirmed HNPCC was estimated to be 68% to 75% by age 65, although the average age at diagnosis is 45 years. The risk of a new primary after limited resection for a first cancer was also high at 30% after ten years. Endometrial cancer was the second most common cancer seen in HNPCC.

Skin tags

(Radack and Park, 1993)(160)

A systematic review was undertaken of articles identified by search of Medline for all relevant studies from 1983 until January 1992 to assess the clinical utility of skin tags (skin appendages occurring on almost any part of the body, especially the axilla, neck, or groin) as a biomarker for colonic polyps. The article aimed to identify subjects at increased risk of adenomatous colonic polyps (a predisposing factor in colon cancer) that could lead to earlier recognition of either polyps or colon cancer. Of the 15 reports, ten with sufficient data were eligible for analysis. Only four of the ten studies reported a statistically significant association between skin tags and colonic polyps; the remaining studies reported outcomes indicating no association.

Significant statistical heterogeneity across studies indicated sharp differences in the direction and magnitude of the odds ratios for the association between skin tags and colonic polyps (Chi square test of homogeneity = 37.42, nine degrees of freedom; $P<0.005$). The marked disparity prevented meaningful pooling of the individual data.

Limitations potentially responsible for the varying outcomes included lack of blinded ascertainment of clinical information, noncomparability of subjects, differing diagnostic investigations of the colon, and uncontrolled confounding. All but one study were performed in a tertiary care setting, seriously limiting the relevance of the results to the “average” subject seen in primary care settings. There was variability in study populations, methods of diagnostic evaluation and the control of possible confounders (for example age and sex) that could affect the potential relationship. For these reasons, the review did not provide a reliable estimate of any association between skin tags and polyps.

11.2 Investigations

11.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

11.2.2 Evidence Question:

In people attending primary care services with lower Gastro Intestinal symptoms, which investigations when compared with the “gold standard” are predictive of a diagnosis of cancer, and which are not?

11.2.3 Evidence Statements:

Biochemical markers, including CEA, are not sufficiently sensitive or specific to be used as a diagnostic aid (III)

The principal investigations are double contrast barium enema, colonoscopy, and flexible sigmoidoscopy (III).

Competence in colonoscopy and flexible sigmoidoscopy improves with experience (III).

In symptomatic patients, the sensitivities, specificities, and positive predictive values of faecal occult blood tests are too low to make these tests helpful (III).

Laboratory tests (haemoglobin, ESR, white blood cell count) have low sensitivity in detecting colorectal cancer (III).

Symptom score questionnaires have been investigated for use among referred patients, but insufficient evidence is available about their use in primary care (III).

Two relevant secondary studies and two primary studies were identified. No study was entirely satisfactory for our needs. Several related to investigations in referred patients, and extrapolation to primary care attenders requires caution. No primary care study included adequate numbers of patients with and without rectal cancer, a full range of presenting symptoms (i.e. inclusion of patients with symptoms other than rectal bleeding, or an adequate 'gold standard' (colonoscopy).

Secondary studies

(Duffy et al, 2003)(161)

These guidelines of the European Group on Tumour Markers (EGTM) were an extensive review of relevant evidence. The most widely used biochemical marker was carcinoembryonic antigen (CEA), a high molecular weight glycoprotein that has been implicated in cancer metastasis. CEA was not sufficiently sensitive (30-40%) or specific (87%) to be used as a diagnostic aid. For example, it can be elevated in the absence of malignancy. CA 19-9 is the most widely investigated gastrointestinal tumour marker, but is less sensitive than CEA in the detection of colorectal cancer. Other markers including CA 242, tissue polypeptide antigen (TPA), tissue polypeptide- specific antigen (TPS), and TIMP-1 were under investigation, but there was insufficient evidence to indicate whether they have a role either singly or in combination in the early detection of colorectal cancer. Preliminary investigation of cell and tissue markers such as cellular oncogenes and tumour suppressor genes suggested that these may be sensitive and specific markers for use in early detection, but confirmation is required in further research. However, these markers were unlikely to be specific for colorectal cancer, but would probably occur in other cancers.

(NHS Centre for Reviews and Dissemination, 1997)(162)

This review was undertaken to support the NHS Service Guidance on Colorectal Cancer, and was focused on management, although it included some consideration of diagnostic methods. The methods discussed did not include blood tests for anaemia or raised erythrocyte sedimentation rate (ESR). The review concluded that the large bowel may be completely examined by one of two methods: colonoscopy, or sigmoidoscopy plus double-contrast barium enema. These methods have similar yields and costs, although their equivalence depends on operator competence. Colonoscopy can produce reliable results if the tip of the colonoscope reaches the caecum or proximal end of the colon ('completion'). Completion rates of up to 85% have been reported in studies, although rates achieved in routine practice may be lower. Colonoscopy technique improves with practice; in one study of training, physicians were normally able to achieve a completion rate of 80% after 50 colonoscopies, rising to 95% after 200.

Competence in flexible sigmoidoscopy can be achieved after 24-30 examinations.

Primary studies

(Steine et al, 1994)(163)

Information about the investigations undertaken prior to referral for barium enema was obtained from patients and referral letters (83% from general practitioners). The study does not contain information about the utility of tests, but does show that 76% of patients had a haemoglobin test, although a rectal examination was performed in only 45%.

(Muris et al, 1995)(152)

This was a prospective observational study in 80 general practices in the Netherlands. 933 patients presented to their general practitioner with new non-acute abdominal complaints lasting two or more weeks. A structured history was obtained, an examination performed, and the following laboratory tests undertaken: haemoglobin, white blood cell count, ESR, faecal occult blood (three times, with peroxidase-free diet). 24 (2.6%) of the sample of 933 were diagnosed to have cancer during the following year. Multiple logistic regression was used to estimate the odds of cancer given certain symptoms, signs and investigation results. Only an ESR greater than 20mm/hour was associated with a diagnosis of cancer (odds ratio 3.0 [95% CI 1.1-8.2]). The paper did not report sufficient data to enable the sensitivity or specificity of a raised ESR to be calculated.

(Pierzchajlo et al, 1997)(164)

This study reports a case series of 751 colonoscopies performed by a family physician in the US. Completion was achieved in 91.5%. Only three cancers were identified. No patient suffered a complication resulting in death or necessitating surgery.

(Meyer et al 2000)(165)

In this study, a random 5% sample of Medicare claims relating to gastrointestinal endoscopy were investigated to compare patients examined by generalists and specialists. Only 7.7% of colonoscopies were performed by generalists, although they performed higher proportions of rigid sigmoidoscopies (35.2%) and flexible sigmoidoscopies (42.7%). Specialists were more likely to perform the procedure to investigate cancer.

(Rodney et al 1987)(166)

An educational course on flexible sigmoidoscopy was delivered to 114 physicians. After the course, the physicians reported undertaking more examinations. The study was limited to a simple survey of course participants, and gives no information about the sensitivity or specificity of flexible sigmoidoscopy by family physicians for the detection of lower colorectal cancer.

(Fijten et al, 1995)(145)

This study was a further analysis of Fitjen et al, (1993)(144). The objective of the study was to determine the diagnostic value of combinations of signs, symptoms and simple laboratory test results for colorectal cancer in patients presenting with rectal bleeding to the general practitioner (83 general practitioners in the Netherlands). The tests were haemoglobin, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and faecal occult blood. The sensitivity, specificity and positive predictive value (PPV) of these tests are shown in *Table 32*. In a multiple logistic regression that included symptoms and signs, none of the tests were significant independent predictors of colorectal cancer in patients with rectal bleeding.

Table 32 Diagnostic values of laboratory test results for colorectal cancer in patients with rectal bleeding (Fijten et al 1995(145))

Laboratory test results	N	Sensitivity	Specificity	PV +	Odds	P

		%	%	%	ratio	
Haemoglobin						
low (♀<7.5mmol/l, ♂<8.5 mmol/l)	14	33	95	14	8.8	***
ESR						
high (♀>28mm/h, ♂>12mm/h)	23	40	91	9	6.3	**
high (>30mm/h)	12	40	96	17	14	***
White blood cell count (n=219)						
high (> 10^9/1)	25	75	90	12	26.3	***
Haemoccult ≥ 1 positive out of 3	41	50	82	5	4.6	*

n = 225; Prevalence = 2.2%; *0.1 > P ≥ 0.05; **0.05> P ≥ 0.01; ***P < 0.01.

(Sorensen et al, 1992)(167)

The number of proctoscopies performed by general practitioners and the Duke's stage at diagnosis of rectal cancer were compared using information on a central register of general practitioner activities and a cancer register. No association was identified between numbers of proctoscopies performed per year and the stage of cancer. The study did not collect patient-level data about proctoscopy examinations.

(Church, 1991)(168)

This study included 269 patients presenting to a colorectal surgery department. Bleeding was categorised into outlet (bright red blood during or after defaecation, on the toilet paper or in the bowl, with no family history of colorectal neoplasia and no change in bowel habit), suspicious (dark red blood and/or blood mixed with stool, any bleeding with a family history or past history of colorectal neoplasia, bleeding in association with a change in bowel habit or the passage of mucus), haemorrhage (large bleed needing urgent admission and transfusion of one or more units of blood), and occult (rectal bleeding and anaemia, or positive stool occult blood test). All patients underwent colonoscopy. The findings of colonoscopy were compared to the results of barium enema in a group of patients who had undergone radiology before referral. With colonoscopy as the gold-standard, sensitivity of barium enema was 75%, specificity 43%, PPV 71% and NPV 47%.

(Tate et al, 1990)(169)

Three different faecal occult blood tests (Haemoccult, Fecatwin, E-Z Detect) were compared in a sample of patients referred for investigation by double- contrast barium enema (used as the gold standard). The sensitivities of the tests were 80.0%, 93.3% and 57.1% respectively; the specificities were 88.8%, 71.6%, and 88.9%; the PPVs were 32.7%, 13.3% and 19.0%. The authors concluded that a negative Haemoccult test should not influence the management of symptomatic patients because treatable disease would be missed. Fecatwin is more sensitive, but the number of false positives was high (a positive result in a symptomatic patient would have just over a 1:8 chance of being due to colorectal cancer).

11.3 Delay and Diagnostic Difficulties

11.3.1 Key Clinical Questions:

In people attending primary care services with lower gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with lower gastrointestinal

symptoms/signs may or may not need urgent referral with suspected cancer?

11.3.2 Evidence Questions:

In people attending primary care services with lower gastrointestinal symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with lower gastrointestinal symptoms/signs may or may not need urgent referral with suspected cancer?

11.3.3 Evidence Statements:

Delay

There are no associations between personal characteristics such as age and social class and patient delay. Personal advice to go to the doctor is important in reducing delay. (III)

Delay in consulting for rectal bleeding is unrelated to age, sex, ethnic origin, competence in English, length of schooling, social status, availability of social support, measured psychological traits, and to the belief that the cause might be cancer. (III)

Overall delay does not differ significantly between male and female patients, although men are more likely to have patient-related delay. (III)

Patient delay can be the result of not knowing the importance of bowel symptoms. (III)

The most common reason for delay or failure to consult is thinking that the bleeding is not serious, or is caused by haemorrhoids. (III)

The second most frequently reported reason for delay or failure to seek care is the fear that the resultant tests will be unpleasant or embarrassing. (III)

Patients consult more quickly if their symptoms produce considerable initial discomfort and embarrassment, or have abdominal pain, nausea or vomiting. (III)

Colorectal patients with more advanced disease at diagnosis have more noticeable symptoms and are less likely to delay, as are also those with another chronic disease. (III)

No association is demonstrated between general practitioner delay and patient social class, age, physical isolation, or the regular consulting rate of the patient. (III)

Failure to investigate iron deficiency anaemia, and perform rectal examination at first consultation have been linked with inappropriate referral and increased delay. (III)

Not recognising symptoms suggestive of colon carcinoma increases delay. (III)

Initial referral to a non-surgical specialty appears to contribute to delay. (III)

Failure to undertake a rectal examination of patients with rectal symptoms is associated with delay in referral of patients with rectal cancer (III).

Diagnostic Difficulties

Lower gastrointestinal symptoms are common in people attending primary care, and symptoms become more frequent with increasing age (III).

Most general practices do not undertake sigmoidoscopy; a few do not undertake proctoscopy (III).

A family history of colorectal cancer is common among people attending primary care (III).

Delay

Introduction

In establishing a diagnosis of colorectal cancer there are three stages that may be associated with delay: the time from initial symptoms to the first visit to a doctor (patient-related delay), the time from the first visit to referral for specific investigations (general practitioner-related delay), and the time from referral to final diagnosis and treatment (hospital-related delay). This paper outlines the evidence surrounding the psychosocial and socio-demographic factors - including age, sex, ethnicity and socio-economic status - that influence both patient-related and general practitioner-related delay. Hospital delay is usually related to the positive predictive value of diagnostic investigations (covered elsewhere), or either to organisational aspects of secondary care that are beyond the scope of these guidelines. It is, however, not always possible for a given study to clearly distinguish between general practitioner and hospital related delay because of imprecise definition of the study outcomes.

All evidence we have identified is exclusively based on observational studies of similar grade of evidence. Most studies evaluate the factors that cause delay within a relatively small sample of patients, and information about the psychosocial and socio-demographic profile of patients is usually either absent or incomplete. It appears from the evidence that follows that delay in diagnosis is mostly related to the symptoms patients experience and their beliefs about them, and the readiness of general practitioners to examine patients at the first consultation, together with their suspicion thresholds. The few studies that have examined the relationship between socio-economic status or ethnicity and diagnostic delay have generally identified a non- significant association. More research into this issue may be warranted.

Secondary studies

(NHS Executive, 1997)(170)

The authors of this guidance undertook a systematic review of studies that examined reasons for the delay between the onset of symptoms of colon or rectal cancer and treatment. They identified 12 retrospective observational UK studies that gave figures for delay. Relatively short delays by clinicians appeared to be linked with active encouragement to investigate all cases in which there is any suspicion of cancer. Some general practitioner delay appeared to be due to misdiagnosis, most commonly the assumption that symptoms were caused by haemorrhoids. Inadequate investigation, notably of anaemia, could increase delay. There was evidence of failure by some general practitioners to carry out adequate rectal examination, leading to delay. In studies that investigated patients' reasons for delaying consulting, respondents were most likely to report that they did not consider that their symptoms were likely to signify serious illness. Hospital delay may be caused by false negative results of investigations such as barium enema and endoscopy.

Primary studies

(Young et al, 2000)(171)

This retrospective observational study sought to assess the incidence and reasons for delay in the diagnosis of colorectal cancer, and the effects of delay, gender, age and tumour site on the stage of disease. Delay was defined to have occurred if more than a three month period had lapsed from the time when initial symptoms were clearly established to the time of operation.

For 100 patients presenting with colorectal cancer to a hospital based colorectal unit during a one year period, the authors collected data on principal presenting symptoms, time to first presentation to a doctor, time to diagnosis and treatment, reasons for delay, diagnostic procedures, tumour site, operation, and Australian clinicopathological stage of the tumour. Only symptomatic patients with invasive adenocarcinoma who underwent excisions of their tumours were included in the study.

34 patients were diagnosed and treated more than three months from the onset of symptoms. The overall distribution of delay did not differ significantly between male and female patients,

although men were more likely to have patient-related delay (31% of men vs. 10% of women; P=0.011). The mean age of the delay group was not significantly different to the non-delay group (mean: 69.4 vs. 71.0 years; P=0.53). In the 18 patients with patient-related delay alone, 16 were due to a delay in presentation. Reasons why these patients had presented late were not easy to quantify, but included: not seeking medical help until the symptoms (bleeding, abdominal pain, anaemia) were severe (4); not being concerned by symptoms (change in bowel habit, abdominal pain) (4); assuming that bleeding was due to haemorrhoids (2), hoping that the bleeding would go away (1), and no reason at all (5). The other two patients in this group had refused investigations recommended by their doctors after initial visits, and both delayed for 24 months.

Of the 13 patients with doctor-related delay alone, in seven patients symptoms had not been adequately investigated. Five had an incorrect original diagnosis (haemorrhoids, N=2; peptic ulcer, N=1; biliary colic, N=1), and for two patients the doctor was slow to investigate symptoms. Three patients experienced delay because an initial rectal examination was not performed. One sigmoid cancer was missed on barium enema with a resulting 11.5 month delay; another cancer was missed on colonoscopy with an 11 month delay. One other patient failed to be diagnosed on both colonoscopy and barium enema which resulted in a 12 month delay. All 13 patients with doctor-related delay alone had presented within three months from the onset of symptoms.

For the three other patients with both patient-related and doctor-related delay (>six months total delay), the delay was a combination of the patient's failure to seek help early enough because of competing pressures or misperception of the symptoms' significance, and the doctor's incorrect initial diagnosis or slowness to investigate.

(Robertson et al, 2004)(140)

This study reviewed the presentation of cases of colorectal and breast cancer in three Scottish health boards, 1997-8. A total of 1071 cases of colorectal cancer were included. The mean time from presentation to treatment was 138 days for colorectal cancer, but was faster for those in the 50-64 age group and for women. A history of abdominal pain, tensmus or presence of an abdominal mass decreased the time to treatment. People with a history of anxiety and depression were only half as likely to be treated within 90 days, and those on iron therapy at presentation were more likely to be treated quickly.

(Potter and Wilson, 1999)(172)

This was a one-year retrospective audit carried out in a specialist teaching hospital to calculate the time to diagnosis for colorectal cancer from first hospital attendance, and to identify any remedial factors felt to contribute to an undue delay in diagnosis.

The authors inspected the hospital records of 59 patients who were undergoing surgical resection for colorectal carcinoma. Twenty patients (34%) waited more than 30 days for their diagnosis. Incomplete examination or initial referral to a non-surgical specialty appeared to contribute to this delay. Rectal examination was documented in 23 (39%) general practitioner referrals and 52 (88%) the hospital case notes at initial consultation. The reason for the delay in diagnosis was deciding on an alternative diagnosis leading to no initial gastrointestinal investigation in 13 patients; in seven patients, despite initial suspicion of colorectal cancer with gastrointestinal investigation, the diagnosis was missed (of these patients, four were incompletely investigated as recommended by guidelines current at the time of the study). The general practitioner had organised a colonoscopy or barium enema for 13 patients (22%) prior to referral. The same investigations were arranged after first hospital consultation in 34 (58%) patients.

(Crossland and Jones, 1995)(173)

The aim of this study was to determine the prevalence of rectal bleeding in the community, and to examine factors that lead patients to consult their general practitioners about rectal bleeding. 1,200 patients completed a questionnaire on whether they had consulted a doctor for any of a variety of lower bowel symptoms. 287 admitted to having noticed rectal bleeding at some time in their lives, and 231 had noticed it within the previous 12 months. Bleeding was most commonly reported by those aged under 50. Only 118 (41%)

respondents who had noticed rectal bleeding had sought medical advice. Patients aged over 60 were most likely to have consulted a doctor, and those aged 40-60 were least likely to have done so (56% vs. 34%, P<0.022). Patients with blood in their stools were more likely to have consulted a doctor than were those who had seen blood on the paper only (53 vs. 64, P<0.001).

Sixty of the respondents (30 consulters, 30 non-consulters) who had experienced rectal bleeding in the previous 12 months were then interviewed in order to assess their reasons for consulting or not consulting a doctor. The most common reason given for consulting a doctor was worry that rectal bleeding might be a sign of serious disease, the next most common reason given was that the bleeding and associated symptoms were causing pain, discomfort or embarrassment. For others the consultation arose while consulting for another reason. The main reason for not consulting a doctor was the belief that the bleeding was not serious. Most non-consulters thought that haemorrhoids were the cause of their bleeding. Haemorrhoids were recognised as the most common cause for rectal bleeding by respondents in the two groups, while cancer was recognised as the second most important cause, also in both groups. Most respondents, whether they had consulted a doctor or not, had also discussed their rectal bleeding with a relative or friend before consulting a doctor.

(Goodman and Irvin, 1993)(174)

The case records of 152 consecutive patients with carcinoma of the right colon admitted to a single surgical unit were examined to assess the incidence of delays in the treatment, reasons for the delay and effects on survival. Treatment of right-sided colonic cancer was delayed for more than 12 weeks in 61 patients (40%). The factors involved in delay included late presentation to the general practitioner (17 patients), failure of the practitioner to investigate or refer the patient (18), and failure of hospital clinicians to investigate or diagnose the illness (36). The most common error on the part of general practitioners was failure to determine the cause of iron-deficiency anaemia (16), which was also a frequent error (17) during hospital management if the anaemia was an incidental finding during treatment of another illness.

(Byles et al, 1992)(110)

The aims of this study were to estimate the incidence of rectal bleeding in the community, and to determine the proportion of individuals who delay or fail to seek medical advice after a first episode of rectal bleeding. The authors interviewed 1,213 individuals who had taken part in a large-scale general population survey of the health practices and attitudes of individuals, and who had admitted to a first episode of rectal bleeding within the last five years. 239 people (20%) reported noticing rectal bleeding at some time in their life. Of the 77 individuals who had noticed a first occurrence of rectal bleeding more than three months but less than five years prior to the interview, 23 (30%) had either not sought medical advice or had only done so after a period of delay. The most commonly reported reason (52%) for delay or failure to consult was thinking that the bleeding was not serious and would clear up by itself. The second most frequently reported reason (13%) for delay or failure to seek care was the fear that the resultant tests would be unpleasant or embarrassing.

(Dent et al, 1990)(175)

The aim of this study was to identify demographic or psychological factors, or beliefs or behaviours related to delay in presentation of rectal bleeding. The authors interviewed 93 patients, aged 35 years and older, who consulted their general practitioners because of rectal bleeding. Delay ranged from 0 to 249 days with a median of seven days; 29% delayed more than 14 days. Delay was unrelated to age, sex, ethnic origin, competence in English, length of schooling, social status, availability of social support, psychological traits, and to the belief that the cause might be cancer. The proportions delaying more than 14 days were statistically significantly elevated among those who were not worried by the bleeding (47% delayed), those who did not regularly look at their faeces or the toilet paper after use (37%), and those who took some other action before presenting to their general practitioner (43%). The main reasons given for delay were that the patient believed the bleeding was caused by haemorrhoids, it was of minor concern, and that it was not convenient to see a doctor when the bleeding first occurred.

(Mor et al, 1990)(176)

In this study, patients with a hospital diagnosis of lung, breast, and colorectal cancer were requested to participate in one home and two telephone follow- up interviews over the one-year period following diagnosis in an attempt to investigate the determinants of cancer symptom recognition and delay in seeking medical care.

24.6% of patients who reported noticing symptoms prior to diagnosis delayed longer than three months in seeking medical care. No demographic or social support factors were predictive of symptom recognition or delay, with the exception that older patients with colorectal cancer were less likely to notice symptoms, but also less likely to delay (patients in the youngest age category were almost three times more likely to delay than patients in the oldest age category; OR=2.76; 95% CI=1.10,6.91). Patients with more advanced disease at diagnosis were less likely to delay (P<0.5), as were also those with another chronic disease (P<0.5).

(Ratcliffe et al, 1989)(177)

The aim of this study was to examine delay in patients with colorectal cancer, those with risk factors and those with diverticular disease, and to assess the influence of delay on stage of disease at presentation, and patient survival. Patients with large-bowel cancer, as recorded in three consultant surgeons' databases, were interviewed about the history and duration of symptoms, and family history. The site of the tumour and Duke's staging were recorded from the operation notes. Left-sided cancers had a significantly shorter general practitioner delay. There were no significant differences between total delay times for patients with risk factors, family history or diverticular disease and those patients without risk factors or diverticular disease (patients with risk factors had previously had a colon cancer or adenomatous polyps removed, or the diagnosis of ulcerative colitis, or Crohn's disease established). There was no significant difference in delay times between the three Duke's stages.

(Funch, 1988)(178)

Data from a sample of 294 patients with colorectal cancer were used to examine factors influencing symptom reporting. The number of symptoms reported spontaneously by the subjects in response to open-ended questions was compared with the total number of symptoms reported using this technique plus a variety of other techniques. Of the symptoms reported, 54% were reported spontaneously by the subjects. Subject and symptom characteristics were examined for an association with symptom reporting patterns. Subject characteristics associated with spontaneous reporting were higher socio-economic status, better prior health status, and psychological status (more depressed) at the time of the interview; age and sex were not related to symptom characteristics, with symptoms that were severe, unusual, and developed quickly being reported more often. Incomplete symptom reports also were associated with inaccurate estimates of patient delay.

(MacDonald and Freeling, 1986)(179)

The aim of this study was to determine from a group of people aged 55 years and over their present experience and beliefs concerning bowel habit, their understanding of the terms "regular", "diarrhoea", "constipation", and what they would do if they had a change in bowel habit. The authors mailed a questionnaire to a randomly selected 10% (266) sample of patients, aged 55 years and above, registered at a group general practice. The questionnaire consisted of both structured and open questions.

10% of the respondents reported no predictable frequency of movement, with women more likely to report so (14% vs. 5%). 79% believed that a daily movement is important and 90% that "regularly" is necessary for good health. 14% were dissatisfied with their bowel habits and 16% regularly self-treated.

95% gave reasonable definitions of "regular" and "diarrhoea", 10% were unsure about the definition of "constipation". Although 76% believed there were bowel symptoms that require immediate medical attention, 98% would in the first instance treat themselves for constipation, 90% for diarrhoea, and 25% for rectal bleeding. Bowel symptoms for which a doctor should be seen without delay included passing blood (41%), pain (19%), constipation

(16%), diarrhoea (12%), and “anything unusual” (9%). A third of respondents had in fact consulted a doctor about their bowels at some time prior to the questionnaire. A greater proportion (42%) of those aged 65-74 years had done so than those in other age groups. The reasons for which they consulted were: constipation (25%), pain (21%), bleeding (12%), diarrhoea (12%), and piles (9%). All comparisons are significant at the P<0.05 level.

(MacArthur and Smith, 1984)(180)

127 patients with large bowel cancer were interviewed shortly after having received treatment to identify factors associated with delay in presentation, diagnosis, and referral for treatment (patient delay, general practitioner delay, and hospital delay). Further data were obtained from general practitioners and abstracts from case notes.

Of those patients included in the study, 45% had consulted within a month, although few did so within a week of first noticing their symptoms. 28% delayed more than three months before consulting a doctor. The authors found no associations between personal characteristics such as age or social class and patient delay. Personal advice to go to the doctor was important in reducing delay. Patients with abdominal pain, or nausea and vomiting as an initial symptom, went more quickly to the doctor; those with both these symptoms went most quickly. Symptoms associated with long delay were loss of weight and rectal discomfort or pain. Patients with cancer of the colon were more likely to experience the symptoms of abdominal pain and vomiting, and this explains why they delay less than patients with rectal cancer.

Only 32% of patients in this study were referred to a specialist immediately. 30% of the patients were delayed for longer than three months. Mean delay was 120.5 days and median delay 25.3 days. There was a little more delay in patients with cancer of the rectum than colon. The nature of the symptoms the patient presented to the doctor did not play a large part in affecting this phase of delay; patients with constipation were referred a little more quickly than patients with diarrhoea or those with only one symptom. Patients from the manual social classes also waited a little longer than middle class patients. Examination of patients by the doctor at the first consultation was found to be associated with the speed of referral. Median delay for patients who had been examined was 1.5 compared with 89.5 days in the 42 cases where no physical examination took place. A longer duration of symptoms did not seem to prompt the doctor into more immediate action.

Most patients (90.5%) reported that they had not considered cancer as a possible cause of their symptoms and had delayed consulting their doctor until such symptoms became either more severe or more persistent. The only patients who consulted quickly were those whose symptoms produced considerable initial discomfort.

(Holliday and Hardcastle, 1979)697}

The authors of this study interviewed 200 patients admitted to hospital with colon or rectal carcinomas. They recorded data on the following: total duration of symptoms, delay in presentation to the family doctor, number of visits to the family doctor, type of clinical examination performed, and department to which the patient was referred.

Mean delay between the onset of symptoms and treatment was 30.5 weeks in a hundred patients with colon carcinoma, and 38 weeks in a hundred patients with rectal carcinoma. Most of this delay occurred outside hospital, and delays attributable to the patient and family doctor were almost equal in duration. Patient delay was largely the result of not knowing the importance of bowel symptoms, while delay with the family doctor was the result of not examining patients with possible rectal carcinomas and not recognising symptoms suggestive of colon carcinoma. There was no relation between the duration of symptoms and the Duke’s stage of the tumour.

(Macadam, 1979)(181)

The author of this study interviewed 150 patients admitted to hospital with gastrointestinal cancer as soon after admission as possible with the aim of exploring their presenting symptoms, and delay in diagnosis and treatment. Responses were contrasted with hospital records and general practitioners’ recollections. In approximately 50% of cases there was an

interval of weeks between the patient consulting the general practitioner and being referred for hospital investigation. No association was demonstrated between delay and social class, age, physical isolation, or the regular consulting rate of the patient.

(Jones, 1976)(182)

The author undertook a survey in a group of over 40-year-olds in an attempt to derive information on people's beliefs and perceptions of what constitutes "normal bowel habit". The sample was randomly selected from a local population database, and all respondents were personally interviewed about a standard set of outcomes. The majority of respondents had a set pattern for their bowel habit; of these 80% had one bowel motion per day; the majority realised that a severe change in bowel habit should lead them to consulting a doctor, 24% had noticed blood on their bowel motions and 32% had noticed blood on the toilet paper. There were deficiencies in the understanding of the terms diarrhoea and constipation. The majority of patients treated themselves for slight changes in bowel habit.

(Rowe-Jones and Aylett, 1965)(183)

200 consecutive patients with carcinoma of the colon or rectum who attended a hospital clinic were interviewed and their case notes analysed to examine where diagnostic delay occurred. The authors recorded the main presenting symptom together with its date of onset, the date the patient first sought medical advice with symptoms referable to the disease, and the date of first attendance at any hospital. Both patient and doctor (general practitioner/hospital) related delays were examined. Doctor related delay was defined as failure to diagnose within two months of the patient presenting with symptoms.

For patients with colon cancer, symptoms were on average present for seven months with a standard deviation of 5.3 months (patient delay). Medical delay occurred in 22% of the patients, 68% of those at the hospital and 32% (seven patients) with the general practitioner. The average delay was 7.8 months, hospital delay 7.9 months, general practitioner delay 7.7 months. Of the seven cases with general practitioner delay, rectal examination was only carried out in one patient. In patients experiencing medical delay, a more advanced stage of disease was statistically significantly more likely (P=0.025) at the time of treatment.

For patients with rectal cancer, symptoms were on average present for 10.3 months (standard deviation 8.82 months) before seeking medical advice. Medical delay occurred in 22% of cases. In contrast with cancer of the colon, the delay in rectal carcinoma was mainly with the general practitioner. In 82% of those experiencing delay, the delay was due to the general practitioner, and in the remaining 18% to delay at the hospital. The principal reason for general practitioner delay was that in 18 patients with bowel symptoms, only two underwent a rectal examination, although all returned at least once to their general practitioner with continuing symptoms of bleeding, or constipation, or diarrhoea, or with a lump. The commonest problem was the presumptive diagnosis of haemorrhoids as the cause of bleeding without any examination. As in patients with colon cancer, a more advanced stage of disease at the time of treatment was significantly more common in those who experienced medical delay (P<0.025).

Diagnostic Difficulties

Introduction

We were unable to identify studies that directly investigated the reasons why primary care professionals experience difficulties in suspecting cancer in some patients. Qualitative studies involving interviews of professionals would have been one suitable study design; the direct observation of consultations with real or simulated patients would have been another. Neither did we find randomised controlled trials of interventions to improve professionals' ability to detect colorectal cancer.

Primary studies

(Bankhead et al, 2001)(184)

A postal questionnaire was sent to 909 practice nurses in four English health authorities, and

600 (66.0%) replied. 49.8% collected information about a family history of colorectal cancer in new patient appointments, 45.6% in well person appointments, and 22.7% in chronic disease clinics. Only 33.2% expressed confidence in making a basic risk assessment in the case of colorectal cancer, 25.0% felt confident in reassuring those at low risk, and 61.1% felt confident in advising on relevant symptoms

(Henningan et al, 1990)(185)

A postal questionnaire was sent to 859 general practitioners in London, and 609 (71%) responded. 279 general practitioners did five or fewer rectal examinations a month, 211 did six to ten, and 96 did more than ten. Factors associated with doing fewer examinations were a small partnership and being a female general practitioner, and expectation that the examination would be repeated. Lack of time in the surgery and an urgent outpatient appointment waiting time of less than two weeks were also important. The reasons given for deciding not to do a rectal examination in symptomatic patients were reluctance of the patient (278 respondents, 45.6%), the expectation that the examination would be repeated after referral (141, 23.2%), lack of time (132, 21.7%), or lack of a chaperone (39, 6.4%). General practitioners who thought they had been poorly taught, were more recently qualified, or worked in inner London were significantly more likely to be deterred by one or more of these factors.

12 Breast cancer

1 A patient who presents with symptoms suggestive of breast cancer should be referred to a team specialising in the management of breast cancer. D

2 In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. However, primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will be naturally concerned. C

3 People of all ages who suspect they have breast cancer may have particular information and support needs. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them. D

4 Primary healthcare professionals should encourage all patients, including women over 50 years old, to be breast aware7 in order to minimise delay in the presentation of symptoms. D

Specific Recommendations

5 A woman's first suspicion that she may have breast cancer is often when she finds a lump in her breast. The primary healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of age. C

6 In a woman aged 30 years and older with a discrete lump that persists after her next period, or presents after menopause, an urgent referral should be made. C

7 Breast cancer in women aged younger than 30 years is rare, but does occur. Benign lumps (for example, fibroadenoma) are common, however, and a policy of referring these women urgently would not be appropriate; instead, non-urgent referral should be considered. However, in women aged younger than 30 years with:
- a lump that enlarges, [C] or
- a lump that has other features associated with cancer (fixed and hard), [C] or
- in whom there are other reasons for concern such as family history. [D]

an urgent referral should be made. C/D

8 The patient's history should always be taken into account. For example, it may be appropriate, in discussion with a specialist, to agree referral within a few days in patients

reporting a lump or other symptom that has been present for several months. D

9 In a patient who has previously had histologically confirmed breast cancer, who presents with a further lump or suspicious symptoms, an urgent referral should be made, irrespective of age. C

10 In patients presenting with unilateral eczematous skin or nipple change that does not respond to topical treatment, or with nipple distortion of recent onset, an urgent referral should be made. C

11 In patients presenting with spontaneous unilateral bloody nipple discharge, an urgent referral should be made. C

12 Breast cancer in men is rare and is particularly rare in men under 50 years of age. However, in a man aged 50 years and older with a unilateral, firm subareaolar mass with or without nipple distortion or associated skin changes, an urgent referral should be made. C

Investigations

13 In patients presenting with symptoms and/or signs suggestive of breast cancer, investigation prior to referral is not recommended. D

14 In patients presenting solely with breast pain, with no palpable abnormality, there is no evidence to support the use of mammography as a discriminatory investigation for breast cancer. Therefore, its use in this group of patients is not recommended. Non-urgent referral may be considered in the event of failure of initial treatment and/or unexplained persistent symptoms. [B (DS)]

Introduction

Pathology

Breast carcinoma develops from the epithelial cells within the terminal duct/lobular unit (186). It is categorised as either *'invasive'* or *'in situ'.* Before malignant cells breach the basement membrane the cancer is *'in situ',* but once that membrane has been breached the cancer is *'invasive'*.(186). Breast cancers can be classified as either 'ductal' or 'lobular' on the basis of carcinoma type. The terms 'ductal carcinoma *in situ*' (DCIS) and lobular carcinoma *in situ*' (LCIS) are widely used but carry no more relevance than *invasive* cancer.(186)

<u>Staging breast cancer</u>

Staging is used to classify cancers on their anatomic extent. Tumour staging is based on size and the whether there is fixation of the cancer to surrounding tissue(186). The TNM staging system (Table 33) was developed from work in the 1940s by Pierre Denoix and is now the most widely used system of cancer classification.(187)

Table 33 TNM classification and stage grouping for breast tumours ((186))

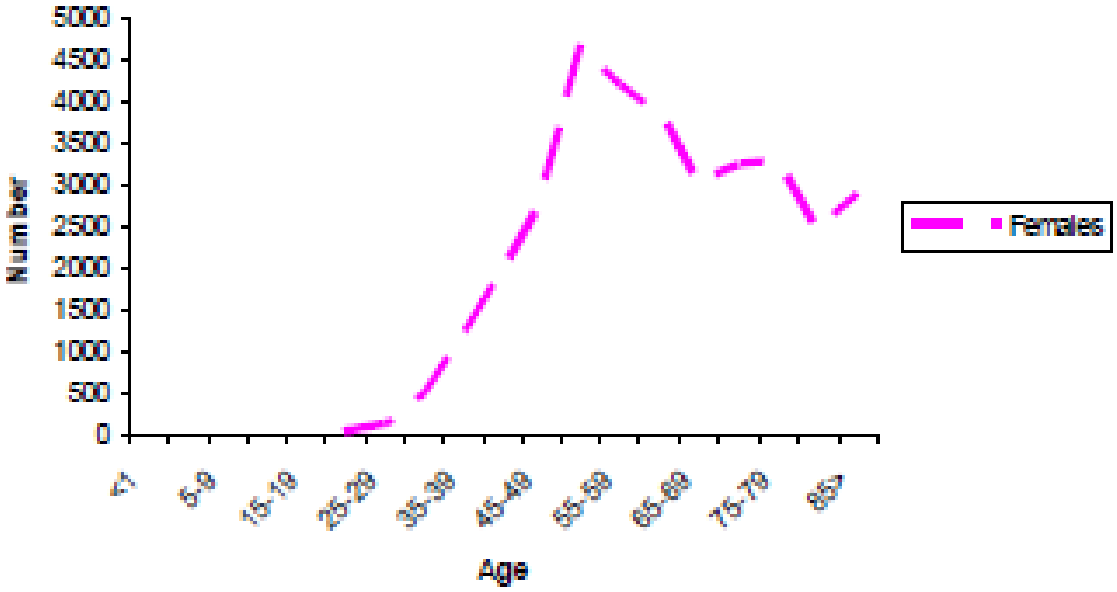
TNM classification	Stage grouping			
Tis In Situ	Stage 0	Tis	N0	M0
T1 ≤2 cm	Stage I	T1	N0	M0
	Stage IIA	T0	N1	M0
		T1	N1	M0
		T2	N0	M0
T2 >2 to 5 cm	Stage IIB	T2	N1	M0
T3 >5 cm	T3	N0	M0	
T4 Chest wall/skin	Stage IIIA	T0	N2	M0
		T1	N2	M0
		T2	N2	M0
		T3	N1, N2	M0
	Stage IIIB	T4	Any N	M0
		Any T	N3	M0
N1 Mobile axillary nodes involved	Stage IV	Any T	Any N	M1
N2 Fixed axillary				
N3 Internal axillary				
M1 Distant metastases				

T = tumour; N = node; M = metastasis

Incidence

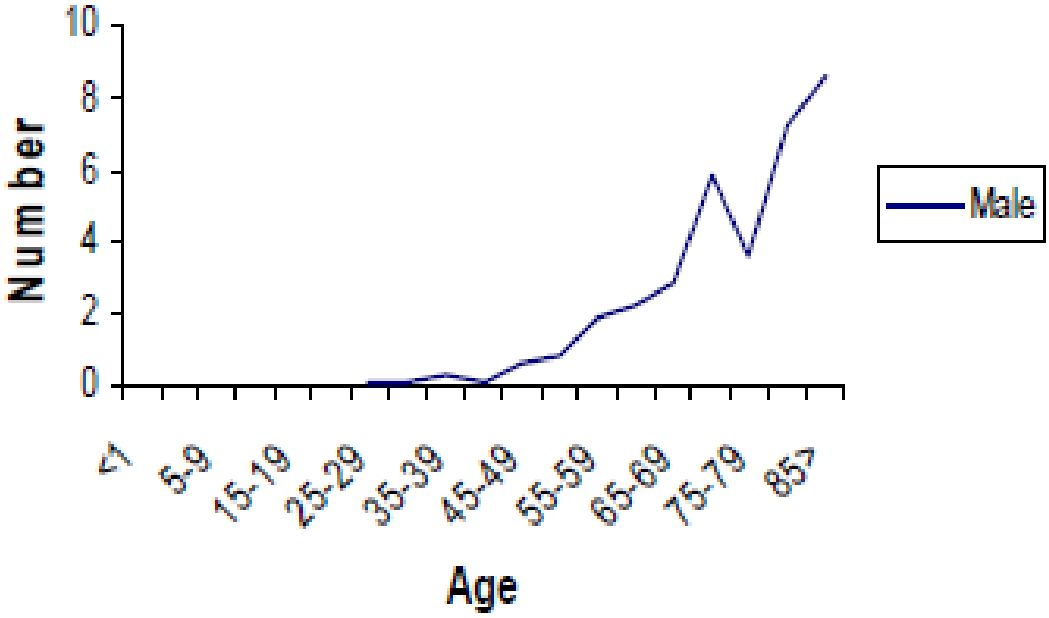
Breast cancer is the most common malignancy in women, accounting for almost 30% of female cancers. A general practitioner can expect to encounter one new case of breast cancer approximately every 11 months. It is estimated that more than 75% of cases present symptomatically and not through screening programmes. In 2001 there 40,740 cases in women.

Figure 15 2001 Registrations of Malignant Neoplasm of the Breast in England and Wales. (77)



Breast cancer in males is rare occurring approximately 100 times less than in women(128). The distribution of incidence by age is shown in *Figure 16.*

Figure 16 2001 Registration rates of Malignant Neoplasm of the Breast in Males in England and Wales. (77)

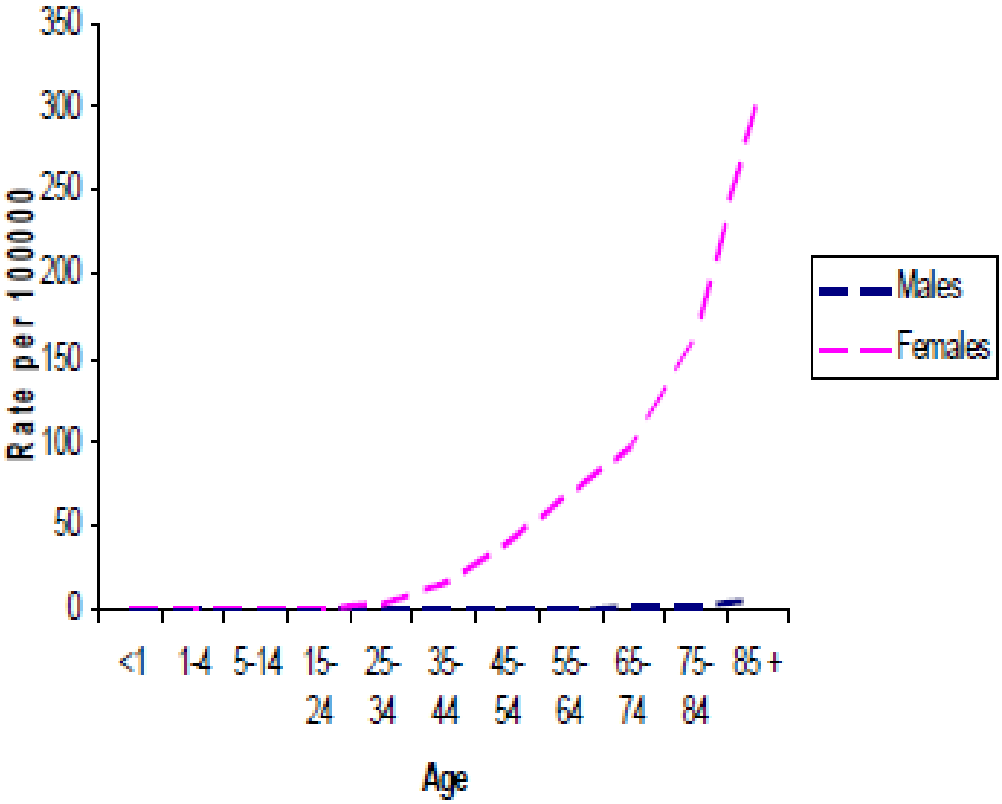


Mortality

Despite increased incidence rates, mortality among women from breast malignancies has

been falling since 1990 decreasing from approximately 38 to 32 per 100,000 population between 1971 and 1999. In 2002, there were 11,476 deaths among women and 81 among men (Figure 17).

Figure 17 2002 Mortality rates per 100,000 population from Malignant Neoplasm of the Breast in England and Wales. (78)



Review of cancer referral audits

The review (CRD, 2004) identified 72 clinical audits. The proportion of two week referrals in accordance with the symptoms listed in the Department of Health (2000) guidelines ranged from 65% to 99% (20 audits). The proportion of patients found to have cancer who had been referred under the two week system ranged from 0% to 34% (37 audits). The proportion of patients referred as 'urgent' but not under the two week system ranged from 4% to 20% (five audits). The proportion of patients found to have cancer who had been referred non-urgently ranged from 0% to 10%. Of the patients found to have cancer, between 4% and 83% had been referred under the two week system (nine audits). The proportion of two week referrals considered by the consultant to be appropriate or warrant an urgent appointment ranged from 18% to 96%.

Demographic information

(ONS, 2001) (17)

Breast cancer is the most common cancer in women worldwide, although cervical cancer is more frequent in some developing countries. It accounts for about 30% of all malignancies in women in England and Wales and recorded rates are higher in women in western, developed, countries. Breast cancer in men is extremely rare.

In 1997 there were 33,100 new registrations of breast cancer in women in England and Wales (Table 34), almost 30% of all cancers in women, and more than twice as many as for the second most common site, colorectal cancer. Worldwide, the highest recorded incidence rates occur in the USA and other western, developed countries. Rates in Japan, China and India are only about a quarter of those in the USA.

Table 34 Breast Cancer incidence and mortality, England and Wales, 1997 (ONS, 2001. (17))

Total number of new cases	33,100
Rate / 100,000	124.6
Mortality	11,500
Mortality / 100,000	43.3

Before the introduction of screening, incidence rates rose with age from the late 20s, but slowed at around 45-54 years, the age of the menopause. The effect of breast screening has been to raise the incidence in women aged 50-54, because many women were being screened for the first time with cancers being detected at an earlier stage. Rates in women aged 55-64 also rose during the early years of screening, but have since returned to levels expected based on the earlier trends. Incidence in women aged 65-69 has fallen in recent years: many cancers in these women will have been detected at earlier ages during screening; their rates in 1995-97 were lower than those in women aged 50-64.

As the incidence of breast cancer is high and survival is relatively good compared with many other cancers, there are large numbers of women alive who have been diagnosed with breast cancer. About 81% (75,000) of those diagnosed in 1990-92, and 62% (168,000) of those diagnosed in 1983-92 were still alive at the beginning of 1993.

One-year survival rates for patients in England and Wales diagnosed in 1991-

93 was 92%; five-year survival was 74%. Women aged under 40 at diagnosis had worse survival than those aged 40-49. In the late 1980s, mortality in England was not only higher than in most western European countries, it was among the highest in the world. However, survival has improved steadily over time, and in all regions. Five-year survival rose by 14% points between the early 1970s and the late 1980s and by a further 6% for patients diagnosed in 1991-93. The five-year survival from breast cancer in the UK is now 75.9%, (www.cancerresearchuk.org/aboutcancer/statistics/survival). and for screen- detected cancers five-year survival is 94.1% (http://www.cancerscreening.nhs.uk/breastscreen/publications/ba00-01.html).

12.1 Signs and Symptoms

Women

12.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of cancer in women consulting in primary care and those that make cancer less likely as a diagnosis?

12.1.2 Evidence Question:

In women attending primary care services with breast symptoms, which symptoms and signs and other features when compared with the "gold standard" are predictive of a diagnosis of cancer; and which symptoms and signs are not?

12.1.3 Evidence Statements:

The incidence of breast cancer in women in England and Wales rises sharply with age and is rare in women aged under 30 (III).

In studies of risk factors associated with a diagnosis of breast cancer, age is the only factor consistently reported in association with breast symptoms and a diagnosis of cancer (III).

Women with breast symptoms commonly consult general practitioners. In one study, the

typical general practitioner was consulted by one woman with breast symptoms every two weeks (III).

Among women presenting in general practice with breast problems, the most common presenting features are a lump and/or pain (III).

Women who attend primary care with the following features have an increased likelihood of having breast cancer:
Palpable mass

Skin or nipple change (III)

The likelihood of having a diagnosis of breast cancer is highest in women who present to primary care with a palpable mass. However, the absence of a palpable mass does not rule out the possibility of cancer (III).

There is little or no research evidence on the characteristics of breast lumps among women presenting in primary care and the likelihood of cancer. Benign lumps are said to be more likely to be smooth and well demarcated, whereas less mobile lumps with poorly defined margins are more likely to be malignant (IV).

Guidelines

(Austoker and Mansel, 2003) (188)

These guidelines quoted Barclay et al (1991) and Cochrane et al (1997). Cochrane et al (1997) reported that of 2332 new patients presenting to a breast clinic, 147 had symptomatic carcinomas. The symptoms and signs reported by the general practitioners in patients referred with carcinoma were:

lumps 90%
painful lumps 21% nipple
discharge 3.4% nipple
change 10.2%
skin contour change 4.8%
any family history 6.1%.

The guidelines recommended urgent referral for patients with a discrete lump in the appropriate age group, or definite signs of cancer such as: ulceration, skin nodule, skin distortion (<3 months). Nipple discharge or pain in the absence of a lump were said to be much less common presentations of breast cancer.

(All Wales Minimum Standards, 2000) (189)

Standard 10 stipulated that there should be a mechanism to provide general practitioners with rapid access to an appropriate specialist, urgent referrals being seen within ten working days of receipt of the referral by the hospital. The Standards did not include guidance on the presenting symptoms or signs.

(Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998) (190)

This publication is a Canadian evidence-based guideline to assist decisions in excluding or confirming the presence of cancer when a breast lump is detected. The guidelines were based on published evidence supplemented by expert opinion. Articles were identified through a database search using MEDLINE (from 1966) and CANCERLIT (from 1985) to January 1996. A non systematic review of breast cancer literature continued to January 1997. The guidelines made recommendations on how to establish a reliable diagnosis using the minimum of procedures. Evidence graded I-III was used as far as possible, but when experimental evidence was weak or lacking, the opinion of respected authorities (level IV) was employed. The conclusions arising from the review are outlined below.

Most lumps are not caused by cancer, but the possibility of malignancy must always be

considered. The first step is to obtain a clinical history and carry out a physical examination. When necessary, this is followed by further diagnostic procedures (mammography, fine needle aspiration [FNA], ultrasonography) and, if uncertainty still remains, by tissue biopsy (core or open surgical). The clinical history should establish how long the lump has been noted, whether any change has been observed and whether there is a history of biopsy or breast cancer. Risk factors for breast cancer should be noted, but the guidelines advised that their presence or absence should not influence the decision to investigate a lump further.

The presence of certain factors increases the likelihood of breast cancer. These include a history of a biopsy of either breast showing atypical hyperplasia, lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS), a history of resected carcinoma or radiation treatment for Hodgkin's disease in childhood, or a strong family history of breast cancer (level III evidence). Although known risk factors, including ageing, all increase the risk of breast cancer, they do not substantially influence the probability that any particular lump will be malignant. The fact remains that most women in whom breast cancer is diagnosed have no identifiable risk factors and breast cancer does not develop in most women with common risk factors.

The physical examination of the breast should aim to identify those features that distinguish malignant from benign lumps. Breast examination should be accompanied by a thorough examination of the axilla and supraclavicular areas to check for nodal involvement. Premenopausal women are best examined one week after the onset of the last menstrual period when engorgement of the breast is at a minimum (level IV evidence).

Paget's like lesions of the nipple are frequently caused by breast cancer. The condition may resemble a benign dermatitis that is sometimes moist and eczematous or sometimes dry and psoriatic and usually accompanied by thickening of the nipple-areolar complex. These features usually reflect centrifugal spread of cancer cells from the ductal epithelium into the overlying skin of the nipple. Biopsy is indicated when the condition fails to respond rapidly to topical treatment.

Smooth, well demarcated lumps are usually benign (level IV evidence). These are either cysts or fibroadenomas. Lesions that are less smooth and less mobile, with poorly defined margins, increase the suspicion of carcinoma.

Nipple discharge is not a common feature of cancer. Persistent unilateral discharge may be due to cancer in 4% to 21% of cases. The discharge may be watery, sanguineous, serosanguineous or serous. A non-bloody discharge is unlikely to be caused by cancer, and even a sangineous discharge is often not due to cancer. Also, a bilateral discharge is unlikely to be caused by cancer.

Breast cancer may or may not be painless. Although breast cancers are usually painless, the cancer may be accompanied by discomfort. Thus, the presence or absence of pain and tenderness should not influence the investigation of a suspicious lump.

(SIGN, 1998)(191)

The SIGN guidelines recommended referral of patients who presented with any new discrete lump, a new lump in pre-existing nodularity, asymmetrical nodularity that persist at review after menstruation, an abscess or breast inflammation which does not settle after one course of antibiotics, or a cyst persistently refilling or recurrent cyst (if the patient has recurrent multiple cysts and the general practitioner has the necessary skills, then aspiration is acceptable). It was also recommended that pain in association with a lump, or that was intractable or unilateral in a post-menopausal women should be an indication for referral, and nipple discharge is also an indication for referral in women over the age of 50 and also under 50 if the discharge is blood stained, persistent single duct or sufficient to stain clothes.

Secondary studies

(Centre for Reviews and Dissemination, 2002)(192)

This Service Guidance Evidence Review did not find any studies of the effectiveness of routine physical breast examination in self-presenting well women in the primary care setting.

The review identified two large randomized controlled trials, a non-randomised trial, two cohort studies and three case control studies but no reliable evidence to suggest that breast self-examination (BSE) among asymptomatic women reduces mortality rates from breast cancer. In fact some evidence suggested that BSE can do harm through increased rates of biopsy for benign lesions (grade of evidence I [systematic review of randomised controlled trials] and III [systematic review of non-randomised controlled trials]).

(Levine et al, 2001) (193)

In this systematic review undertaken by the US Agency for Healthcare Research and Quality, studies published from 1994 to 1999 were searched using Medline and Current Contents databases. The review included observational studies, randomised and non-randomised trials, and uncontrolled case series. The first question addressed in the review was 'What are the recommendations for evaluation of breast symptoms, mammographic findings and other suspicious findings based on menstrual status, use of hormone replacement therapy (HRT), pregnancy, age, and family history?'

Information about the association of symptoms and signs and a diagnosis of breast cancer could only be drawn from those studies that reported individual rather than aggregated data. Patients who presented with palpable masses were much more likely to be diagnosed with cancer than those with non- palpable masses, nipple discharge or breast pain. Ten studies reported the number of patients with palpable masses who developed cancer. Of a total of 2027 patients with masses, 303 (14.9%) had cancer. Six studies reported patients with 'lesions' as clinical findings; of 1094 with lesions, 358 (32.7%) were cancer. Four studies reported on nipple discharge, and among the total of 570 patients with discharge, 18 (3.2%) had cancer. Only two studies reported the incidence of cancer in association with breast pain, the proportions being seven of 216 (3.2%) in one study, and four of 221 (1.8%) in another. However, it should be noted that the reviewed studies included samples of women after referral.

Primary studies

There were few studies of the symptoms and signs associated with breast cancer among women presenting to primary care. Most studies involved only a small number of practices and patients, and consequently the numbers of women with cancer were usually too few to draw any meaningful conclusions about the predictive value of symptoms and signs in primary care. Since general practitioners encounter around one new patient with breast cancer per year, studies of presentation in primary care would require the participation of a large number of general practitioners.

The gold standard used in several studies was referral rather than subsequent diagnosis. One study provides more detail (Barton et al, 1999(194)), and this is described at greater length. There are several studies of the symptoms and signs of women attending specialist services, and we have included two of these only to highlight the different patient features found among a specialist service in contrast to primary care. Considerable caution is needed, therefore, in extrapolating from studies undertaken in specialist clinics to patients presenting to primary care.

Studies of patients presenting in primary care

(Newton et al, 1999) (195)

In this case series, data were collected prospectively from 508 women consulting 248 general practitioners in Sheffield over a four week period between January and July 1995. The general practitioners used a standard pro-forma to record information about women consulting primarily for a breast problem. The pro-formas were not completed for women who had a breast examination as part of a consultation for any other reason.

Table 35. Presenting features among 508 women consulting with breast problems (Newton et al, 1999 (195))

Presenting symptoms	Referred Lump
- 218	126 (57.8%)
Pain -196	33 (16.8%)
Nipple discharge – 21	7 (33.3.%)
Skin/nipple change -21	3 (14.3%)
Family history -7	4 (57.1%)
Other – 45	13 (28.9%)
Total 508	186 (36.6%)

Referral rates increased according to patient age: 16-39 32.6%, 40-49 38.7%, 50-64 40.6%, 65+ 50.0% (*Table 35*). The mean number of consultations was 2.05 over the four week period, suggesting that a general practitioner would see 15.8 women with new breast problems in one year. However, this figure excludes women who consulted for primarily other problems but also had a breast problem.

(Nichols et al, 1980) (196)

In this case series, 193 general practitioners were recruited in Southampton to record in a booklet all women seen with breast symptoms over four weeks. There were 331 consultations recorded by 323 women for breast conditions (mean: 3.5 per general practitioner). Of those consultations 241 were for new episodes (*Table 36*).

Table 36. Presenting features among 323 women consulting with breast problems (Nichols et al 1980)

New episodes	Referred
1 lump only – 29	18 (62.1%)
2+ lumps - 7	3 (42.9%)
Pain only - 125	7 (5.6%)
Other - 24	24 (20.8%)
Lump and pain - 29	14 (48.3%)
Lumps and pain – 19	11 (57.9%)
1 lump + other – 1	1 (100%)
2+lumps + other– 1	0
Pain and other - 6	2 (33.3%)
Total – 241	61 (25.3%)

(Bywaters, 1977)(197)

This study involved six general practitioners in one UK practice recording 451 consultations for breast problems by 180 women. Details of consultations were recorded and a list was created of women consulting with breast complaints between October 1972 and December 1974. The presenting features are summarised in *Table 37*.

28 of the 180 had cancer (18 new cases -10%); All these were aged 30 or over. Of 57 patients seen with a discrete lump, 32 (56.1%) were referred immediately.

Table 37 Presenting features among 180 women consulting with breast problems (Bywaters 1977).

Feature	Number
Lump	68 (38%)
Pain	51 (28%)
Nipple discharge	8 (4.4%)
Change in shape	8 (4.4%)
Post-mastectomy –	5 (2.8%)
Anxiety	4 (2.2%)
Cosmetic	3
Ulceration	(1.7%)
	2 (1.1%)
Other	7 (3.9%)

(Roberts et al, 1987)(198)

This was a study to ascertain the effects of a recent health campaign on the number of general practitioner consultations for breast problems. The study involved giving each patient consulting with breast problems a questionnaire; women having a breast examination associated with contraceptive care or routine cervical cytology tests were not included. 262 women returned questionnaires from five UK general practices over 18 months. Their symptoms and referral rates are shown in *Table 38*.

In addition, the study suggested that public health campaigns had little measurable affect on consultation rates.

Table 38 Presenting features among women consulting at primary care with breast problems (Roberts et al, 1987 (198))

Presenting symptoms/signs	Referrals
Pain – 124	54 (43.5%)
Lump – 93	63 (67.7%)
Discharge – 3	3 (100%)
Other – 40	19 (47.5%)
Total – 262	total 132 (50.4%)

Studies of referred patients

(Seltzer, 2004)(199)

This study reviewed data on 10 000 consecutive new surgical referrals for breast complaints in the US. Female patients referred between 1987 and 1999 completed a comprehensive medical history form. The aim of the study was to demonstrate those situations which are likely to yield a cancer diagnosis.

Across all ages, 9% of patients presenting with lump yielded cancer; 16% of those presenting with pain; 4% of those presenting with discharge; 11% of those found by mammogram and 5% presenting withg miscellaneous complaints.

(Campbell, 2004)(200)

This study reviewed prospective audit data from patients referred to a symptomatic breast unit in the UK. The patients with a breast lump were significantly more likely to have breast cancer than patients without a lump (OR = 5.0765, CI = [3.06662-8.4047], $p < 0.001$). The likelihood of breast cancer increased with age (OR = 1.0808, CI = [1.0712-1.0906], $p < 0.001$). Pain was the least likely to indicate the presence of cancer (OR = 0.1351, CI = [0.0664-0.22749], $p < 0.001$), as was breast lumpiness (OR = 0.3192, CI =0.1718-0.5930], $p < 0.003$), nipple discharge (OR = 0.5337, CI = [0.1821-1.5647], $p > 0.05$), HRT use (OR = 0.6995, CI = [0.4431-1.1042], $p < 0.05$) and signs of cancer (OR = 0.6842, CI = 0.4156-1.1265], $p < 0.003$). Family history was not found to be statistically significant within their model.

(Patel et al, 2000)(201)

This study was prospective case series involving new patient referrals from general practitioners to a specialist breast clinic in Glasgow. Of the 321 patients referred, 10% had breast cancer and 90% had either benign disease or no pathology. The study concluded that one third of the referrals were inappropriate (*Table 40*).

Table 39. Features among 321 women referred to a breast clinic (Patel et al 2000)(201).

i) 10% with breast cancer	
Lump/nodularity –	21 (91%)
Nipple change –	2 (6%)
Axillary lump	1 (3%)
ii) 90% without cancer	
Lump –	175 (60%)
Pain –	55 (19%)
Nipple discharge/change	22 (8%)
Family history only	12 (4%)
Anxiety only	3 (1%)
Other	22 (8%)

(Barclay et al, 1991)(202)

In this case series, information was collected about women referred to breast or surgical outpatient clinics in Dundee between 1979 and1989. During this period, 940 women

presented with new breast cancers and 3,500 were referred with benign conditions. The features at presentation among the patients with cancer are shown in *Table 40.* The median age of those with benign disease was 35 years, but for those with cancer the median age was 57 years. The majority (91%) of referrals to the breast unit for benign disease occurred in patients under 55 years.

Among those with cancer, a visible abnormality was noted in the left breast in 362 patients, and the right breast in 320 patients. The most common observed abnormalities were asymmetry (68%), nipple abnormalities (43%) and skin changes (7%).

Of those diagnosed with breast disorders, 15% reported a family history of breast cancer, compared with only 18% of the 940 who had cancer reporting family history.

Table 40. Features at presentation among 940 women with breast cancer (Barclay et el 1991).

	Cancer n (%)	Benign conditions n (%)	
		Right breast	Left breast
Lump only	459 (50)	519 (29)	579 (26)
Pain only	26 (3)	301 (17)	373 (17)
Lump and pain only	124 (13)	316 (17)	371 (17)
Nipple discharge only	14 (1)	64 (4)	75 (3)
Nipple retraction only	29 (3)	13 (1)	27 (1)
One other symptom only	45 (5)	160 (9)	174 (8)
Combination of symptoms	259 (28)	445 (26)	597 (27)

(Barton et al, 1999) (194)

This US population-based retrospective cohort study was undertaken at a large health maintenance organisation in New England over a ten year period. The study sought to determine 1) how often women presented with breast symptoms to primary care providers 2) how these symptoms were evaluated, and 3) how often symptoms led to a diagnosis of breast cancer. The study population was 2400 women aged 40-69 years, sampled in a random age stratified manner and from people who had been continuously enrolled in the health maintenance organisation (HMO) from July 1983 to June 1993. For this sample, information was abstracted on all breast related encounters and diagnoses of cancer subsequent to presented symptom(s) were recorded.

Patient symptoms were classified as 1) mass (a single lump or nodule); 2) pain (a report of pain or tenderness in either breast or bilaterally), 3) skin or nipple change (including nipple discharge) 4) multiple lumps or nodules often described by clinicians as ‘fibrocystic’ or ‘diffuse cystic change’, or 5) other symptoms (such as increasing breast size). Clinicians’ diagnostic interpretations were classified as normal (even if fibrocystic), abnormal-benign (no further follow up required), indeterminate (record of firm or fixed lumps, or follow up by surgeon recommended, or suspicion of cancer noted). The meaning of such terms as benign or normal had to be inferred because clinicians did not use a standard taxonomy to describe their examination findings nor a standard metric to convey level of concern.

Over the ten year period, 372 (16%) of the HMO population presented with a breast symptom

(22.8 presentations per 1000 person years). Women younger than 50 years of age presented nearly twice as often as older women (P=0.0001). Rates did not differ by ethnic group. Women with a family history of breast cancer were more likely to present with breast symptoms than those without a family history (22% compared with 14%; P=0.001).

The most common symptom was pain, followed by a mass, skin or nipple change, lumpiness and other symptoms. Two symptoms were noted in 59 episodes (13%); the most frequent combinations were pain and mass (31 episodes [7%]) and pain and skin or nipple changes (14 episodes [3%]). In 69 episodes, no specific symptom was documented. Presenting symptoms and signs varied by age. A mass was the most common feature among women in their 40s, and pain was the most common feature among women in all other age groups. Pain was unilateral in 91% of episodes and bilateral in 9% of episodes.

On physical examination, the clinicians found a mass in 184 episodes (34%), skin changes or nipple discharge in 43 episodes (8%), fibrocystic changes in 112 episodes (21%) and other findings in 32 episodes (6%). More than one finding was documented in 45 episodes and no specific findings were documented in 214 episodes (40%). Of the 196 episodes in which a patient reported a mass, the clinician confirmed the mass in 160 (82%). Of the 343 episodes in which mass was not one of the patient's symptoms, the clinician documented a mass in 24 (7%).

Clinicians interpreted physical findings as normal in 33% of episodes, abnormal-benign in 27%, indeterminate in 35%, and suspicious for cancer in 6%. Breast cancer was diagnosed in 23 of the 372 women who presented with breast symptoms (6.2%); 21 had invasive disease (six with stage 1 disease, 14 with stage 2 disease, and one with stage 3 disease) and two had ductal carcinoma in situ.

Of the 23 women with cancer, 11 (6.4%) presented while in their 40s, six (4.4%) while in their 50s, three (4.4%) while in their 60s, and three (8.3%) in their 70s. Clinicians had found a mass in 22 (96%), skin findings in two (9%), fibrocystic changes in three (13%) and other findings in three (9%).

The 23 women with symptomatic breast cancer had higher tumour stages at diagnosis than 58 women whose breast cancer was detected by screening mammography during the study period (P=0.02). The likelihood of breast cancer varied by symptom or sign. A report of a mass was associated with a 10.7% chance of breast cancer and a likelihood ratio of 65, whereas a report of pain led to a diagnosis of cancer in 1.8% of episodes, with a likelihood ratio of 10. A mass accompanying any other symptom or sign increased the risk for cancer. At the same time, each symptom or sign alone was associated with a significantly higher risk for cancer than in the population at large.

Although younger women presented more frequently with breast symptoms or signs, cancer rates did not vary significantly by age group. The study indicated that 4.3% of breast symptom or sign episodes led to a diagnosis of breast cancer, but it should be noted that the incidence of cancer may be lower in this study than in an unscreened population because of the use of screening mammography in the study population. A mass was the feature most often associated with breast cancer. Only two of 23 women (8.7%) who were found to have cancer presented with pain as the only feature.

It should be noted in interpreting these findings that the study did not include women younger than 40 years of age, and that a relatively high proportion (18%) had a family history of breast cancer.

<u>(Chalabian and Dunnington, 1998) (203)</u>

This study involved 66 graduating primary care physicians, assessing the link between observed breast examination skills during an objective structured clinical examination (OSCE)

and ability to detect lumps in silicone models. The correlation detected between lump detection and examination skills, although statistically significant, was only 0.34. No relationship was found between breast model sensitivity and specificity. Although the authors commented that thorough clinical breast examinations are imperative as they can identify 10% of breast cancers not visible on mammograms (204), no specific manoeuvres or techniques could be recommended.

(Khan and Apkarian, 2002a) (205)

In this study, a modified version of the McGill Pain Questionnaire was administered to 271 women with breast pain but without breast cancer. 134 women had cyclic breast pain and 152 non-cyclic. Cyclical breast pain tended to be a diffuse, heavy ache, most prominent towards the end of the cycle, although may also be severe during menstruation. It may occur in one breast, but commonly in both. However, there are very few studies of women with breast pain in primary care, and the significance of pain as an indicator of cancer is difficult to determine.

(Khan and Apkarian 2002) (206)

This study was a retrospective case controlled investigation into the relationship between breast mastalgia and cancer studying a population of 5463 women aged over 30 attending a New York breast care centre. Of those women, 861 were diagnosed with breast cancer, of whom 141 (16.4%) reported breast pain (mastalgia). Of the 4602 women who did not have cancer, 1391 (30.2%) reported mastalgia. Breast pain was reported as an incidental complaint at first visit to the centre by 1532 (28%) of all the women in the study.

This investigation found that within their study population, women who experienced breast pain were less likely to be diagnosed with breast cancer than those without, regardless of age or other risk factors. Additionally the study found that risk factors associated with breast cancer (age, age of menarche, age at first full term pregnancy, age at menopause, family history, alcohol use) were associated with a decreased frequency of breast pain, with the exception of exogenous hormone use.

Risk Factors

Evidence Statements:

Epidemiological studies have reported a number of risk factors as being associated with an increased probability of developing breast cancer. Such risk factors include: age; family history of breast cancer; age of having first child and use of hormone replacement therapy. (III)

In a woman who presents to a medical practitioner with a palpable breast lump, the presence or absence of any given risk factor has no significant effect on the likelihood of that woman having breast cancer. (III/DS)

There is no evidence that information on risk factors is of use in selecting those symptomatic women who should be referred (III)

Guidelines

(NICE: The Classification and care of women at risk of familial breast cancer 2004) (207).

This evidence based guideline is limited to women over 18 who have not been previously diagnosed with breast cancer. The evidence searches were wide ranging and papers were graded according to NICE specifications, while quality of studies was assessed using modified SIGN checklists.

The guideline states that although most breast cancer occurrences are random, in 16-19% of cases a family history of the disease is identifiable. The probability of a 20 year old woman developing breast cancer by 80 increases with the incidence of breast cancer within her family. With no affected relatives the risk is 7.8%, with one 13.3%, and with two 21.1%(207).

The evidence used in assessing the specific risk factors of breast cancer evaluated by the guideline was of varying quality and a summary of the findings and subsequent recommendations follow.

Family history

Risk increases with the proximity of the relationship to an affected relative, the number of affected relatives and with the decrease in age of those relatives at the time of developing breast cancer. The high risk genes BRCA1 or BRCA2 account for only a small amount of this increased risk. However, the risk of carrying one of these mutated genes is related to the strength of the family history, and risk of breast cancer is increased by their occurrence (BRCA1 60- 80% risk, BRCA2 40-80% risk).

Hormone Replacement Therapy (HRT)

The risk of breast cancer is increased and continues to increase in association with the duration of HRT use. Increased risk reduces once treatment is stopped and risk returns to same level as a woman who has never taken HRT after five years. Thus, it was recommended that treatment time is restricted to short term (no definition of short term was given) in women with familial risk, and alternative treatments should be considered and the woman informed of the increased risk.

Oral Hormonal Contraceptives

Evidence concerning ever-use, current use, duration, and cessation of oral contraceptive use is contradictory and inconsistent. Ever–use was not associated with increased risk in breast cancer in women of any age. Findings on current use and duration of use were inconclusive and contradictory as some studies suggested an increase in risk and some did not. A 16% increased risk was observed within the first four years after stopping oral contraceptive use and a 7% increase between five and nine years. After ten years no increased risk was observed. A statistically significant increase in risk was found in women using oral contraceptives prior to their first full term pregnancy (72%). No specific increase in risk was recorded among those with familial risk taking oral contraceptives. One study identified carriers of the BRCA1 mutation gene as having a 20% increased risk when using oral contraceptives, but no increased risk in carriers of the BRCA2 mutation gene.

Breastfeeding

Breastfeeding has a protective affect against breast cancer, which is proportionate to the total duration of breastfeeding. There is a 4% reduction in risk for every 12 months of breastfeeding and the risk is similar in women with familial risk. It was recommended that women be advised to breastfeed.

Alcohol consumption

Risk increases with alcohol consumption by 7.1% per 10g daily intake and is unaffected by familial risk. It is recommended that information is provided to women with familial risk.

Smoking

Evidence reviewed reached different conclusions ranging from no association of smoking with increased risk of breast cancer, to significant increases in both current or former smokers, with additional particularly high risks in premenopausal women or those who began smoking very early. The guideline concludes that as scientific studies have produced inconsistent findings a relationship is merely speculative.

Weight and physical activity

No specific link between diet and familial risk of breast cancer was found, although moderate exercise was thought to confer a decrease in risk of cancer. However, high BMI was associated with an increase of risk in postmenopausal breast cancer. Thus it was recommended that women are informed of the increase in risk associated with being overweight.

Menstrual/reproductive factors

Menstrual and reproductive factors carry the same risks among women with or without a family history of breast cancer. In both groups of women, older age at first birth and earlier menarche were associated with increased risk.

Risk decreases with the number of live births. It was recommended that the practitioner should provide information about hormonal risk factors.

Secondary studies

(Levine et al, 2001) (193)

This review undertaken by the Agency for Healthcare Research and Quality is outlined in the section dealing with symptoms and signs above. Age was the only risk factor consistently reported in association with symptoms and cancer diagnosis. The influence of family history varies depending on the age of the patient and the closeness of the affected relative(s), the ages at which the relatives developed cancer, the number of relatives with breast cancer, and the number with other gynaecological or other cancers. Women whose mother or sister had breast cancer before the age of 40 had the highest risk (relative risk 2.2, 95%CI 1.5-4.2). HRT was reported as not significantly increasing the risk among women who have a family history.

Risk of breast cancer increases with duration of oestrogen exposure. Women who had an early menarche are at increased risk (before age 12 RR 1.1-1.3), as are those with a late menopause (after age 55 RR 2.0). Women who delay their first child until after age 30 have an increased risk (RR 1.3-1.9). The impact of pregnancy is not well understood, since there is an increased risk for up to 10 years after delivery.

The review did not consider the impact of smoking, diet, alcohol, lactation or genetic factors on risk of breast cancer.

(Collaborative Group on Hormonal Factors in Breast Cancer, 2002) (208)

The authors analysed individual data from 47 epidemiological studies in 30 countries to estimate the association between breastfeeding patterns and childbearing with breast cancer. For women who had never breastfed, the relative risk of breast cancer declined by 3% for each year younger they were when their first child was born. The relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding (not necessarily consecutively) in addition to a decrease of 7% for each birth. The size of the decline in the relative risk of breast cancer associated with breastfeeding did not differ significantly for women in developed and developing countries, and did not vary significantly by age, menopausal status, ethnic origin, the number of births or age when the first child was born. It is estimated that the

cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently.

Primary studies

(McPherson et al, 2000)(78)

This paper reviews the risk factors for breast cancer in the UK, the findings are summarised in *Table 44* below.

Table 41 Established and probable risk factors for breast cancer

Factor	Relative Risk	High Risk Group
Age	>10	Older people
Geographical location	5	Developed country
Age at Menarche	3	Menopause before age 11
Age at first full pregnancy	3	First child in early 40s
Family history	>2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmonopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age ten
Taking exogenous hormones:		
Oral contraceptives	1.24	
HRT	1.35	
Diethylstilbestrol	2	

12.1.2 Men

12.1.2.1 Key Clinical Question:

Which are the symptoms, signs and other features that raise a suspicion of cancer in a man presenting with a breast abnormality, and those that make cancer less likely as a diagnosis?

12.1.2.2 Evidence Question:

In men attending primary care services with breast symptoms, which symptoms and signs and other features when compared with the "gold standard" are predictive of a diagnosis of cancer; and which symptoms and signs are not?

12.1.2.3 Evidence Statements:

A subareolar mass is the most common presenting sign in men with breast cancer. Less common signs include nipple retraction, local pain, nipple ulceration, discharge or bleeding (III).

In men, breast cancer is more common, but not confined to, those over 50 years of age (III).

There are several risk factors for breast cancer in men, but their significance in estimating the likelihood of cancer among men presenting with symptoms is unclear (III).

Secondary studies

(Giordano et al, 2002) (209)

This is an up to date systematic review. The authors sought articles published between 1942 and 2000, and used CancerLit, Medline and study bibliographies to identify articles. They included studies on the epidemiology, risk factors, genetics and pathology of breast cancer in men. The review reports the following conclusions.

The incidence of breast cancer in men has remained stable in the past 40 years, and the median age at diagnosis is 68 (compared to 63 in women). However, the disease has been reported in males from ages 5 to 93 years. The incidence increases exponentially with age. Breast cancer in men may be hormonally driven, as in women. The risk factors include: testicular abnormalities (undescended testis, congenital inguinal hernia, orchidectomy, orchitis, testicular injury); infertility; Klinefelter syndrome; positive family history; benign breast conditions (nipple discharge, breast cysts, breast trauma); radiation exposure; increasing age; Jewish ancestry. The rate of gynaecomastia in men with breast cancer is similar to the rate in the general population.

Approximately 90% of all breast tumours in men are invasive carcinomas, the remaining 10% being non-invasive (most being ductal carcinoma in situ). Approximately 85% (ranging between 50-97% in different studies) of affected men present with a painless subareolar mass. Other common signs include nipple retraction (10-51%), local pain (4-20%), nipple ulceration (4-17%), nipple discharge (1-12%), and nipple bleeding (2-9%). Men are more likely than women to have a delay between the onset of symptoms and diagnosis. Mammography is reported as being helpful in distinguishing a benign from a malignant lesion, and fine needle aspiration has been found to be sensitive and specific.

No primary studies are included in this evidence review as the systematic review of Giordano et al (209) is recent and comprehensive.

12.2 Investigations

12.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

12.2.2 Evidence Question:

In women attending primary care services with breast symptoms, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer; and which are not?

What investigations to diagnose a suspicious breast lump are available to primary care practitioners in the UK?

12.2.3 Evidence Statements:

Evidence from studies in Britain and Sweden indicate that decisions on whether to refer women presenting with breast symptoms are commonly made at the first consultation, and without recourse to investigations (III).

There is no evidence that laboratory tests have a role in initial investigation of women presenting with breast lumps in primary care (III).

In some countries, some primary care physicians undertake FNA for cytological examination. However, success in obtaining a satisfactory sample is dependent on the skill of the physician. There is no evidence on the role of FNA in primary care in the UK (IV).

There is no evidence from the UK to suggest that a policy of investigation with mammography and/or FNA accelerates referral to secondary care of patients with cancer. It is possible that use of these investigations would delay referral (IV).

Women presenting to primary care with breast pain and in whom cancer is not suspected but who are referred for a mammogram are unlikely to have a suspicious mammogram. (III)

Background

Established management of women suspected of having breast cancer includes the triple assessment of physical examination, mammography and percutaneous biopsy (also referred to as fine needle aspiration – FNA).

We found very few studies of the role of investigations in women presenting with breast symptoms in primary care. The majority of studies of investigations involved women who had been referred, and since the findings cannot be extrapolated to the population of symptomatic women before referral, these studies have been excluded.

Guidelines

(Austoker and Mansel, 2003).(188)

These guidelines did not suggest any primary care investigations before referral in patients presenting with a breast lump, breast pain, or severe cyclical mastalgia. In the case of nipple discharge in women less than 50 years of age, a test for blood was advised if the discharge is from multiple ducts. Referral was recommended when the test is positive. Other

investigations, including triple assessment, were restricted to patients who had been referred, the investigations being carried out by the specialist.

(All Wales Minimum Standards, 2000) (189)

Standard 11 requires that all diagnostic tests are carried out in one visit. The standard related to patients referred to and attending specialist services.

(Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998) (190)

These guidelines were based on a systematic review of evidence (Medline from 1966, Cancerlit from 1985, through to 1996). However, the studies cited were not confined to those involving patients in primary care. Mammography was found to be unlikely to give useful information in younger women, although is more useful from aged mid-30s. The overall level of sensitivity of mammography was reported as possibly no higher than 82% (level III evidence), and therefore a normal mammogram cannot exclude cancer. The guideline indicated that fine needle aspiration can be carried out in office settings, and that cytologic examination should be ordered if the obtained fluid is bloody. Success in obtaining satisfactory samples, however, is operator dependent. The false negative rate in one reviewed study had been 15.2%. When physical examination, mammography and cytology are combined, the diagnosis is likely to be confirmed in 99% of cases in which all three tests are positive; cancer will be found in 0.5% of cases if all tests are negative.

(Royal Australian College of General Practitioners 1997) (210)

These guidelines are reported as based on a review of evidence, although there is insufficient information to judge the extent and quality of the review. The guidelines encourage the use by general practitioners of imaging and fine needle aspiration. Ultrasound is recommended in place of mammography in women under age 35.

Secondary Studies

(Kerlikowske, 2003)(211)

A review of papers found on Medline between January 1966 and March 2003 to determine the most accurate and least invasive means to evaluate an abnormal mammography result and palpable breast abnormality.

This study found that a diagnostic mammography is most helpful in deciding whether a nonpalpable breast lesion should be biopsied but not whether a palpable breast abnormality should be. For palpable masses, fine needle aspiration biopsy or core-needle biopsy were preferred. However in order to determine whether a lesion is a simple cyst and therefore benign, core needle biopsy or needle localisation with surgical biopsy was usually preferred.

Primary studies

(Duijm et al, 1998a) (212)

In a study of 987 women with a painful breast referred to the radiology department of a Netherlands hospital between 1992-1996, follow up was undertaken for two years. The gold standard was a recorded diagnosis of breast cancer during follow up. 84.1% of the sample had been referred by general practitioners. The findings were compared with a control sample of 987 asymptomatic women undergoing a screening mammogram. Four (0.4%) of the women with pain were diagnosed with cancer, in comparison with seven (0.7%) of the controls. Mammograms were classified as suspicious or malignant in only 1.2% of the symptomatic cases.

(Mansson et al, 2001) (213)

This study was undertaken in four primary health care centres in Sweden 1995-1997, and investigated the diagnostic actions of general practitioners in relation to colorectal, pulmonary, breast and prostate cancer. The total patient population in the area served by the health centres was 9556, and 125 women were recorded as presenting with breast problems. In most, no laboratory test had been performed, although 80 mammographies were undertaken, with a yield of three cancers. Seven breast cancers were diagnosed in total, six at the first consultation; one was interpreted as a benign tumour, and six were referred to a surgeon. Two patients had haemoglobin tests, one ESR, and four various other tests not related to breast cancer (e.g. urine dipslide). The study did not indicate whether these laboratory tests served a useful role in the initial assessment of the patients with breast cancer.

(Mansson and Bengtsson, 1992) (214)

The primary care records of all 62 women with a diagnosis of breast cancer between 1981 and 1983 in Kungsbacka in Sweden were reviewed. Information was collected about the investigations ordered before diagnosis. The article does not report the number of women who underwent laboratory investigations, but notes that 12 (19%) were found to have an elevated erythrocyte sedimentation rate, eight (13%) had anaemia, and six (10%) had a leucocytosis. However, in another report from this study (Mansson et al, 1999), it was reported that 59 (95%) had a haemoglobin estimation and 57 (92%) an erythrocyte sedimentation rate estimation. The authors concluded that haematology and erythrocyte sedimentation tests did not assist in the diagnosis of breast cancer.

12.3 Delay and Diagnostic Difficulties

12.3.1 Key Clinical Question:

What influence do age, gender, social class and ethnicity have on the differential at presentation?

What diagnostic difficulties do primary care professionals themselves report in determining whether a woman/man who presents with breast symptoms/signs may or may not need urgent referral with suspected cancer?

12.3.2 Evidence Question:

In women attending primary care services with breast symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation of breast cancer?

What diagnostic difficulties do primary care professionals themselves report in determining whether a woman/man who presents with breast symptoms/signs may or may not need urgent referral with suspected cancer?

12.3.3 Evidence Statements:

Delay

There is strong evidence of an association between older age and delay by patients, and strong evidence that marital status is unrelated to delays by patients (III).

There is an association between socioeconomic status and survival (III)

There is moderate evidence for an association with delay by patients with five other factors:

- fewer years of education
- presenting with breast symptoms other than a lump
- not disclosing the breast symptom to another not attributing the breast symptom to breast cancer (III).

Younger age and presentation with a breast symptom other than a lump were strong risk factors for delays by health professionals. There is moderate evidence that ethnicity does not influencing delay by providers. (III)

Diagnostic Difficulties

Primary care professionals report that detection of the possibility of breast cancer is often straightforward, but in some cases is difficult (III).

A past history of benign breast conditions, young age, and presentation without a palpable lump are features that can make the detection of possible cancer more difficult (III).

Primary care professionals' referral decisions are influenced by their own and their patients' anxiety. Past experience of a delayed or missed diagnosis can lower the professional's referral threshold (III).

Delay

The following section addresses the influence that socio-demographic and psychosocial factors have on the women's decision to seek help when confronted with symptoms and signs suspicious of breast cancer. The four that will be considered are:

- Psychosocial factors
- Socio-economic status
- Age
- Ethnicity.

(Sainsbury et al,1999)(215)

An retrospective analysis of 36,222 patients with breast cancer listed on the Yorkshire Cancer Registry between 1976 to 1995, in order to investigate whether delay in referral from primary care influences survival. Patients were grouped according to time taken from family-physician referral to treatment (<30 days / 30-59 days / 60-89 days and 90> days).

Results demonstrated no evidence that delay up to three months (90 days) adversely influenced survival. From 1976 to 1995 the time from family- physician referral varied very little with a median of 10 vs.13 days. However the time from first visit to until the patient received treatment doubled for the same time period going from 7-13 days. Of the women included in the study, those who presented early and were in less than 30 days actually had significantly worse outcomes ($p<0.001$).

Secondary studies

(Ramirez et al, 1999) (216)

The authors undertook a systematic review of 23 papers to assess the quality and strength of evidence on risk factors for delays by patients and providers. There was strong evidence for an association between older age and delay by patients, and strong evidence that marital status was unrelated to patient delays. There was moderate evidence for an association

between patient delay and five other factors: fewer years of education, non-white ethnic origin, presenting with breast symptoms other than a lump, not disclosing the breast symptom to another, and not attributing the symptom to breast cancer. Younger age and presentation with a breast symptom other than a lump were strong risk factors for delays by providers. There was moderate evidence against non-white ethnic origin influencing delay by providers.

Primary studies

A. Papers that explore the influence of more than one factor

(Grunfeld et al, 2002) (217)

This study investigated the influence that women's age and socio-economic status play on delayed presentation. 996 women, randomly selected though the postal address file were interviewed by the authors to elicit their knowledge of breast cancer risk, breast cancer symptoms, and their perceptions of the management and outcomes associated with breast cancer. Older women were particularly poor at identifying symptoms of breast cancer, risk factors associated with breast cancer and their personal risk of developing the disease. Professional women and women classified as intermediate had a greater knowledge of risk factors than women from lower socio-economic groups. 32% of professional and intermediate women reported reduced risk compared to 10-15% of partly skilled and unskilled women, and women who were unskilled or had never worked identified significantly fewer symptoms than the other socio-economic groups.

(Grunfeld et al, 2003) (218)

This study primarily investigated the influence of psychosocial factors but in relation to women's age. The authors recruited a sample of 546 women as the second phase of a previous study (Grunfeld et al, 2002 (217)). All women completed a postal questionnaire about beliefs regarding the symptoms, causes and outcomes associated with breast cancer, attitudes towards help seeking and beliefs about one's ability to seek help. The inability to correctly identify a range of potential breast cancer symptoms was a significant predictor of intention delay in seeking help across all age groups. For women aged 35-54, negative attitudes towards medical help seeking for breast symptoms and a negative belief in one's ability to seek help were additional predictors of intention not to seek help. Holding negative beliefs about the consequences of breast cancer (i.e. that the disease could be potentially disabling or disfiguring) was found to be an important additional predictor of delay in help seeking among women aged over 65 years.

(Nosarti et al, 2000) (219)

This paper examined the influence exerted by women's symptoms, psychosocial, socio-economic status and ethnicity. The authors interviewed 692 women referred to a London breast clinic to identify factors associated with delay in presentation. Sixty per cent of women with a breast lump presented to their doctor within 27 days from symptom discovery, compared to 34% of those without a lump. Of patients with breast tenderness or pain, 76% presented to their doctor within 27 days from symptom discovery, compared to 62% of those without pain. Thirty-five per cent of the women delayed presentation 4 weeks or more (median 13 days). The most common reason was that they thought their symptom was not serious. Others thought their symptom would go away or delayed presenting because they were scared. Delay was associated with psychiatric morbidity but not age. Median system delay was 18 days. Patients who thought they had cancer and those so diagnosed were seen more promptly (median 14 days). Most socio- demographic factors, including socio-economic status and ethnicity, were non-contributory to delay.

(Nichols et al, 1981) (220)

In this UK study, women with breast symptoms referred to a specialist outpatient department were interviewed to ascertain the interval between first noticing a breast symptom and consulting a doctor. The largest component of delay was patient delay, with 20% of women delaying longer than 12 weeks. Long delays were related to age and symptoms other than lumps.

B. Papers that explore the influence of psychosocial factors

(Burgess et al, 2001) (221)

The authors interviewed 46 women in the UK with newly diagnosed breast cancer to explore the factors that influence general practitioner consultation by women with breast cancer symptoms. The main factors that influenced help seeking behaviour were: the identification the woman made of their symptoms as suggestive or not of breast cancer; their attitudes to requesting an appointment with a general practitioner; their beliefs about the consequences of cancer treatment; the effect of competing events and difficulties that could be prioritised over and above their personal health; and influences or experiences that functioned as triggers to action.

(Burgess et al, 2000) (222)

In this UK study, 158 women were interviewed five months after diagnosis to examine the influence of adverse life experiences and mood disorders on delayed presentation of breast cancer. The study did not identify statistically significant associations between these factors and delay, and suggested that neither adverse life events nor mood disorders in the year before symptom discovery increased the risk of patients with symptoms of breast cancer delaying their presentation to their general practitioner.

C. Papers that explore the influence of socio-economic status

(Malik and Gopalan, 2003)(199)

This is a prospective study of 138 recently diagnosed (within three months) breast cancer patients who had initially presented with breast lump in Pakistan. The majority (85%) of the patients discovered the lump accidentally, 10% were identified by a family physician and 5% as part of regular self examination. These patients took an average of 8.7 weeks to inform members of their family and 17.2 weeks until their first physician visit.

The initial perceptions of the lump included milk clots, trauma, infection benign growth, other and cancer (however only 17% perceived it as cancer). f those patients included in the study 73 (52.9%) were recorded to have delayed seeking medical advice. The reasons given were; antecedent use of complimentary/alternative therapies (34%), lack of significance attached to the lump (23%), fear of surgery (22%), conflicting personal commitments (7%), fear of cancer (5%) and other reasons (8%).

(MacLeod et al, 2000b) (223)

This was a UK population-based review of the case records of 417 women under 75 with breast cancer. Women living in deprived areas (according to the Carstairs Index) were more likely to present with large, locally advanced cancers or with metastatic disease than those living in affluent areas. There were no major differences in pathological prognostic factors at presentation between socio-economic groups. Although stage at presentation accounts for some of the differences in survival between affluent and deprived women, other unidentified factors adversely affect survival in deprived women.

(Thomson et al, 2001) (224)

The authors analysed two datasets relating to breast cancer patients in Scotland (23,866 women). Survival differences of 8.7% at five years and 10.2% at ten years between affluent and deprived women were observed across all age groups. No differences were observed in tumour size or nodal status at presentation between the deprivation groups. Although deprived women were more likely to have oestrogen receptor negative tumours, this difference explained only about a third of the difference in survival between affluent and deprived women. Women aged under 65 with non-metastatic disease were more likely to have breast conservation than mastectomy if they were affluent (45%) than deprived (32%); the affluent were also more likely to receive endocrine therapy (65%) than the deprived (50%). However, differences in treatment between affluent and deprived women do not seem to account for their different survival.

(Carnon et al, 1994) (225)

The authors carried out a retrospective analysis of data from a cancer registry within the catchment areas of two large hospitals in Glasgow, and attempted to explain socio-economic differences in survival from pathology and biochemistry records for 1361 women diagnosed with breast cancer. They could find no significant relation between socio-economic deprivation and four pathological prognostic factors at presentation: tumour size, negative nodes, tumour grade, and low oestrogen receptor concentration.

(Schrijvers et al, 1995) (226)

The authors explored the association between deprivation and survival from breast cancer in 29,676 women aged 30 and over. There was a clear gradient in survival that increased slightly with time since diagnosis, with better survival for women from more affluent areas. At all ages, women in the most deprived category had a 35% greater risk of death than women from the most affluent areas after adjustment for stage at diagnosis, morphology and type of treatment. In younger women (30-64 years), the survival gradient by deprivation category cannot be explained by these prognostic factors. In older women (65-99 years), part of the unadjusted gradient in survival can be explained by differences in the stage of disease: older women in the most deprived category were more often diagnosed with advanced disease. Other factors, so far unidentified, are responsible for the gradient in breast cancer survival by deprivation category.

(Quinn et al, 2001) (17)

Data from National Statistics provide some information about incidence and survival according to level of deprivation. In 1993, there was a negative gradient in the incidence of breast cancer by Carstairs deprivation category, the rate being about 30% higher in the most affluent groups. In contrast, mortality was not related to deprivation, implying that survival is better in the more affluent groups. The gap in survival between deprived and affluent groups in the 1980s was 6% at one year after diagnosis, and 9% at five years.

(MacLeod et al, 2000) (227)

The authors reviewed hospital and general practice case records of 821 women with invasive breast cancer. Women living in affluent areas did not receive better NHS care for breast cancer than women in deprived areas. Admissions to hospital for problems not related to breast cancer were more common in those living in deprived areas, as also were the number of consultations with their general practitioners in the two years following diagnosis.

D. Papers that explore the influence of age

(Kroman et al, 2000) (228)

The authors undertook a retrospective cohort study in Denmark based on 10,356 women

who were less than 50 years old when diagnosed with breast cancer to investigate the effect of young age on prognosis, and the influence of tumour staging and treatment on such association. Young women with low risk disease who did not receive adjuvant treatment had a significantly increased risk of dying than the women who did, and the risk was increased with decreasing age at diagnosis. This increased risk remained when women were grouped according to presence of node negative disease and by tumour size.

E. Papers that explore the influence of ethnicity

We have not found any relevant papers that exclusively investigated the influence of ethnicity in delayed presentation of women with breast cancer since the publication of the systematic review by Ramirez et al (1999) (216). Most recent identified studies that explore this factor have studied the experiences of African-American women. Caution is required when extrapolating results from these studies to England and Wales because of the different characteristics of the UK and US health care systems.

(Velikova, 2004)(229)

This retrospective UK study examined population based data on 16,879 women with breast cancer diagnosed between 1986 and 1994 with an aim to evaluate patient and provider delays of South Asian patients. Of those included in the study, 120 (0.7%) were South Asian and the standardised incidence rate ratio of South Asian with non-South Asian was 0.56 (95% CI 0.46-0.66).

Asian women were significantly younger than non-Asian at the time of diagnosis with a greater proportion being diagnosed before 50 years of age. The mean age at diagnosis of Asian and non-Asian was 49.7 years compared to 62 years respectively. A significantly higher proportion of South Asian patients presented with tumours larger than 2cm. Asian patients had a longer period of delay between symptom onset and presentation to a general practitioner with a median of 61 days compared to 31 days for non-Asian women which could not be explained. However no significant difference in delay was recorded between general practitioner visit and first hospital visit.

(Coates, 1992)(230)

This study collected retrospective data over 410 black women and 325 white women who were newly diagnosed with invasive breast cancer in 1985 or 1986 in the US in order to evaluate racial differences in delayed presentation.

The study found that black women were diagnosed more commonly at later disease stage. They were twice as likely to be diagnosed with Stage IV breast cancer and one and a half times as likely to be diagnosed with Stage III than white women. Additionally black women were only half as likely to be diagnosed with Stage I breast cancer. Black women were also found to be twice as likely as white women to be diagnosed with tumours larger than 5cm.

There was a low but statistically significant (15%) difference in the rate with which black women obtained initial consultation compared to white women and the median time between symptom recognition and consultation was 16 days for black women and 14 days for white women. The study concluded that although there were significant differences in delay, the differences were small and therefore unlikely to account for differences in survival rates.

(Bassett et al, 1986) (231)

This study used data from the Western Washington cancer surveillance system, and examined the influence of social class and race as predictors of survival in breast cancer in 1506 women in the first 11 years after diagnosis. Although survival was poorer among African-Americans, in

regression analysis, the difference between them and whites was largely explained by socio-economic status.

F. Paper that explore the influence of where people live.

(Robertson, 2004)(232)

This study evaluated data from 1097 patients with breast cancer and 1223 with colorectal cancer in the UK between January 1997 and December 1998 to asses delay in diagnosis in those living further away from treatment centres.

The geometric mean time from presentation to treatment was 42 days. However, it was found that women living further away were treated faster than those living closer (P=0.011) although multilevel modelling discovered that this may be attributable to then receiving earlier treatment at hospitals other than the cancer centres. This study also found that older people were treated more quickly but that deprivation was not a significant factor. Under multilevel model evaluation only one organisational variable remained significant: that treatment was quicker for those referred to general hospitals than for those referred to cancer centres, and quicker still for those referred to private hospitals.

Diagnostic Difficulties

In a comparison of survival of women with breast cancer in 12 countries in Europe, the lowest five year survival rates were in Spain, the UK, Estonia and Poland (55-64%) (Sant el al, 1998 (233)). In the period 1985-1989, one year and five year survival rates in the UK had improved, but were still below the European average (by 3-4% and 6-9% respectively), although were higher than in Slovakia, Poland or Estonia (Quinn et al, 1998 (234)). Variation in survival between regions in the same country were observed, a finding that may in part be related to socio-economic indicators.

However, survival rates in the UK have continued to improve, and recent UK data indicate that five-year survival is now 75.9% among women who present with symptoms [(www.cancerresearchuk.org/aboutcancer/statistics/survival). (http://www.doh.gov.uk/nhsperformanceindicators/hlpi2002/NationalDocument.pdf)], and 94.1% among women who have cancer detected at screening (http://www.cancerscreening.nhs.uk/breastscreen/publications/ba00-01.html).

No relevant, good quality systematic reviews were identified.

Primary Studies

(Ruston, 2004)(33)

This study draws information from 85 women newly referred to four specialist breast clinics and their referring general practitioners in the UK in order to understand the referral decision-making process. The data was collected through semi-structured interviews with the patients and then separately with their matched doctor.

The study reported that the general practitioners felt under pressure from a ‘cloud of medical litigation’ that surrounds breast cancer and symptoms associated with it to refer all cases. Only 25 of the 85 cases reported trying to deal with the patient in primary care. There were three main categories identified where general practitioners would refer, the first that in the professional opinion of the practitioner the symptoms were indicative of cancer and urgent referral required. The second was that the nature of the lump was ‘sinister’ and referral decision was affect by patient anxiety, family history and medico-legal concerns over the implications of not referring the patient. The third category was that the practitioner felt that the symptoms were probably benign and referral was based on patient anxiety and concern

over medico-legal consequences.

(The Bridge Study Group, 2002) (235)

The BRIDGE study evaluated the effects on patient management of breast disease guidelines issued to all general practitioners in the UK in January 1996. The practices in the BRIDGE study were randomised to receive either the breast lump or the breast pain guideline. During the study, general practitioners and practice nurses in the participating 34 practices were invited to take part in discussion seminars. The views of the participants were sought on the management of women with breast symptoms, the problems encountered, and influences on decisions about treatment. The transcripts of the recorded discussions were analysed to identify primary health care decisions emerged as an overarching theme, which set the context for discussions with participants about the nature of clinical presentation.

The “easy” presentation was characterised by a single problem of the breast, where the clinical findings did not conflict with the history, in a woman with no or few preceding breast problems. The “difficult” presentation usually concerned a woman who had presented on numerous previous occasions, and who may have had previous investigation or surgery. Many practitioners expressed considerable uncertainty in establishing diagnoses for patients with breast symptoms on clinical grounds alone. For example, there was a reluctance to make an essentially histological diagnosis on the basis of palpation.

Doctors reported high levels of anxiety running through these consultations, not all confined to the patient. This sometimes resulted in cautious management strategies, perhaps with negative consequences for patients who were exposed to radiation during mammography, but it calmed the general practitioner’s own anxieties. The high level of patient and doctor anxiety about breast symptoms appeared to be a pervasive context for managing women presenting with these conditions. These levels of anxiety reflected underlying perceptions of risk, mainly of breast cancer. There are medico-legal issues about the liability for a delayed or missed diagnosis of breast cancer. Other comments however, suggested that both doctors and patients overestimated the predictive value of symptoms for breast cancer and also did not relate presentation and diagnosis to the overall natural history of the condition.

There was variation between general practitioners about the effects of their past experiences on current practice. Some were open about the fact that adverse previous experiences had had a major impact on subsequent referring behaviour. For example, a young woman with cyclic breast pain, who later had cancer, reduced a general practitioner’s referral threshold. Others highlighted a change in clinical practice resulting from having previously missed a diagnosis. For instance a lump was only suspected as being cancerous when a patient returned with the same complaint, and a lymph node was detected in the axilla after a more thorough examination. There was particular concern about “atypical” presentations, especially those in younger women or those that had culminated in a patient’s death. A case many years previously sometimes continued to have a strong effect on a clinician’s practice.

Risk factors were mentioned frequently, especially a family history of breast cancer. A positive family history was seen as a factor likely to raise anxiety in a woman presenting with a breast problem, and make it more difficult for the general practitioner to reassure her.

The availability and use of investigations in specialist clinics may undermine attempts to rationalise referrals. General practitioners do not deny the need to assess patients, but on occasions they view it as legitimate to arrange referral purely for reasons of reassurance. These general practitioners may be resistant to changing their clinical practice as they feel that they are making ‘safe’ choices.

Management of breast cancer is often complex and is an area in which general practitioners do not feel they have special skills. A single, and often atypical, case may have a profound

influence on the way general practitioners manage their patients. Decision making about referral is often a consequence of a negotiation between patient and doctor. Attempts to modify clinical management of women presenting with breast symptoms must take account of these contextual issues, especially the high levels of patient and doctor anxiety.

(Watson et al, 2002) (71)

This cluster randomised controlled trial of educational interventions on general practitioner management of familial breast and ovarian cancer involved 688 general practitioners in 170 UK practices. Group A were provided an information pack and in-practice educational session, group B were mailed an information pack, and group C received no intervention at all. All general practitioner referral letters between March 1999 and December 2000 were audited and classified as appropriate or inappropriate referral.

The appropriateness of referrals improved among general practitioners who either received the guidelines alone (68.7% of referrals appropriate), or reinforced with an educational session (75.0% appropriate). In the group that did not receive the guideline or any other intervention, only 52.6% of referrals were judged appropriate.

(Burgess et al, 1998) (236)

In an interview study of 185 patients referred to a London breast clinic, referral did not occur at the first general practitioner consultation in 32 (17%). Delayed referral was observed more frequently among patients who were not aware of a lump at the time of presentation to the general practitioner (accounting for 44% of all cases of general practitioner delay). Patients experiencing general practitioner delay were younger (49 years vs. 55 years).

(McLeod et al, 1999) (237)

In this New Zealand study, 30 general practitioners were interviewed in depth to identify the key issues relating to the early detection and diagnosis of breast cancer in primary care. Following the interviews, a postal survey of a national random sample of 639 active general practitioners was undertaken, of whom 524 (82%) returned completed questionnaires.

The general practitioners reported that they were limited in their management of symptomatic women by the availability of services such as mammography and fine needle aspiration, and access to specialist breast surgeons or clinics. In some isolated rural communities, distance to services was a limiting factor. Some general practitioners used investigations to confirm the presence of a lump, or the nature of a lump. In the postal survey, 137 (27%) general practitioners personally aspirated cysts and 39 (8%) personally performed fine needle aspiration for diagnostic purposes. Most considered referral should occur either when a lump was palpated or after abnormal test results, although would refer women over aged 50 more promptly. In younger patients, recall and review were more likely.

Risk was viewed as associated with family history, although the definition of family history varied between respondents. There was a tendency to over estimate the impact of a first degree relative with breast cancer on the risk of cancer.

The key area of difficulty was reported as being the management of young women with lumpy breasts. Concern about the possibility of missing a malignant lump had to be balanced with the risk of causing unnecessary worry. Some general practitioners requested more information on the management of breast pain and nipple discharge.

12.4 Support and Information needs

12.4.1 Key Clinical Question:

What are the relevant patient vulnerability factors? These factors concern the psychological and social factors that influence the patient's ability to manage the consequences of referral for suspected cancer.

12.4.2 Evidence Question:

In women attending primary care services with breast symptoms, which patient vulnerability factors, when compared with patients without vulnerability factors, are associated with the need for psycho-social support; and which are not?

12.4.3 Evidence Statement:

There is little evidence about the support and information needs of women at referral. Before diagnosis, women are anxious and focused on quick referral and diagnosis (III).

General recommendations about the support and information needs of patients undergoing referral for suspected cancer are included in Chapter Seven. This section is confined to a consideration of the particular needs of women being referred with suspected breast cancer. There are very few studies of the needs of women suspected of having breast cancer at the time of referral, although many more studies have been undertaken relating to the time of diagnosis and after diagnosis. We discuss below a review that drew on studies undertaken at or after diagnosis, and also include information from the small number of studies that do consider the stage of referral.

Secondary studies

(Centre for Reviews and Dissemination, 1996) (232)

An Effective Health Care bulletin by the Nuffield Institute for Health and NHS Centre for Reviews and Dissemination (1996) offers a review of relevant trials that explore the information and communication needs of patients with breast cancer, as well as the psychosocial support required.

Information giving

The most common complaints by patients were about poor communication and inadequate information. Focus groups of patients revealed that they wanted information in both verbal and written forms about their cancer, treatment options, the likelihood of treatment success and possible side effects. Patients who are given more complete information showed greater satisfaction without an increase in anxiety.

Studies of consultations suggest that patients and their doctors may disagree about the adequacy of information given. Patients often feel they are not given sufficient information, while doctors tend to overestimate the amount of information they provide. Younger, better educated women, and those with better prognoses, tend to get more detailed information. Patients are likely to get more complete information when it is given in a structured way. They consistently find audiotapes of their consultation and information booklets about treatment helpful (grade of evidence range I-IIC).

Participation in decision-making

The fact that women want to be properly informed does not, however, imply that they want to be responsible for the final treatment decisions. The degree to which women wish to take an active role in decision-making varies between individuals and is affected by age, education and other social and cultural factors.

One study exploring the effects of choice between mastectomy and breast conservation surgery suggested that offering such a choice could cause distress (grade IIA). Other studies reported that a significant proportion of women found the process of making a choice problematic (grade IIA and IIC).

Psychosocial support

The bulletin identified 13 studies that assessed the effects of a range of psychotherapeutic interventions and also two critical reviews of the literature. These studies showed that psychotherapeutic counselling and educational interventions can improve quality of life and may possibly improve immune function and increase life expectancy. In general, interventions that focussed on past problems, as in the psychoanalytic model, were not found to be effective, whereas those that dealt with the woman's current problems were more likely to be helpful. A more definitive statement about the impact of psychosocial interventions was not possible because of the poor quality of the studies, which were often small and poorly controlled. The multiplicity of types of intervention and outcomes made comparisons between studies difficult.

Cognitive/behavioural interventions

Cognitive/behavioural interventions, including psychotherapy, relaxation training, systematic desensitisation, guided imagery, pain control training, biofeedback and physical exercise, have mainly been used to reduce side-effects of cancer therapy such as nausea. They have been assessed in 21 RCTs. 16 of these studies demonstrated some degree of benefit, while the rest were equivocal.

Effectiveness of follow-up policies

The bulletin also reviews trials that explore the effectiveness of different follow-up strategies. Two RCTs from Italy and one from Britain compared general practitioner-based with hospital follow up Results from both trials suggested that patients followed up by their general practitioners experience the same quality of life as those cared for by specialist clinics, and that general practitioner follow-up was acceptable to both patients and general practitioners.

The provision to women of a contact number for the breast care nurse has been shown to lead to better quality of life and lower levels of psychological and physical morbidity than either routine care or support from a local voluntary agency.

(Centre for Reviews and Dissemination 2002) (192)

The Service Guidance Evidence review did not identify trials of interventions to improve communication between professionals and patients leading up to referral.

Primary Studies

We have very little evidence on need for information and support of women who are referred. There are studies of the reasons for delay in presentation of symptoms, and in reaction to investigation and diagnosis (Oktay, 1998), but the needs of women who are referred have not been adequately studied.

(Breakthrough Breast Cancer 2002) (238)

A qualitative study involving individual and group interviews was undertaken and did consider this question. Women had different levels of knowledge about breast cancer. The pre-diagnosis stage was distressing because of fear; women were extremely sensitive to what

was said to them and how health professionals behaved. The focus at this stage was on quick referral for testing and diagnosis. Although no recommendation from the study dealt specifically with initial presentation and referral, it was recommended that women be given clear expectations of services. Highlighted in the study as particularly beneficial was 24-hour access to information, advice and psycho-social support pre-diagnosis and beyond and, in particular, encouragement to use such services.

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The National Collaborating Centre for Primary Care

REFERRAL GUIDELINES FOR SUSPECTED CANCER IN ADULTS AND CHILDREN.

PART TWO

CHAPTERS 13 - 21

April 2011
A recommendation in this guideline (see page 5) has been updated and replaced by section 1.1.1 in 'Ovarian cancer' (NICE clinical guideline 122, 2011).
Available from www.nice.org.uk/guidance/CG122

Contents

13 Gynaecological cancer 4

13.1 Symptoms and Signs _____11

13.2 Investigations _____32

13.3 Delay and Diagnostic Difficulties _____40

14 Urological cancers 48

14.1 Symptoms and Signs.....60

14.2 Investigations.....77

14.3 Delay and Diagnostic Difficulties.....81

15 Haematological cancers.....90

15.1 Signs and Symptoms.....101

15.2 Investigations.....111

15.3 Delay and Diagnostic Difficulties.....118

15.4 Support and Information needs.....122

16 Skin cancer.....124

16.1 Symptoms and Signs.....132

16.1 Investigations.....152

16.3 Delay and Diagnostic Difficulties.....158

17 Head and Neck cancer.....179

17.1 Signs and symptoms.....187

17.2 Investigations.....206

17.3 Delay and Diagnostic Difficulties.....210

17.4 Support and Information needs.....231

18 Brain and CNS cancer.....234

18.1 Signs and Symptoms.....241

18.2 Investigations.....252

18.3 Delay and Diagnostic Difficulties.....255

18.4 Support and Information needs.....263

19 Bone cancer and sarcoma.....265

19.1 Symptoms and Signs.....270

19.2 Investigations.....278

19.3 Delay and Diagnostic Difficulties.....280

20 Children's and Young People's Cancer.....*284*

20.4 Signs and Symptoms.....301

20.2 Investigations.....329

20.3 Delay and Diagnostic difficulties.....330

20.4 Support and Information needs.....345

21 Research recommendations.....*363*

Reference List_____*372*

13 Gynaecological cancer

General recommendations

1 A patient who presents with symptoms suggesting gynaecological cancer should be referred to a team specializing in the management of gynaecological cancer, depending on local arrangements. D

Specific recommendations

2 The first symptoms of gynaecological cancer may be alterations in the menstrual cycle, intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding or vaginal discharge. For a patient who presents with any of these symptoms, the primary healthcare professional should undertake a full pelvic examination, including speculum examination of the cervix. C

3 In patients found on examination of the cervix to have clinical features that raise the suspicion of cervical cancer, an urgent referral should be made. A cervical smear test is not required before referral, and a previous negative cervical smear result is not a reason to delay referral. C

4 Ovarian cancer is particularly difficult to diagnose on clinical grounds as the presentation may be with vague, non-specific abdominal symptoms alone (bloating, constipation, abdominal or back pain, urinary symptoms). In a woman presenting with any unexplained abdominal or urinary symptoms, abdominal palpation should be carried out. If there is significant concern, a pelvic examination should be considered if appropriate and acceptable to the patient.
NOTE: This recommendation has been updated and replaced by section 1.1.1 in 'Ovarian cancer' (NICE clinical guideline 122, 2011). Available from www.nice.org.uk/ guidance/CG122

5 Any woman with a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids or not of gastrointestinal or urological origin should have an urgent ultrasound scan. If the scan is suggestive of cancer, or if ultrasound is not available, an urgent referral should be made. C

6 When a woman who is not on hormone replacement therapy presents with postmenopausal bleeding, an urgent referral should be made. C

7 When a woman on hormone replacement therapy presents with persistent or unexplained postmenopausal bleeding after cessation of hormone replacement therapy for 6 weeks, an

urgent referral should be made. C

8 Tamoxifen can increase the risk of endometrial cancer. When a woman taking tamoxifen presents with postmenopausal bleeding, an urgent referral should be made. C

9 An urgent referral should be considered in a patient with persistent intermenstrual bleeding and a negative pelvic examination. D

Vulval cancer

10 When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made. C

11 Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently. D

12 Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms, it is reasonable to use a period of 'treat, watch and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer. C

Introduction

The gynaecological cancers considered in these papers are those of the uterus (endometrium), ovary, cervix and vulva. Screening is excluded, and the focus is on patients presenting in primary care with symptoms or signs that might be related to cancer.

Incidence

Cancer of the cervix

In 1997 in England and Wales cervical cancer ranked as the seventh most common female cancer accounting for 2.5% of cancers in women. By 2001 there were 2,418 newly registered cases of cervical cancer.

These guidelines do not deal with screening. Guidelines on referral for colonoscopy on the basis of cervical cytology results has been published recently by the NHS Cancer Screening Programme (NHSCSP, 2004).

Ovarian cancer

Classification of ovarian cancer is complicated as it is not a single disease but rather a group of cancers which arise from different cell types.

There were 5,817 new registrations of ovarian cancer in England and Wales in 2001. The disease occurs mainly in post menopausal women peaking in the 70-74 years age group.

Over 90% of primary ovarian malignancies are epithelial adenocarcinomas arising from the surface epithelium. Subgroups of the epithelial malignancies include serous adenocarcinoma, and endometroid, mucinoid and clear call cancers.

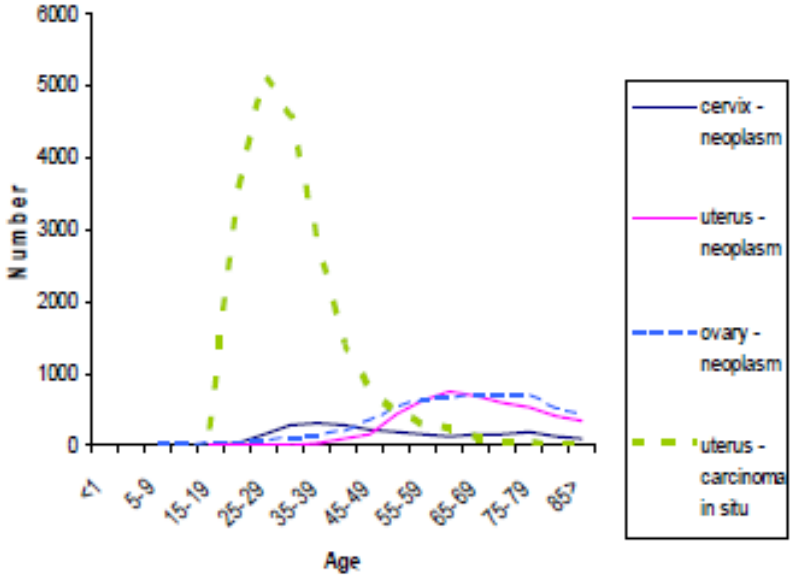
Cancer of the uterus

There were 5,490 cases of cancer in the uterus (endometrial cancer) in England and Wales in 2001. Incidence is low below the age of 25 years and peaks at approximately 60 years.

Endometrial cancer is almost always a disease of postmenopausal women, and is associated with obesity, low parity and late menopause. Approximately
60-70% are adenocarcinomas.

Figure 1 Newly diagnosed cases of gynaecological cancers in 2001 in England and

Wales. (77)



Mortality

Cancer of the cervix

In 2002 there were 995 deaths caused by cancer of the cervix. Mortality from cervical cancer increases steadily from age 30 years and peaking at age 80 years.

Ovarian cancer

In 1997 ovarian cancer accounted for 6% of all cancer deaths in women. By

2002 deaths caused by cancer of the ovary totalled 4,097. Mortality is steady and low until ages 40-44 when it begins to rise with age. Epithelial ovarian cancer in the second and third decade are uncommon but are treatable if diagnosed without delay.

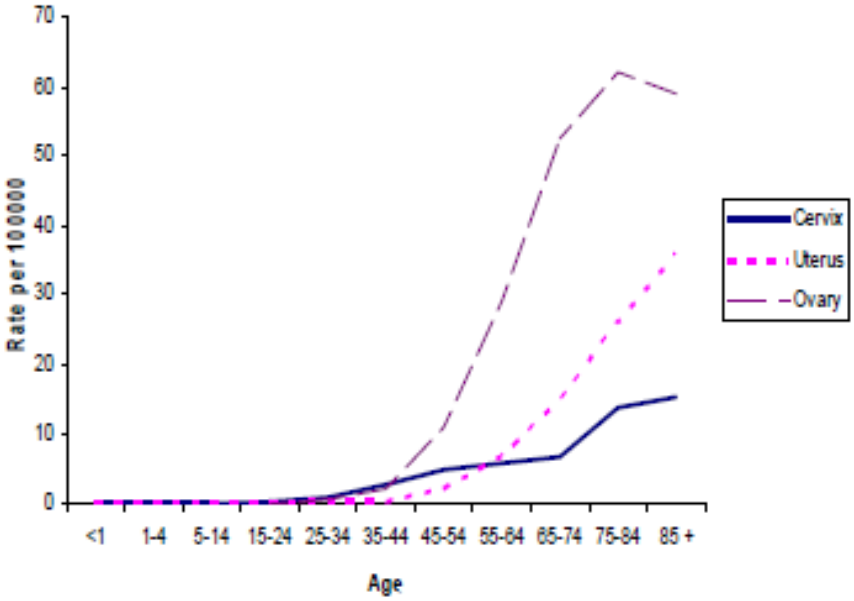
Cancer of the uterus

There were 919 deaths caused by uterine cancer in 2002. Mortality rates are low in those aged 60 years or less.

Vulval cancer

There are around 1000 new cases of vulval cancer each year in England and Wales, accounting for less than 5% of all gynaecological cancers. In 2002, there were 332 deaths from vulval cancer. It usually presents in the elderly, most commonly aged 70 or over. The aetiology is unclear, although there is an association with vulval dystrophy and vulval intraepithelial neoplasia (VIN). Around 90% of vulval cancers are squamous cell in origin, and 5% are melanomas.

Figure 2 Mortality figures from gynaecological cancers for 2002 in England and Wales. (78)



Review of referral audits

The review(13) identified 45 relevant audits. The proportion of two week referrals found to be in accordance with the symptoms listed in the guidelines ranged from 42% to 100% (19 audits). The proportion of patients referred under the two week system who were found to have cancer ranged from 0% to 25% (17 audits). The proportion of patients with cancer who had been referred under the two week system ranged from 0% to 34% (six audits). 64% to 94% of two week referrals had been considered to be clinically appropriate (six audits).

13.1 Symptoms and Signs

13.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of gynaecological cancers (cervix, ovary, endometrium, and vulva), and those that make cancer less likely as a diagnosis?

13.1.2 Evidence Question:

In people attending primary care services with gynaecological symptoms, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer; and which symptoms and signs are not?

13.1.3 Evidence Statements:

Expert opinion suggests that abnormal bleeding (postcoital, postmenopausal and inter-menstrual bleeding) can be presenting features of cancer(IV)

Cancer of the cervix

The incidence of cervical cancer rises rapidly in the years of 25-35 has peaks at around age 35-39 years (20/100,000 population) and continues at a similar rate peak at 75-79 years (20/100,000). (III)

Cervical cancer is rare in women under 20 years of age after this the incidence rises, reaching a peak at 35-39 years of age (20/ 100,000) and this rate is maintained at a similar level. (III)

Ovarian

The incidence of ovarian cancer is below 10/100,000 in women aged 40 and below, and 60/100,000 by age 70 years. (III)

Ovarian cancer may present with a variety of non-specific symptoms including tiredness, abdominal discomfort, gastrointestinal and urinary symptoms, and back pain. (III)

Signs associated with ovarian cancer include increased abdominal size and a palpable mass. (III)

Cancer of the uterus

Endometrial cancer is rare below the age of 35 years, but is more common after the age of 50 (50/100,000 population). (III)

Postmenopausal bleeding is regarded in expert opinion as an indication for investigation for endometrial cancer. (III)

Vulval cancer

The presenting symptoms of vulval cancer included vulval bleeding, pruritis and pain. (III)

The presenting signs of vulval cancer include a lump or other lesion. (III)

Introduction

Evidence about the diagnostic value of symptoms and signs of gynaecological cancer among patients presenting in primary care is limited. There were no secondary studies, and the primary studies largely consisted of case series and case control studies and surveys. The studies only included women after referral and diagnosis, and involved retrospective collection of information about the symptoms and signs before or at diagnosis. No study was identified that had been undertaken in primary care to investigate the presenting symptoms or signs that may, or may not, be explained by cancer.

One article was identified for inclusion on the signs and symptoms of cervical cancer.

Studies of the presenting features of endometrial cancer were generally concerned with postmenopausal bleeding and consequently are discussed in the context of investigations.

Six studies addressed the signs and symptoms of ovarian cancer. However, these compared the signs and symptoms of women presenting with borderline or ovarian cancer and early and late stage diagnosis.

Guidelines

(SIGN, 2002)(239)

The SIGN guidelines on investigation of post-menopausal bleeding did not cite primary studies on indications for referral, the only reference being to the Department of Health (2000) guidelines. The guideline stated:

> General practitioners should take into account the pattern of bleeding, its relationship to the use of HRT and patient preferences when considering referral. Concern by either general practitioner or patient about the possibility of PMB signalling endometrial cancer constitutes sufficient grounds for referral(2)

This statement was followed by a level D recommendation

'The risk of endometrial cancer in non-HRT users complaining of post- menopausal bleeding and in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation.'

Statements of recommended best practice based on the clinical experience of the guideline development group were then listed:

The following questions should be asked in the assessment of patients with abnormal bleeding on HRT:

- When does bleeding occur with respect to the oestrogen and progestogen phase? (Women on sequential regimens should ideally not experience withdrawal bleeding before completion of the progestogen component of the preparation).
- How long does the bleeding last and how heavy is it?
- Was there a period of amenorrhoea before HRT was started?
- Is there a problem that suggests poor compliance?
- Is there a reason to suspect poor gastrointestinal absorption?
- Is the patient taking any other drugs?
- Women presenting with post-menopausal bleeding should receive a pelvic examination at some stage during the course of clinical assessment.
- Whether or not to continue HRT use prior to investigation may depend on the patient's wishes and how long she has to wait for investigations, but there is no specific reason for discontinuing it.

Cancer of the cervix

(Viikki et al, 1998)(240)

This study investigated the predictive value of bleeding for detecting subsequent gynaecological or urinary cancers among women screened negative for cervical cancer in Finland. Data from the Finnish Mass Screening Registry and National Cancer Registry were used to investigate the long term significance of bleeding symptoms. The mean length of follow-up was 7.0 years. A total of 37,596 screened negative women in the national population- based mass screening programme for cervical cancer were classified as having reported bleeding symptoms when screened. These were categorised into bloody discharge, coital bleeding, irregular bleeding, postmenopausal bleeding, and were followed up (1985-1994) to monitor the subsequent risk of cancer.

The prevalence of postmenopausal bleeding among the 37,596 women (all ages) was 0.2%, bloody discharge was 1.1%, coital bleeding 0.7%, and irregular bleeding 3.9%. During follow up 753 cancers were observed among women with bleeding symptoms; 197 (26%) of these were gynaecological. The relative risk of uterine cancer was 3.6 in women with postmenopausal bleeding. The RR of cervical cancer was 1.1, (95% CI 0.8-1.4), not significantly increased during follow up for a maximum period of ten years. Women with bloody discharge had an elevated risk of gynaecological cancers, attributable to uterine cancer (SIR 2.2, CI 1.3-3.4). Coital bleeding was rare and not associated with gynaecological cancer (SIR 1.0). Irregular bleeding was associated with an increased risk of cancer of corpus uteri (SIR 1.8, 1.3-2.5). Risk of uterine cancer increased with any bleeding symptom (SIR 2.1, 95% CI 1.6-2.6) but the RR associated with postmenopausal bleeding was 3.6 (95% CI 2.0-6.0).

It should be noted that the symptoms were reported at the time of screening and it is not clear whether the findings can be related to people consulting with these symptoms.

Ovarian cancer

No secondary studies were identified. No studies of patients presenting in primary care were identified. The primary studies included patients in secondary care after diagnosis. Consequently, they only provided limited evidence to aid differentiation between symptoms and signs that would or would not indicate the need for referral.

Primary studies

(Flam et al,1988)(241)

The symptomatology of ovarian cancer was retrospectively reviewed in a case series of 362 patients who had been referred to a single specialist Swedish centre. The disease was classified at early (stages IA-IIA) or advanced (stages IIB-IV) at diagnosis and no follow up was reported. Patients were asked to give an account of their initial symptoms and those leading to their decision to seek a consultation. The main abdominal symptoms could be divided into three groups: 1) abdominal swelling with increased abdominal girth, 2) pain and 3) gastro-intestinal symptoms such as heartburn and eructation.

The presentation of early and late stage cancer was influenced by the Swedish health care system, patients being able to choose whether to consult a primary care practitioner or gynaecologist.

The most common initial symptoms were abdominal swelling and/or palpable tumour, pain and gastro-intestinal symptoms. The initial symptoms, however, were not necessarily those that prompted patients to seek medical advice. The most common reason for seeking advice was pain in the early group, but abdominal swelling in the advanced group (27.9%). Gynaecological disease was suspected by 55.2% of the early group and 37.9% of the advanced group.

(Vine et al, 2001)(242)

The study investigated the types and duration of symptoms among women with invasive versus borderline ovarian tumours. The people included were women 20-69 years of age, diagnosed histologically as having primary epithelial invasive or borderline (i.e. having histological features of benign as well as malignant disease) ovarian cancer between 1994 and 1998. They were identified from 39 hospitals in the US. Information about symptoms was obtained by interviews conducted in the homes of study participants. To reduce the risk of recall bias, only cases interviewed within six months of diagnosis were included in the study. A total of 1278 cases met age and location of residence criteria. Cases were excluded if English was not spoken or patients were not mentally competent (25), diagnosis greater than 6 months prior to interview (296), critically ill or dead (69), or untraceable (15), physician did not give consent to contact (14) and refusal to participate (92), resulting in 767 (60.0%) completed interviews.

The lack of information about tumour stage and size prevented assessment of the effect of these factors on the reporting and duration of symptoms as well as delay in diagnosis. The percentage of women with symptoms was significantly higher in invasive versus borderline disease (any symptoms 92% versus 84%, P=0.001; pelvic discomfort 71% vs. 66%, P<0.05; bowel irregularity 47% versus 35%, P<0.001). Women with borderline disease had symptoms for longer periods of time than those with invasive disease or pelvic discomfort (P<0.001), bowel irregularity (P=0.002) and urinary frequency/urgency (P=0.011). Pre-diagnostic symptom duration was longer among borderline versus invasive cases (median six vs. four months, P<0.001). Women with invasive cancers were significantly older (mean age: invasive, 53.0 years; borderline 44.7 years, P<0.0001), but there was no difference between women with invasive and borderline tumours with respect to race, education, or household income. Borderline and invasive cases reported similar types of symptoms. However, borderline cases were twice as likely as invasive cases to report not having had symptoms (16 vs. 8%, P=0.005), and twice as likely as invasive cases to be diagnosed through routine examination (28 vs. 16%, P=0.001). Invasive cases were more likely to be diagnosed because of symptoms (62 vs. 48%, P=0.002).

(Goff et al, 2000)(243)

This Canadian study focused on symptoms and other factors that may contribute to the delayed diagnosis of ovarian carcinoma. It was a questionnaire survey of women in cancer support groups, and women were invited to copy the questionnaire to other patients. A total of 1725 questionnaires were returned from women in 46 states and four Canadian provinces (1327 originals and 398 copies). The response rate for the initial survey was 88%. The median age of the surveyed patients was 52 years (range 18-84) and 13% were older than 65 years and 70% had Stage III or IV disease classified according to the International Federation of Gynaecology and Obstetrics (FIGO). The symptoms asked about were selected from published reports and small focus groups. In the survey selection bias may have occurred

because the women who participated in this study were those who chose to subscribe to a newsletter or those active in support groups.

In response to whether they had symptoms before the diagnosis of ovarian carcinoma, 5% of patients reported they had none, 61% reported increased abdominal size, 57% abdominal bloating, 47% fatigue, 36% abdominal pain, 31% indigestion, 27% urinary frequency, 26% pelvic pain, 25% constipation,

24% urinary incontinence, 23% back pain, 17% pain with intercourse, 16% unable to eat normally, 14% had a palpable mass, 13% vaginal bleeding, 11% weight loss, 9% nausea, 3% bleeding with intercourse, 1% deep venous thrombosis and 1% diarrhoea. When responses were grouped according to symptom categories, 77% reported abdominal symptoms, 70% gastrointestinal, 58% pain, 50% constitutional, 34% urinary and 26% pelvic. Only 11% of women with Stage I/II and 3% with Stage III/IV reported they were completely asymptomatic before their diagnosis. Thirteen percent of participants reported being told by their provider that nothing was wrong, 6% were diagnosed with depression, 12% stress, 6% constipation, 15% irritable bowel syndrome, 9% gastritis and 47% were given other diagnoses. Only 20% of patients were told initially they might have ovarian carcinoma.

Women who had the most symptoms were significantly younger. Women with advanced disease were significantly more likely to have symptoms than those with early stage disease. The types of symptoms between both groups were similar however. Those who ignored their symptoms were significantly more likely to have more total symptoms and advanced stage disease compared with those who did not (85% vs. 74%; P=0.002).

(Olson et al, 2001)(244)

A retrospective case control study was conducted in two US hospitals to assess the presence and duration of various symptoms of ovarian cancer and the use of medications in comparison with healthy women. Symptoms of ovarian cancer in recently diagnosed patients (cases N=168) were compared with those experienced by healthy women in the community using a case- control design (N=251). Between 1994 and 1997, women diagnosed with ovarian cancer, aged 18 or above, resident in the US and English or Spanish speaking were approached while awaiting surgery. The mean time from diagnosis to interview was 4.7 months, and 73% were interviewed within nine months. Women were asked whether they had experienced one or more of eight symptoms or used three types of medication in the six to 12 months before diagnosis. Affected patients were grouped into those with earlier and later stage disease.

Recruitment difficulties in an urban area led to a variety of controls being used. One group of controls was randomly selected from the community (N=81) matched by five year age groups, and another through commercial mailing lists (N=78) matched by demographic, socioeconomic and lifestyle factors. Convenience controls consisting of friends of cases and other women (N=92) were also used. A lengthy questionnaire and the collection of biologic specimens led to a low response rate. Although the controls included a convenience sample and a randomly chosen community group, the results did not differ in meaningful ways when the convenience controls were excluded.

The symptoms were selected based on reviews of earlier reports in the literature and in consultation with clinicians. The most common symptoms among cases were: unusual bloating, fullness and pressure in the abdomen (71%); unusual abdominal pain or lower back pain (52%); and lack of energy (43%). The proportions of controls reporting these symptoms were 9%, 15% and 16% respectively, resulting in odds ratios and 95% CIs of 25.3 (15.6,40.9), 6.2 (4.0, 9.6), and 3.9 (2.5, 6.1), respectively, for these symptoms. Bloating, fullness and pressure was of more recent onset among cases than controls (4.9 months compared with 7.6 months, P=.01). Lack of energy was noted by 43% of the cases and 16% of the controls (odds ratio 3.9, 95% CI 2.5, 6.1). Patients who experienced bloating, fullness and pressure were more likely than controls to report that the symptoms were constant. Most of the symptoms were experienced for a longer period of time by women with early rather than late stage disease.

The exact response rates were not mentioned. The study was reported to be limited by

relatively small numbers of cases, especially women with early disease, and 35% of affected patients mentioned other symptoms that were not listed on the questionnaire. The most common additional symptom was pain in the side or ribs, mentioned by seven.

(Smith et al, 1985)(245)

This US case series evaluated characteristics of ovarian cancer symptoms, their perceived cause, and delay in seeking a diagnosis associated with stage, grade and histologic features of disease at diagnosis among patients with cancer of the ovary (N=83) identified in the Iowa National Cancer Institute-Surveillance, Epidemiology, and End Results (NCI-SEER) population-based cancer registry. Cases had been diagnosed 1980 to 1982.

Of a total of 107 eligible cases, data about 82 were obtained. Twenty-five were eliminated either because they could not be interviewed due to severe illness, refusal or physician's refusal of permission, or death, or lack of staging at the time of study.

Patients were asked if they had experienced any symptoms that prompted them to seek a diagnosis. Those who said 'No' (N=26) were asked how their cancer had been discovered; those who said 'Yes' (N=56) listed symptoms they noticed before diagnosis and those that convinced them to seek medical attention. The sample included a large number of asymptomatic patients more likely to have later stage disease. The cohort did not include older patients for whom the results may be less applicable. Only pain was significantly more likely to differentiate those with extensive disease. In contrast, localised disease was associated with a greater probability of reporting urination problems, irregular menstrual cycles and fatigue.

A majority (56, 68.3%), regardless of stage, had experienced symptoms that prompted a consultation. Asymptomatic women were more likely to be identified with later stage disease ($P<0.10$). Among those (N=26) believing they had no symptoms before diagnosis, in 34.6% the tumour was detected during a yearly health check. The most common number of symptoms occurring together was two (72.2%), with abdominal swelling most likely to be identified with other conditions: fatigue (23.5%), urination problems (17.6%), and pain (17.6%). Swelling, pain and fatigue were commonly seen together (29.4%). Only abdominal pain and swelling were significantly associated ($P<0.05$) with later stage disease. Pain was likely to convince women to seek a diagnosis. Those aged 40-49 years were more likely to report symptoms than patients in other age groups ($P<0.05$). No relationship between age and type or number of symptoms was found, nor associations with other sociodemographic factors. Less frequently noticed symptoms were irregular vaginal bleeding, metrorrhagia, indigestion and urination problems (frequency or difficulty). Symptoms were viewed less seriously if they were believed to be related to indigestion or menopausal conditions. Irregular menstrual cycles often convinced patients with early-stage cancers to seek a diagnosis.

(Wikborn et al, 1993)(246)

This case series investigated symptoms by reviewing the clinical records of patients with ovarian cancer to identify information from first consultation to operation and diagnosis. A total of 160 patients diagnosed in a Swedish specialist centre between 1981 and 1986 with epithelial ovarian cancer that could be staged constituted the study population.

No specific group of symptoms could be linked to type or stage of ovarian cancer. Gastrointestinal symptoms were more common in patients with histological class IC tumours. Only 21% complained of gynaecological symptoms. The majority of women did not experience symptoms in the genital organs. Women with class IC cancer had significantly more advanced disease than those with 2C-5C cancer as 77% had a stage III-IV tumour compared with 40% of class 2C-5C patients. The mean age was 62.6 years (range 25-87 years). Several women had more than one type of symptom, pain and abdominal swelling being the most common combinations. Irrespective of stage, 37% had symptoms related to the bladder; approximately 65% had pain and 60% had abdominal swelling. Gastrointestinal and general symptoms were less common in stage 1 than in higher stages. This was not the case with tumour classes 2C-5C disease.

Vulval cancer

Secondary studies

(Ghurani and Penalver, 2001)(247)

This paper is a recent authoritative review. The most common symptoms were reported to be pruritus, a visible or palpable mass, pain, bleeding, ulceration, dysuria, and vaginal discharge. The authors recommended that any vulval lesion discovered on physical examination should be biopsied to rule out neoplasm.

Primary studies

(Rosen and Malmstrom, 1997)(248)

This study was a retrospective review of the hospital records of 328 patients with histologically confirmed primary invasive vulval cancer (Sweden). It was performed to evaluate the survival after treatment of vulval cancer in relation to various prognostic factors (FIGO staging, tumour grading, age at diagnosis, heredity for any cancer, childbirth, and prior history of any cancer).

Mean and median age at diagnosis was 69 (range, 26-105) years. The most common presenting symptoms were pruritus (24%), smarting pain (15%), and a vulval lesion (15%). Patient's median delay was six months, and the average was 16 (range, 0-360) months. Squamous cell carcinoma was the most common histological form of vulval cancer, constituting 91.4% of the cases (N= 300). Melanoma constituted 3% (N = 10), Paget's disease 2.4% (N= 8), cancer of the Bartholin's glands 1.8% (N = 6), adenocarcinoma 0.6% (N = 2), and basal cell carcinoma 0.6% (N = 2). Survival analyses were limited to the 300 patients with squamous cell vulval cancer.

The majority of patients with squamous cell vulval cancer were stages I (35%) or II (37%) at diagnosis, 36% were well-differentiated tumours, 43% moderately differentiated tumours, and 15% poorly differentiated tumours. There were significant differences in survival when comparing patients older than mean age at presentation (69 years) with the patients who were younger than mean age ($P < 0.01$). There were significant ($P < 0.00001$) differences in corrected survival times between different FIGO stages: five year survival rate was 93% for stage I, 60% for stage II, 40% for stage III, and 13% for stage IV. Histologic grade was also shown to be a significant prognostic marker for survival ($P = 0.02$): well-differentiated tumours had a five year survival rate of approximately 70% while moderately or poorly differentiated tumours had a five year survival rate of approximately 55%. Both parity and previous history of cancer did not influence survival times significantly.

(Messing and Gallup, 1995)(249)

The authors undertook a retrospective review of the hospital medical records (USA) of 78 women treated for squamous cell carcinoma of the vulva over a period of 15 years. They compared women younger than 45 years with those 45 years and over for historic risk factors, treatment modality, and outcome.

The mean age was 60.7 years (median 63, range 29-91). Two age peaks were noted at ages 50 and 70. Over the study interval, the average presenting age of these patients decreased from 69 to 55 years. Eighteen (23%) of the cases were in women younger than 45 years of age. The median duration of symptoms before seeking medical care was six months. Patients presented with complaints of a lesion, lump, or pain in 70% of cases. There was no significant difference in the duration of symptoms for younger versus older women.

Women under 45 were found to have a stronger history of condyloma ($P<0.001$, 95% confidence interval 3.69-87.96). There was no significant difference by age in smoking history, alcohol consumption, or tumour size. Older women were more likely to have advanced stage disease ($P=0.03$, 95% CI 0.43-0.91) but no metastatic disease. The median tumour size at presentation was 4cm (range 0-27). Lesion size over 2cm was significantly associated with the presence of metastatic disease ($P < 0.001$). The following were associated with decreased survival: FIGO stage IV ($P <0.001$, 95% CI 1.6-5.1), presence of metastases ($P < 0.001$,

95% CI 1.5-3.6), and tumour size greater than 2cm (P=0.002, CI 0.09-0.34). There was no detected difference in survival for women in either group.

(Jones et al, 1997)(250)

The objective of this study was to determine trends in the clinicopathology of vulval squamous cell carcinoma over the past two decades, with particular reference to vulval intraepithelial neoplasia (VIN) during this time. The authors reviewed retrospectively the clinical records of two groups of women presenting with squamous cell carcinoma of the vulva to a New Zealand gynaecological oncology unit. One group involved 56 cases presenting between 1965 and 1974, and the other involved 57 cases presenting between 1990 and 1994.

The mean age at presentation was 68.4 (44-92) years (median 72 years) in the 1965-1974 cohort, and 69.2 (22-93) years (median 71 years) in the 1990- 1994 cohort. In the 1965-1974 cohort, only one patient was younger than 50 years of age, whereas in the 1990-1994 cohort, 12 women (21%) were younger than 50 years (P = 0.001). There were no statistical differences in FIGO stage between the two cohorts.

When stratified according to age, 11 of 13 women younger than 50 years, compared with 10 of 100 women older than 50 years of age, smoked cigarettes (P < 0.001). Ten of the 13 women younger than 50 years of age, compared with 13 of 100 women 50 years of age or older, had warty and/or basaloid VIN III associated with their invasive carcinoma (P < 0.001). Multiple lower genital tract neoplasia was also more common in women younger than 50 years of age (P < 0.001).

Warty and basaloid VIN was associated with 16 of 19 (84%) warty or basaloid carcinomas and with seven of 94 (7.4%) typical squamous cell carcinomas (P< 0.001). In contrast, non-neoplastic epithelial disorders were associated with 55 of 94 (58.5%) typical squamous cell carcinomas and with none of the 19 basaloid or warty carcinomas.

(Sturgeon et al, 1991)(251)

The authors identified 2,948 cases of in situ and 2,346 invasive squamous cell tumours of the vulva diagnosed between 1973 and 1987 from population- based cancer registries (USA), in order to examine recent trends in the incidence of vulval cancer.

The annual incidence of in situ vulval carcinoma for all races combined nearly doubled from 1.1 to 2.1 per 100,000 woman years, during the period from 1973 to 1976 and 1985 to 1987. The largest proportional increase occurred among white women <35 years old, for whom the rate nearly tripled. Increases were more modest among black women than among white women, with the rate not quite doubling among black women <35 years old. In situ rates among blacks of all ages were higher than those among whites before 1977, but the black-white differential had diminished in more recent years. The peak in situ rate has shifted over time from women > 54 years to women aged 35 to 54.

The invasive squamous cell carcinoma incidence for all races combined was relatively stable over 1973 to 1976 and 1985 to 1987. Rates in each age group were also relatively steady, although among white women they tended to decline among those aged >55. Little racial difference was evident under age 35; rates were higher at ages 35 to 54 among black women and at ages >54 among white women. In contrast to in situ cancers, invasive rates increased steadily with age.

Risk Factors

Cancer of the cervix

(Parikh et al, 2003)(252)

The authors conducted a meta-analysis after pooling the data from previously reported case-control studies (N= 57) of cervical cancer or dysplasia, which contained individual-level information on socio-economic characteristics, to investigate the relationship between cervical

cancer, social class, stage of disease, geographical region, age and histological type.

Overall, an increased relative risk of dysplasia and cervical cancer with decreasing social class was observed. Women in the middle social class group were at approximately a 26% increased risk of cervical disease (95% CI 17-36%, whereas women in the lower social class tertile were at approximately 80% increased risk when compared to women in the upper tertile (95% CI 69-92%). These elevated risks persisted after analysis was restricted to those studies which included only women aged <50 years (97% increase in risk of invasive cancer for the low socio-economic group; 95% CI 80-115%, and 58% increase in risk of dysplasia for the low socio-economic group; 95% CI 41-78%). When stratified by geographical region, the increased risk identified in studies that originated from Western Europe appeared to be only moderate, with a 45% increased risk of cervical disease in the low social class group as opposed to the high social class group (95% CI 29-62%). When the analysis was restricted to studies that only included cases of cervical cancer, the increase in risk between social class and invasive cervical cancer was reduced to 28% (95% CI 10-49%) for Western European studies.

There was significant unexplained heterogeneity in most of the pooled odds ratios, which might have been possible because of the inability to control for variables such as background HPV prevalence.

(Paley, 2001)(253)

This authoritative review reported that risk factors for cervical cancer are well defined and those with the most impact on risk of developing cervical cancer include early sexual activity, smoking, multiple sexual partners and an immunocompromised state. Due to the link between sexual activity and cervical cancer, infection with human papillomavirus (HPV - the most common sexually transmitted viral disease) is believed to be a strong predictor of cervical cancer.

Ovarian cancer

(Bell et al, 1998)(254)

Although a wide variety of risk factors have been proposed for ovarian cancer, this review of the use of CA125 for screening identified four main risk factors of epithelial ovarian cancer which are summarised in Table 1.

Information from pooled data from 12 US case control studies indicated that pregnancy and oral contraceptives had a protective effect, with risk reducing for each term of pregnancy or length that the contraceptive is used. The findings indicate that the strongest risk factor for epithelial cancer is a first or second degree relative with ovarian cancer although they concede that only 7% of women diagnosed with ovarian cancer report a family history of the disease.

Table 1 Major risk factors for epithelial ovarian cancer(254)

Risk Factor	Relative risk/odds ratio (95% confidence interval)
None	0.1
Oral contraceptive use	0.66 (0.55-0.78)
Any term pregnancy	0.47 (0.4 – 0.56)
One first or second degree relative with ovarian cancer	3.1 (2.2 – 4.4)
Two or three relatives with ovarian cancer.	4.6 (1.1 – 18.4)

(Paley, 2001)(253)

This authoritative review concluded that the majority of women who are diagnosed with ovarian cancer have no identifiable risk factors. Nevertheless there are some risk factors that have been identified in some cases, the most significant of which being genetic predisposition, with up to 10% of epithelial ovarian cancer being familial. Additionally this review suggests that 90% of these familial ovarian cancers are attributable to mutations in BRCA1 or BRCA2 genes, resulting in a life time risk for ovarian cancer of 40-60% in women with BRCA1 mutation.

(Stratton et al, 1998)(255)

A UK systematic review of published case-control and cohort studies sought to estimate the relative and lifetime risk of ovarian cancer in women with various categories of family history. The outcome measures of relative and lifetime risks of developing ovarian cancer were calculated for women with 1) an unaffected first degree relative, 2) an affected mother, 3) an affected sister, and 4) women with more than one affected relative. Published articles were identified using the MEDLINE databases from 1966 to 1998. Data from electronic databases were supplemented by hand searches. Sixteen studies were identified. Three of these were retrospective cohort studies and 13 were case-control studies. One study was excluded because of probable selection bias.

The 15 studies were assessed for homogeneity. Although there was heterogeneity in the studies used to estimate risk in first-degree relatives, this did not alter the estimate of the pooled relative risk. Two studies reported the relative risks to first-degree relatives according to age at diagnosis or death of the index case. The pooled estimate of RR was 1.7 (95% CI 1.2-2.5) where the index case was diagnosed or dies from ovarian cancer before the age of 40, compared with 3.8 (95% CI 2.6-5.5) if the index case was diagnosed or died at an older age. Four studies reported RRs according to the ages of first- degree relatives. For women younger than 50 with an affected first degree relative the RR was 2.9 (95% CI 1.9-4.3), while for women older than 50 with an affected first degree relative the risk was two (95% CI 1.5-2.5). The risk to daughters of an affected mother was given in three case-control studies which provided a pooled estimated RR of six (95% CI 3.0-11.9). The risk to mothers with an affected daughter was given by two cohort studies and one case- control study. The estimated RR was 1.1 (95% CI 0.8-1.6). Four studies reported risks associated with having an affected sister. The pooled estimate from these studies gave an RR of 3.8 (95% CI 2.9-5.1). Only two case-control studies and no cohort study examined the risks associated with having a second degree relative with ovarian cancer. The pooled relative risk estimated from these studies was 2.5 (95% CI 1.5-4.3). Two studies examined the risks involved in having more than one affected relative (either first or second degree) with ovarian cancer. The pooled risk estimate was 11.7 (95% CI 5.3-25.9).

Cancer of the uterus

(Paley, 2001)(253)

This recent authoratitive review of endometrial cancer summarised risk factors and considered the case for screening. The review reported that principal risk factors for endometrial cancer are conditions that result in high oestrogen levels. Therefore, the risk factors include diabetes, obesity, chronic anovulation, oestrogen secreting tumours, tamoxifen use and unopposed exogenous oestrogen administration.

Vulval cancer

(Ghurani and Penalver, 2001){979]

In this authoritative review, factors associated with the development of vulval cancer were reported as including granulomatous infection, herpes simplex virus, and human papillomavirus. The DNA of human papillomavirus has been identified in invasive carcinomas and preinvasive lesions of the vulva. Other factors associated with vulval cancer include chronic immunosuppression, hypertension, diabetes and obesity.

13.2 Investigations

13.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral in women with suspected gynaecological cancer?

13.2.2 Evidence search question:

In women attending primary care services with gynaecological symptoms, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

13.2.3 Evidence Statements:

Despite an effective screening program cervical cancer occurs among women who have had, and who have not had, regular cervical screening tests, and even among women who have had two or more smears in the past 5 years (III).

There is no evidence about the value of investigations that may be used routinely in primary care to investigate women suspected of having cervical, endometrial, ovarian or vulval cancer (III).

Cancer of the cervix

Primary studies

Janerich et al, 1995{581}

Patients with invasive cervical cancer diagnosed in Connecticut from March 1985 to February 1990 were identified for the study. Cases were selected from new cases as soon as possible after diagnosis in 35 hospitals. Information was obtained through interviews for 481 (72%) of the 664 eligible patients. Verification of invasion was based on a biopsy or hysterectomy report, or both. In cases where invasion had not definitely been established, pathology slides from biopsies or hysterectomies or both were requested and reviewed to establish the diagnosis.

A total of 137 cases (28.5%) occurred among women who had never had a Pap test, and another 113 cases (23.5%) in women whose last Pap test was more than five years before diagnosis of cervical cancer. The average age of women who were never screened was 64.5 years compared with 46.5 years for the remainder of the 481 case patients. Of the 481 patients, slides could be obtained for 137, and of these 6.9% were classified on re-evaluation as misread i.e. had originally been incorrectly classified as normal. Delay in the follow-up of suspicious smears occurred in 52 of the 481 cases (10.8%).

(Carmichael et al, 1984)(256)

A Canadian retrospective review was conducted of the cytologic history of 245 patients who developed invasive carcinoma of the cervix and were registered with the Ontario Cancer Foundation Clinic between January 1973 and October 1982. The aim of the study was to delineate causes for failure of cervical cytologic screening in a group of patients who eventually developed invasive cervical carcinoma. Three groups of patients were identified. Group 1 included 149 patients (60.8%) who had never had a cervical cytology examination, group 2 included 26 patients (10.6%) whose cytology history in terms of frequency of examination and or timing was considered to be unsatisfactory and group 3 included 70 patients (28.6%) whose cytology history was satisfactory. A satisfactory cytology history was defined as two or more smears within five years, and three or more smears within ten years. Smears within three months of the patient's anniversary date were excluded. The original smears that were obtained from the identified laboratories were requested and reviewed by a senior pathologist who was not aware of the original cytology diagnosis.

Fifty three (35.6%) of the patients in group 1 had stage 1 disease. Stage 1 disease was

present in 16 patients (61.5%) of group 2 and in 55 patients (78.6%) of group 3. There was no significant difference between the three groups with respect to site of residence or access to the health care system. Of the patients in group 3, 20 (28.6%) had normal findings and 50 (71.4%) had abnormal cytology findings. A review of 229 original cervical smears revealed that 52 (17.4%) had been significantly undercalled (i.e. the severity of abnormalities had been adequately identified), but only 21 (7.0%) had been undercalled as normal. In these patients, staging was unrelated to screening.

(Woodman et al, 1997(257)

A questionnaire survey of all general practices (N=111) and family planning doctors (N=62) in Manchester Health Authority was undertaken to determine why more smears were taken in primary care than were scheduled by the screening programme. An 82% response rate was obtained. Questionnaires were addressed to the senior partner in the practice with a request that they determine the most appropriate person within the practice to complete it.

Ninety-one general practices (82%) and 50 family planning doctors (81%) eventually responded; 22 (24%) of the questionnaires returned by general practices had been completed by the practice nurse. The indications for additional smear tests most frequently cited by responders were postcoital (88%), postmenopausal (84%), or intermenstrual bleeding (55%), genital warts (87%) and multiple sexual partners (52%). Forty-six percent maintained that a woman should have a repeat test within one year of her first ever test. Family planning doctors were less likely than general practices to take an extra smear if a woman was starting the oral contraceptive pill, having an intra-uterine contraceptive device (ICD) inserted, or attending for a postnatal check; or if she had a history of multiple sexual partners.

Ovarian cancer

Secondary studies

(Royal College of Obstetricians and Gynaecologists, 2003)(254)

This guideline was developed following a review based on a search of relevant databases for publications from 1966 onwards. It was recommended that ovarian cysts in postmenopausal women should be assessed using CA125 and transvaginal grey scale sonography, and that a 'risk of malignancy index' should be used to select those women who require primary surgery in a cancer centre by a gynaecological oncologist. The guidelines did not deal with primary care assessment.

(SIGN, 2003)(254)

SIGN has published guidelines on epithelial ovarian cancer. Although the guidelines were principally focused on managed of diagnosed cases, it was recommended that GPs should include ovarian cancer in the differential diagnosis when women present with recent onset persistent non-specific abdominal symptoms (including women whose abdominal and pelvic clinical examinations appear normal). No studies were identified that assessed the usefulness of the measurement of CA125 in women with vague abdominal symptoms and the guideline did not recommend the routine measurement of CA125. It was recommended that women with a pelvic mass should be referred to a gynaecologist irrespective of CA125 test results.

Primary studies

(Andolf et al, 1986)(258)

Ultrasound scan for detection of ovarian enlargements was performed in a target group of out-patients attending a specialist Swedish outpatient clinic for various reasons in the 40-70 years range. Overall 805 women were examined, in 99% of whom the ovaries and/or their vessels could be identified. The findings at the ultrasound examination were compared with those at pelvic examination, surgery and with subsequent histological examination (gold standard). All patients had a manual pelvic examination before the ultrasound scan. Pelvic examination

was performed by one of the 30 or so experienced gynaecologists available at the clinic.

The findings of the manual examination were not available to the ultrasonographer. Pelvic examinations were performed by gynaecologists whilst all ultrasound examinations were made by one technician, a specially trained midwife. The ultrasound examination was performed with the full- bladder technique using a 'real' time sector scanner. The uterus and ovaries were measured in three planes and the volume of the ovaries was calculated using a simplified version of the ellipsoid formula: length x width depth x 0.52. Pathological findings were suspected in 83 of the 805 women at the first scan and were confirmed in 50 after a repeat scan, of whom 39 subsequently underwent surgery. None of the borderline or malignant ovarian lesions were found by manual pelvic examination.

Cancer of the uterus

Secondary studies

(Tabor, 2002)(259)

The review was limited to original research reports written in English concerning symptomatic women having vaginal ultrasonography before a diagnostic test and not receiving tamoxifen. Blinding did occur as those studies reporting only Doppler indices or abdominal scans, or those in which the ultrasound examination was done after the diagnostic test were excluded. A literature search was conducted using the MEDLINE database from January 1 1991 to September 30, 1997. A total of nine UK and Danish studies were identified from 48 in the meta analysis. The nine studies yielded data on 3483 symptomatic women. 710 women were premenopausal, 2407 postmenopausal who were not taking HRT and 366 taking HRT) and 330 symptomatic women with endometrial cancer (seven premenopausal and 293 postmenopausal not on HRT and 30 on HRT). In six studies a dilation and curettage was done, in two studies an endometrial biopsy was taken, and in one multicentre study a dilation and curettage or an endometrial biopsy was taken.

The value of endometrial thickness was used as a test for endometrial cancer in postmenopausal women with vaginal bleeding (symptomatic women). In all studies, a histologic examination was performed to determine whether or not the women had endometrial cancer at the time of screening. Studies were included in the analysis only if the authors' original data could be obtained to calculate each centre's median endometrial thickness in unaffected symptomatic women. A questionnaire was sent to the corresponding author of each paper requesting supplementary information. The authors were asked to give the mean, standard deviation, median and 10th and 90th centiles of endometrial thickness.

The median endometrial thickness in women with endometrial cancer was 3.7 times that in unaffected women with the same menopausal status and same hormone replacement therapy use category. The detection rate was 63% (95% CI 58, 69) for a 10% false-positive rate, or 96% (95% CI 94, 98) for a 50% false-positive rate. It was concluded that 4% of the endometrial cancers would still be missed with a false-positive rate as high as 50%. It underlined the importance of determining the median and distribution of endometrial thickness in each centre, and not using a fixed cut off. In the two centres which reported medians for premenopausal women who did not take HRT, the median endometrial thickness was 2-3mm higher than in postmenopausal women who did not take HRT ($P<0.01$ for each).

There were statistically significant differences in endometrial thickness between centres presumed to reflect differences in measurement techniques or the populations studied. The multiples of the median (MoM) endometrial thickness in different studies of women with endometrial cancer ranged from 2.1 to 5.9 multiples of the median. The overall median endometrial thickness was 3.7 multiples of the median.

Primary studies

(Gredmark,1995)(260)

A Swedish prospective cohort study designed to investigate endometrial histopathology in a geographically defined population of 457 postmenopausal patients presenting with uterine bleeding. The main outcome measures involved the frequency of bleeding and its correlation to endometrial histopathology and in relevant cases to pathological conditions in cervix and ovaries. Dilation and curettage using general anaesthesia was performed on the 457 postmenopausal women. All women referred to the county gynaecological departments because of uterine bleeding, appearing one or more year after menopause were eligible for inclusion. The study covered an 18 month period between September 1986 and March 1988.

Menstrual status, obstetric and medical history as well as pharmacological therapy were recorded and a general physical and gynaecological examination was performed. Women using HRT (N=19) for vasomotor symptoms were excluded from the study. Two women who had undergone subtotal hysterectomy were also excluded from the study.

The incidence of postmenopausal bleeding decreased with increasing age while the probability of cancer as the underlying cause increased. The peak incidence of endometrial carcinoma was found in women between 65 and 69 years of age. The mean age of the women with bleeding was 61.4 years (41- 91) and the median age when menopause occurred was 50.6 years. Endometrial histopathology showed: atrophy (50%); proliferation (4%); secretion (1%); polpys (9%); different degrees of hyperplasia (10%); adenocarcinoma (8%); not representative (14%); other disorders (3%). In six women a squamous carcinoma of the cervix was found and eight proved to have ovarian tumours.

A high percentage (14.2%) of the endometrial specimens obtained in this study were unsatisfactory. One fourth of these showed fibromuscular tissue, while the remaining samples did not contain any tissue that could be evaluated.

13.3 Delay and Diagnostic Difficulties

13.3.1 Key Clinical Question:

In people attending primary care services with gynaecological symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by the patient and which delay by the provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a women who presents with gynaecological symptoms/signs may or may not need urgent referral with suspected cancer?

13.3.2 Evidence Question:

In people attending primary care services with gynaecological symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by the patient and which delay by the provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman who presents with gynaecological symptoms/signs may or may not need urgent referral with suspected cancer?

13.3.3 Evidence Statement:

Delay in the detection of ovarian cancer may be associated with the non- specific nature of the symptoms (III).

Delay

Introduction

There were few studies of diagnostic delay, and most were limited to a description of the time intervals to diagnosis and its association to disease characteristics.

Secondary studies

No papers were identified.

Primary papers

Cancer of the cervix

No studies of delay in diagnosis among symptomatic patients were identified

Ovarian Cancer

(Kirwan et al, 2002)(261)

The authors of this UK study undertook a retrospective review of the general practice records of 135 patients with epithelial ovarian cancer. The aim of the study was to identify referral pathways from primary care for women with ovarian cancer, and particularly to examine delays between the onset of symptoms and presentation to the general practitioner and delays between presentation and referral to hospital.

105 patients (78%) presented to the general practitioner within one month of developing symptoms and 64 (47%) within two weeks. Only 11 patients (8%) delayed more than three months before seeking medical advice. Primary symptoms in the patients' notes were abdominal swelling (65), change in bowel habit (34), weight loss (11), backache (3), vaginal bleeding (15), and other (30). General practitioners referred 68 (50%) patients to hospital directly after their first consultation, 82 (60%) within two weeks, and 99 (73%) within one month. 36 patients (27%) experienced delays of over three months, half of whom were misdiagnosed as having irritable bowel syndrome. The mean age of the survivors was less than that of patients who died (63.7 years vs.
69.0 years, P=0.014).

Multivariate analysis with survival as the dependent variable identified age (odds ratio 0.96, 95% confidence interval 0.93 to 0.99), cancer stage III or more (0.15, 0.05 to 0.43), and non-specific symptoms (0.36, 0.14 to 0.89) as significant variables. The study suggests that delays attributable to the patient and general practitioner are roughly equal but that these intervals do not affect survival beyond 18 months in women with ovarian cancer.

(Goff et al, 2000)(243)

The study's aim was to evaluate preoperative symptoms and factors that may contribute to delayed diagnosis for women with ovarian carcinoma. The authors conducted a postal survey among 1,725 women with ovarian carcinoma who subscribed to a newsletter about ovarian carcinoma. All women who returned the questionnaire were North America residents (USA and Canada).

The median age of the surveyed patients was 52 years (range, 18-84), and 13% were older than 65 years. At the time of diagnosis, 71% of respondents had FIGO stage III/IV disease.

95% of patients had symptoms before the diagnosis of ovarian carcinoma. Duration of symptoms was reported as two months or less by 30% of patients, three to six months by 35%, 7-12 months by 20%, and longer than 12 months by 15% of women. Women who ignored their symptoms were significantly more likely to be diagnosed with advanced disease compared to those who did not (85% vs. 74%; P = 0.002). There was no correlation between specific symptoms and delayed diagnosis (no P value given).

Women with the most symptoms required significantly more time to make the diagnosis (P = 0.001); they were also more likely to be treated for another condition (P = 0.001), were

younger (P = 0.001), were less likely to receive a diagnosis at an early stage (P = 0.001), and more likely to perceive that health care provider attitude towards them was a problem (P = 0.001).

The type of health care provider initially seen was a family practitioner in 34% of cases, an obstetrician-gynaecologist in 37%, an internist in 16%, a nurse practitioner in 3%, and other in 10%. The type of insurance did not correlate with delayed diagnosis. The time required by a health care provider to make the diagnosis was reported as less than three months by 55%, but greater than six months by 26%, and greater than one year by 11%. Time required to make the diagnosis was similar for the main three health care provider types (family practitioner, obstetrician-gynaecologist, internist). Significantly more stage I/II tumours were diagnosed by obstetricians-gynaecologists than by other health care providers (P = 0.009).

Other factors significantly associated (by univariate analysis) with delay in diagnosis were omission of pelvic examination at first visit (P = 0.016), and not initially organising an ultrasound, computed tomography, or CA125 (P = 0.001).

Multivariate analysis was performed with linear regression to evaluate factors that were associated with the number of months to make a diagnosis. Only 20% of the delay was explained by the factors evaluated by the authors. The factors most significantly associated with delay in diagnosis were amount of time patients had symptoms (P = 0.001), the number of health care providers seen (P = 0.06), symptoms being ignored (P = 0.07), and initial incorrect diagnosis (P = 0.08).

The findings of this study should be interpreted with caution. Responses from women to the questionnaire were not verified, as the authors had no access to medical records, or indeed population cancer registries. The study identified associations, and these must not be assumed to indicate causation.

(Smith and Anderson, 1995)(245)

The study aimed to evaluate characteristics of symptoms, their perceived cause, and delay in seeking a diagnosis associated with stage, grade, and histologic features of disease at diagnosis among incident cancers of the ovary. Women included in the study (N= 82) had a histologically confirmed primary of the ovary within the last three months, were all white, and identified from a US population-based cancer registry.

The authors interviewed all women to ascertain reasons for, and extent of, delay in diagnosis. Women were also asked to provide information on individual socio-demographic factors (income, education, occupation, age, and marital status). Disease related information was extracted from the cancer registry and medical records.

56 (68.3%) women noticed symptoms before diagnosis. Women who were 40 years of age or older were significantly (P < 0.05) more likely to report having symptoms that convinced them to see a physician for diagnosis. Overall, fewer than 10% thought that they had cancer, and most women believed that their problems were due to either menstrual conditions or to unknown causes. There was a trend (P < 0.10) for earlier-stage disease and the perception that symptoms were due to cancer. There was no association between perceptions of the causes of symptoms and socio-demographic factors.

The median number of weeks delay in seeking medical attention was four. More than half (52.5%) saw a physician in one month or less, but about one fourth (22.5%) waited three months or longer. Nonetheless, there was no association between stage and delay, regardless of symptoms, nor was there an association between delay and perceived cause or seriousness of symptoms. The most frequent reasons given for delay were: “fear” (22.7%), repeat appearance of a previous benign condition (22.7%), and symptoms interpreted as “not serious” (18.2%). Fear showed a weak association with greater delay (P < 0.10).

(Wikborn et al, 1996)(246)

The study attempted to investigate the process from first recognition of symptoms to final

diagnosis at operation in patients with epithelial ovarian cancer. The authors studied the medical records of 160 women diagnosed with epithelial ovarian cancer at a Swedish hospital between 1981 and 1986 in order to obtain information on patient- and doctor- related delay. Data were collected on age, symptomatology, diagnostic process time span, tumour histopathological class, and tumour stage.

The patients' mean age was 62.4 years with a range of 25-85 years. The mean symptom duration before consulting a doctor was 12 weeks for serous cancers (SD 16.1) compared with seven weeks for the others (SD 11.2)($P < 0.05$). Of all the women, 56% were diagnosed within four weeks; no significant differences were found between different histopathological groups. In the eight weeks following recorded first consultation, as many as 30% of women had not been correctly diagnosed.

Cancer of the uterus

(Crawford et al, 2002)(262)

The authors investigated links between delays in treatment and survival by collecting data from the case notes of all women resident in Scotland who were diagnosed in the two year period 1996-1997 as having endometrial carcinoma. 703 cases that involved operative treatment were analysed (out of a total of 781 cases identified).

The study exclusively examined secondary care provider delay, as the authors looked at the time interval from referral to definitive operation and not the delay.

The median interval from referral to definitive operation was 62 days (90th centile 150 days), with large variations between health board areas. Delay and survival were inversely related: women with the shortest delay had more advanced disease and survival was least likely for these patients (P values not provided by the authors).

(Aziz et al, 1993)(263)

The purpose of the study was to compare the prognostic factors - including grade, stage, depth of myometrial invasion, status of lymph nodes, and peritoneal cytology - and survival of black and white patients with endometrial carcinoma. The authors undertook a retrospective study of 290 patients with endometrial carcinoma who were treated at two US hospitals between 1975 and 1990.

136 (47.2%) patients were black, 135 (46.9%) were white, 15 (5.2%) were Hispanics, and the racial origin of four patients was not known. The mean age was 63 years in the range of 28-95 years (standard deviation 10.6). Black and white patients had similar treatments.

Black patients had more advanced stage disease than white patients (stage I, 45.9% *vs.* 54.1%; stage II, 48.4% *vs.* 51.6%; stage III, 88.9% *vs.* 11.1%; stage IV, 100% *vs.* 0%; $P = 0.034$). Black patients also had more advanced grade disease ($P = 0.008$), myometrial invasive disease ($P = 0.038$), and lymph node involvement ($P = 0.01$).

The corrected ten year survival for white patients was 72% compared to 40% for the black patients ($P = 0.0003$). The overall survival for blacks vs. whites less than 60 years of age ($P = 0.002$), and for blacks vs. whites more than 60 years of age ($P = 0.003$) was significantly lower in black patients as compared to white patients. Survival comparison stratified by both age and race indicated that black patients under 60 years of age had the worst survival rate. Survival comparisons, when stratified by race and each prognostic group, showed statistically significant overall survival differences in favour of white patients.

Vulval cancer

(Jones and Joura, 1999)(264)

The authors examined the preceding clinical events in 102 women presenting to a New Zealand tertiary care gynaecologic oncology unit with squamous cell carcinoma of the vulva

between the years 1989 and 1996. History, clinical findings, previous physician contact, investigations and treatment were analysed.

The age range was 36-94 years. Vulval symptoms were present for more than six months in 88% of patients and for more than five years in 28%. No statistical differences were noted in the duration of symptoms when the patients were grouped according to age. A history of intermittent or chronic vulval irritation was elicited in 94% of patients.

In 31% of cases the women had had three or more medical consultations on account of vulval symptoms more than six months before the diagnosis of invasive cancer. The length of the history and the number of consultations were independent of age.

A history of the prior application of topical oestrogen or corticosteroid to the vulva was elicited in 27% of women. Twenty-five percent of patients had previously had a diagnostic biopsy. Seventeen women (68%) with a history of preceding biopsy presented with stage I disease as compared with 26 (34%) in the cohort without a preceding biopsy ($P < 0.01$).

Diagnostic Difficulties

No articles reporting studies of the difficulties encountered by primary care professionals in identifying patients to be referred for suspected gynaecological cancer were identified.

14 Urological cancers

General recommendations

1 A patient who presents with symptoms or signs suggestive of a urological cancer should be referred to a team specialising in the management of urological cancers, depending on local arrangements. D

Specific recommendations

Prostate cancer

2 Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate specific antigen (PSA) test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive. C

4 Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms:
- erectile dysfunction
- haematuria
- lower back pain
- bone pain
- weight loss, especially in the elderly.

These patients should also be offered a DRE and a PSA test. C

4 Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection. C

5 If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients do not need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range[13]. C

[13] The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50−59 years ≥ 3.0 ng/ml; aged 60−69 years ≥ 4.0 ng/ml; aged 70 years and older ≥ 5.0 ng/ml. (Note that there are no age-specific reference ranges for men aged over 80 years. Nearly all men of this age have at least a focus of cancer in the prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment.)

6 In a male a patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age-specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other comorbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate. C

7 Symptomatic patients with high PSA levels should be referred urgently. C

8 If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently. D

Bladder and renal cancers

9 Male or female adult patients of any age who present with painless macroscopic haematuria should be referred urgently. C

10 In male or female patients with symptoms suggestive of a urinary infection who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed the patient should be referred urgently. D

11 In all adult patients aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria, an urgent referral should be made. C

12 In patients under 50 years of age with microscopic haematuria, the urine should be tested for proteinuria and serum creatinine levels measured. Those with proteinurea or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made. C

13 In patients aged 50 years and older who are found to have unexplained microscopic haematuria, an urgent referral should be made. C

14 Any patient with an abdominal mass identified clinically or on imaging that is thought to be arising from the urinary tract should be referred urgently. C

Testicular cancer

15 Any patient with a swelling or mass in the body of the testis should be referred urgently. C

16 An urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished. D

Penile cancer

17 An urgent referral should be made for any patient presenting with symptoms or signs of penile cancer. These include progressive ulceration or a mass in the glans or prepuce particularly, but can involve the skin of the penile shaft. Lumps within the corpora cavernosa not involving penile skin are usually not cancer but indicate Peyronie's disease, which does not require urgent referral. D

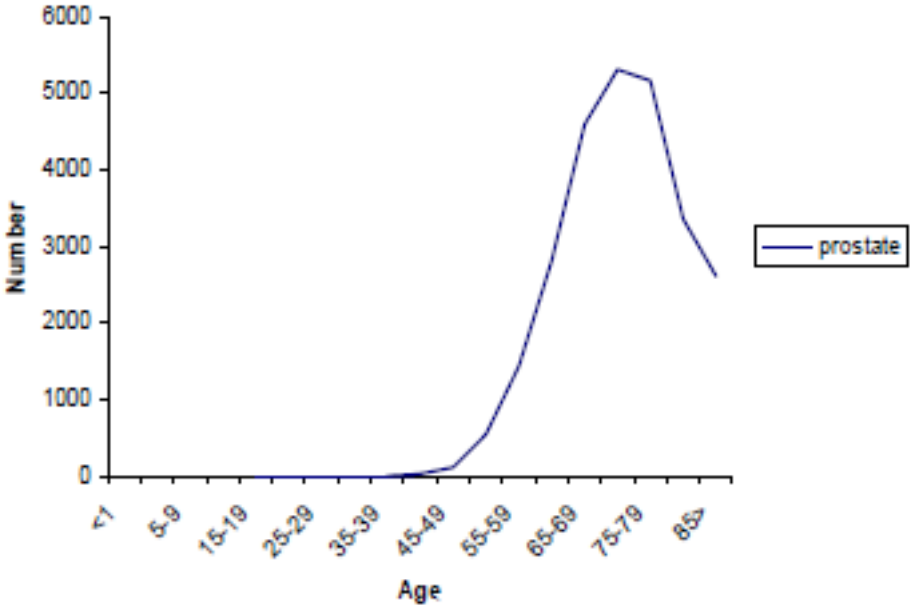
Introduction

Incidence

Prostate cancer

The total registrations of newly diagnosed cased of prostate cancer in 2001 in England and Wales was 26,027 per 100,000 population. Prostate cancer is rare in men below 50 years of age, with only 0.5% of cases occurring in men in this age group. Incidence rises steeply with increasing age until peaking in those aged 85 years.

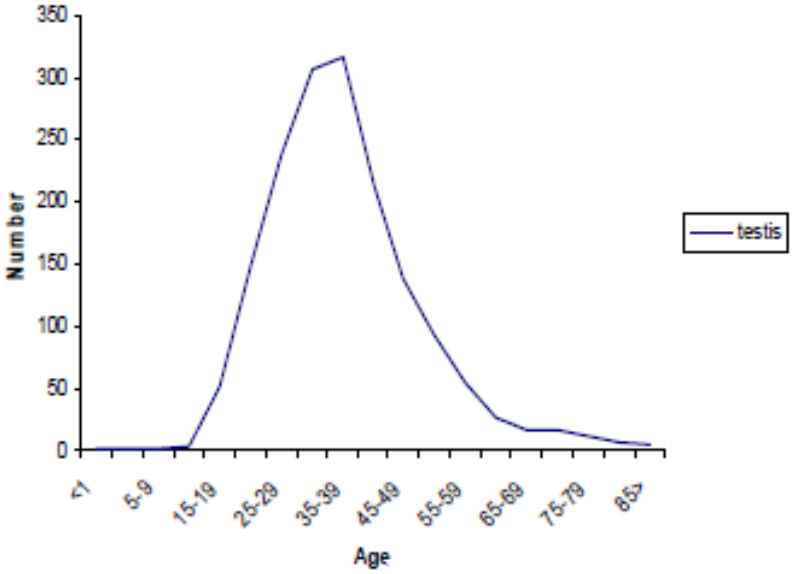
Figure 3 2001 Registrations of prostate cancer in England and Wales. (77)



Testicular cancer

In England and Wales in 2001 there were 1,997 cases of newly diagnosed testicular cancer. Incidence is low in those aged under 20 years, but increases steeply and peaks between the ages of 30-34 years. Almost 50% of cases occur in those aged under 35 years and 80% in those aged under 45 years.

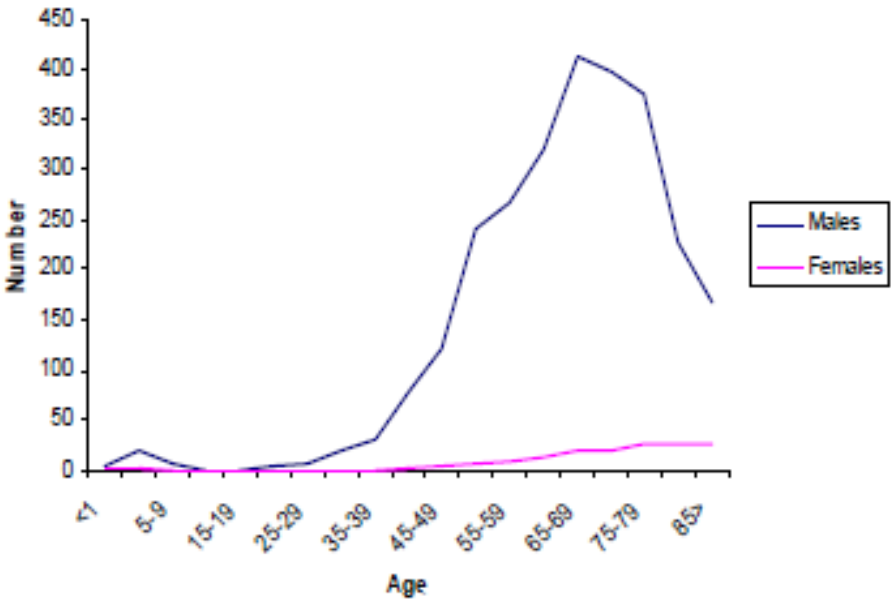
Figure 4 2001 Registrations of testicular cancer in England and Wales. (77)



Cancer of the kidney

There were 5338 new diagnoses of cancer of the kidney registered in 2001 in England and Wales. Of those cases 3,281 were in males and 2,057 in females. Cancer of the kidney is rare below the age of 40 years and increases with age in both sexes. The disease peaks between ages 80-84 years in males. In females the incidence is generally much lower but peaks within the same age group.

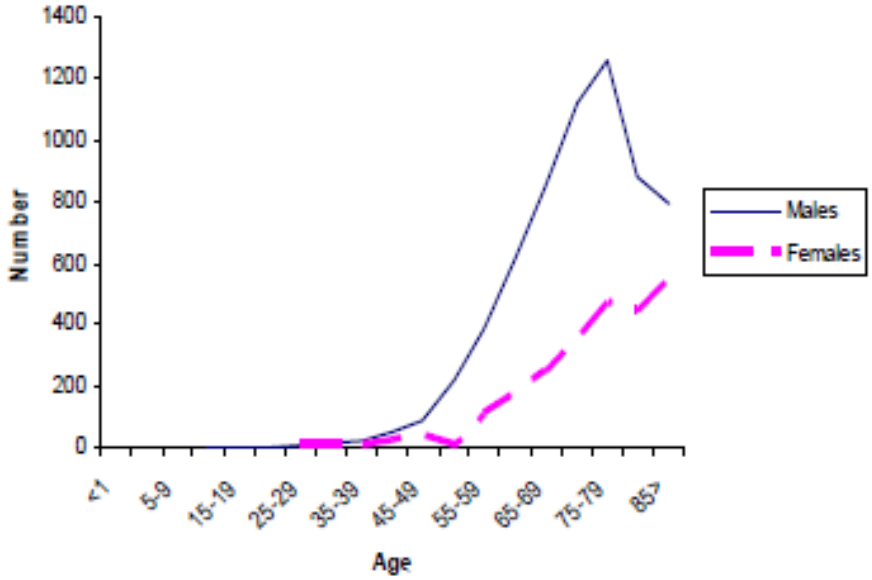
Figure 5 2001 Registrations of cancer of the Kidney in England and Wales. (77)



Cancer of the bladder

In 2001 there were 11,403 cases of bladder cancer in England and Wales. Of those 8,101 were in males, and 3,302 in females. Incidence is low below the age of 50 years in both sexes, after which incidence increases sharply in males and more gradually in females.

Figure 6 2001 Registrations of cancer of the bladder in England and Wales. (77)

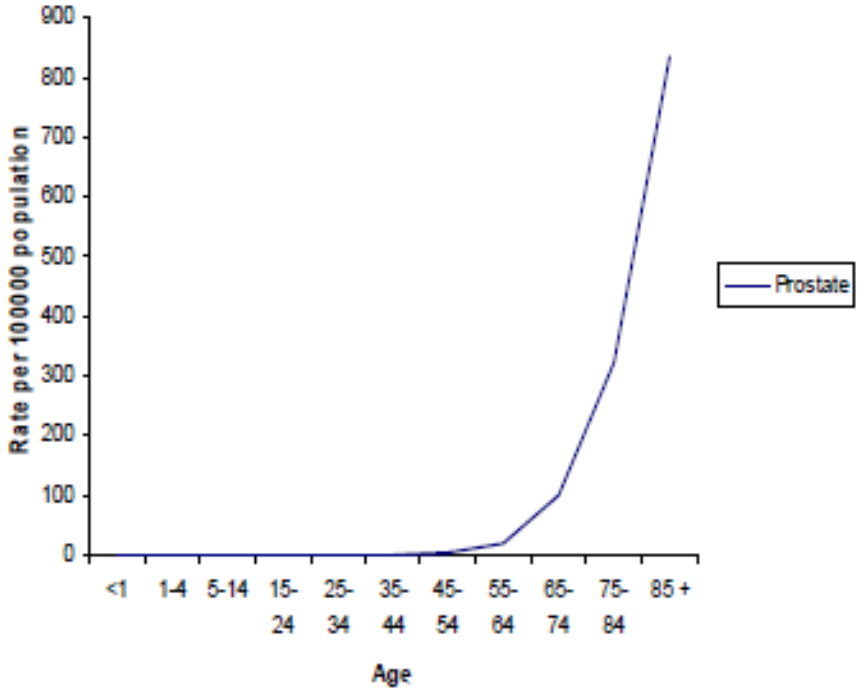


Mortality

Prostate cancer

Age specific mortality is similar to incidence, increasing with age from 50 years onwards. In 2002 in England and Wales there were 8,973 deaths from prostate cancer. Age distribution is shown in Figure 7 24.

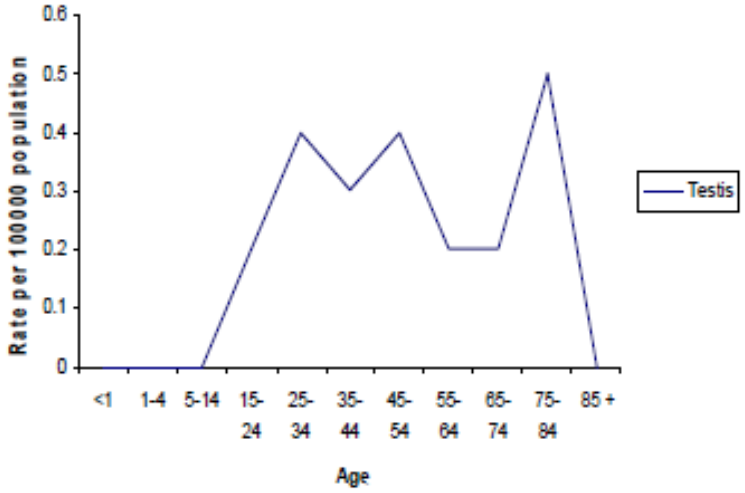
Figure 7 2002 Mortality rates from prostate cancer in England and Wales. (78)



Testicular cancer

Age specific mortality from testicular cancer varies vary little across the age groups. In 2002 in England and Wales there were 120 deaths from testicular cancer. Age distribution is shown in Figure 8.

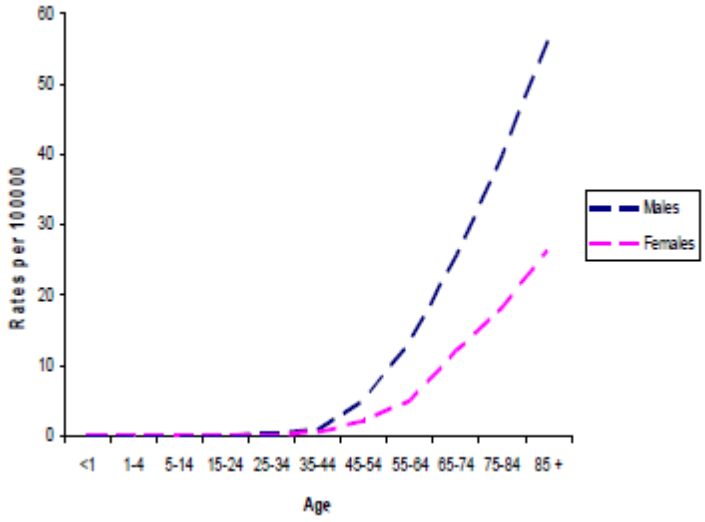
Figure 8 2002 Mortality rates from testicular cancer in England and Wales. (78)



Cancer of the kidney

Mortality is low in both sexes in those aged under 40 years. In 2002 in England and Wales, there were 1,035 deaths from cancer of the kidney in females and 1,749 in males.

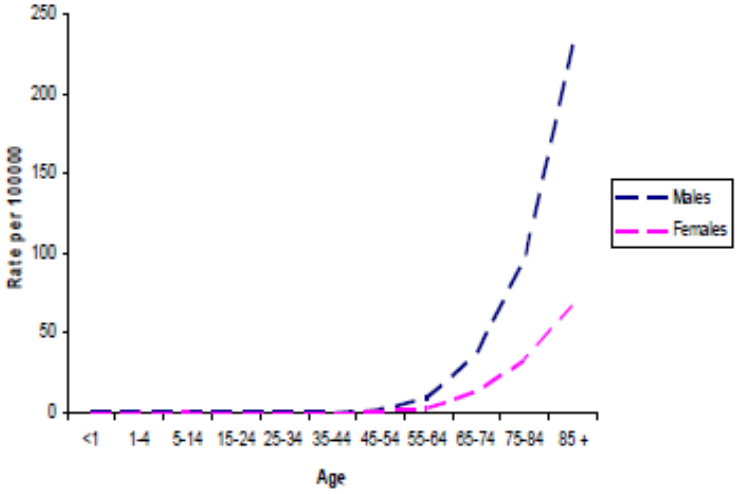
Figure 9 2002 Mortality rates from Kidney cancer in England and Wales. (78)



Cancer of the bladder

Mortality is low in those aged under 60 years in both sexes in England and Wales. In 2002 in England and Wales there were 1,501 deaths from bladder cancer in females and 2,919 in males. Age distribution is shown in Figure 10.

Figure 10 2002 Mortality rates from cancer of the bladder in England and Wales. (78)



Review of cancer referral audits

The review(13) identified 43 relevant clinical audits. The proportion of two week referrals found to be in accordance with the symptoms in the guidelines(2) who were found to have cancer ranged from 70% to 100% (14 audits). The proportion of patients referred under the two week system who were subsequently found to have cancer ranged from 13% to 40% (15 audits). The proportion of patients with cancer who had been referred under the two week system ranged from 0% to 39% (six audits). The proportion of two week referrals assessed as clinically appropriate ranged from 78% to 91% (four audits).

14.1 Symptoms and Signs

14.1.1 Key Clinical Question:

In people attending primary care services with urological problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

14.1.2 Evidence Question:

In people attending primary care services with symptoms and signs that might be associated with upper urological cancers, which symptoms and signs and other features including family history, when compared with the 'gold standard', are predictive of a diagnosis of cancer, and which symptoms and signs are not? Are any non-clinical features associated with a diagnosis of cancer?

14.1.3 Evidence Statements:

Prostate cancer is rare below the age of 45 years, but the incidence rises steeply thereafter. (III)

Testicular cancer can occur at almost any age, but is most common below the age of 40. (III)

Renal cancer is rare below the age of 35, but increases in incidence thereafter. It is more common in males. (III)

Bladder cancer is rare below the age of 50, but increases in incidence thereafter. It is more common in males. (III)

Prostate cancer often presents with symptoms of urinary outflow obstruction. Other presenting symptoms include urinary tract infection, and features of metastasis, such as bone pain. (III)

Most prostate cancers can be palpated on digital rectal examination by the primary care professional, but an abnormality on examination may be caused by conditions other than cancer. (III)

The most common presenting feature of testicular cancer is enlargement of the testis, which may or may not be associated with pain. (III)

Testicular cancer may first present with features of metastasis, for example with back pain or breathlessness. (IV)

Penile cancer is rare, and presents as an area of induration, erythema or warty growth. (III)

Bladder cancer commonly presents with macroscopic haematuria. (III)

Introduction

The urological cancers considered in this guideline included prostate, testicular, kidney, and bladder. Carcinoma of the scrotum is rare and was not included. There were few primary care studies dealing with urological cancer (especially so for testicular and penile cancers). In addition, many of the studies dealing with prostate cancer concentrated on examinations and tests for screening rather than on the assessment of patients presenting to primary care with symptoms. Although the scope of this guideline excluded papers dealing with screening, the quantity of primary evidence in this area was so limited that some screening focused reviews have been included, to enable cautious extrapolation to symptomatic patients.

Guidelines

(NICE, 2001)(265)

This document was classified by NICE as guidance and was commissioned by the Department of Health and the National Assembly for Wales to provide advice to health professionals on the appropriate referral of patients from general to specialist services. A consensus method was used to generate the advice. A multidisciplinary panel was established for each topic considered, and selected research evidence was considered.

One of the topics considered was urinary tract outflow symptoms. The advice recommended that patients be offered a prostate specific antigen (PSA) test with the reasons for doing the test being explained and the patient counselled with regard to the possible consequences. Patient information on PSA tests can be obtained from the National Electronic Library for Cancer (www.nelc.org.uk). Immediate referral was advised if the patient has acute urinary retention or evidence of acute renal failure; urgent referral was advised if the patient has (a) visible haematuria, (b) there is a suspicion of prostate cancer based on the findings of a nodular or firm prostate, and/or a raised PSA, (c) culture negative dysuria, (d) they develop chronic urinary retention with overflow or night-time incontinence. Referral to be seen soon was advised if the patient has recurrent urinary tract infection or microscopic haematuria. Referral within an appropriate time was advised if the patient has chronic renal failure or renal damage, or symptoms have failed to adequately respond to treatment in primary care. Use of a scoring system such as the WHO International Prostate Symptom Score was encouraged.

(SIGN, expected 2005)(230)

SIGN is publishing guidelines on the management of transitional cell carcinoma of the bladder. The guidelines are directed at management in secondary care and do not consider identification and referral of suspected cases in any detail. However, the guidelines do recommend that patients with frank haematuria should be seen within two weeks by a specialist, and that those with occult asymptomatic (microscopic) haematuria should be seen within six weeks.

(Lobel et al, 1998)(266)

These guidelines were developed by an international group, and included reference to 89 original articles, although the methods of guideline development were not described in detail. The guidelines gave detailed consideration to initial assessment in primary care, but did state that all patients with gross haematuria should be examined and referred to a urologist for assessment for possible bladder tumour. Patients with asymptomatic microscopic haematuria should be referred if they are aged over 50 years. In those under aged 50, the guidelines were uncertain, but noted that the incidence of cancer in this group was 5% with asymptomatic microscopic haematuria and 10.5% with symptomatic microscopic haematuria.

(Mickisch et al, 2001)(267)

These guidelines were prepared by the European Association of Urology following a literature search using Medline, with articles being graded by a panel of experts. The presenting features include haematuria, palpable tumour and flank pain. However, presentation with clinical features is becoming less common and many cases are being diagnosed at the asymptomatic stage. The majority of tumours are diagnosed by abdominal ultrasound performed for various reasons.

Secondary studies

Prostate cancer

(Muris et al, 1993)(268)

In this review, publications were identified from Medline dated 1982 to 1991, and those included involved studies of patients with complaints in which rectal examination was indicated. Eight studies met the inclusion criteria, two of which involved men attending outpatient departments because of prostate related symptoms. These studies included a total of 325 patients. The sensitivity of rectal examination in detecting prostate cancer was 98% and 92% in the two studies, specificity was 53% and 48%, and likelihood ratio 2.09 and 1.77.

(Selley et al, 1997)(269)

This was a systematic review of the diagnosis, management and screening of early localised

prostate cancer. From the included studies of digital rectal examination (DRE), it was concluded that 50-95% of localised prostate tumours are palpable and could be detected by DRE. A proportion of the lesions detected on palpation are benign, and include benign prostatic hyperplasia (BPH), retention cysts, prostatic calculi, prostatic atrophy, fibrosis associated with prostatitis, and non-specific granulomatous prostatitis. False positive rates on DRE are as high as 40-50%.

The sensitivity of DRE ranged from 44% to 97% in the four studies reporting this, and specificity from 22% to 96%. The reasons for these variable findings were probably related to the different sizes of the studies, case selection and variable final diagnostic criteria.

(Fowler et al, 2000)(270)

The aim of the study was to determine whether features used to detect prostate cancer are different in black and white American men. The study subjects were 179 black and 357 white men who had undergone prostate biopsy 1992-1999 at one medical centre. The patients had an abnormal DRE, a PSA of less than 4ng/ml and no history of prostate surgery. Cancer was detected in 38 black (21%) and 65 white (18%) men. There was no difference in the overall or PSA stratified cancer detection rate.

Testicular cancer

No relevant articles dealing with the diagnosis of testicular cancer in primary care were identified, and therefore this review was included.

(Gospodarowicz, 1999)(271)

Testicular cancers are uncommon, occurring most commonly in men aged 15 to 35 years. The majority are primary germ cell tumours (GCT). Although the incidence of germ cell tumours has doubled in the past 30 years, the mortality has declined.

There is considerable geographic and ethnic variation in incidence of germ cell tumours, it being less common in non-white men. Men with a history of cryptorchidism have an approximate five-fold risk. Family clusters have been reported, and patients with XY gonadal dysgenesis are at increased risk. Prior testicular cancer is also a risk factor for cancer in the surviving testis.

Patients with tumours most commonly present with painless testicular enlargement. Up to 45% have testicular pain. Less common presentations include features of metastasis, for example back pain and dyspnoea.

Penile cancer

No other relevant articles were identified, specifically no studies of presentation in primary care, and therefore this review was included.

(Burgers, 1992)(272)

This was a comprehensive review of penile cancer. Cancer of the penis is rare, accounting for only 0.4-0.6% of all male malignancies in the US (incidence 0.2/100,000 males/year). Squamous cell carcinoma accounts for at least 95% of cases, sarcomas being the most common non-squamous type. It usually presents in the sixth decade of life, with a mean age at diagnosis of 58. There is an association between absence of circumcision and penile cancer, but the precise aetiology is unclear. The possible role of pre- malignant conditions has not been clarified.

Presentation is varied, ranging from innocuous areas of in-duration, erythema or warty growth to obvious extensive carcinoma with sloughing. The earliest symptoms include itching or burning, and ulceration which progresses to a lump, mass or nodule if left untreated. Pain is usually minimal in relation to the other features. It can occur at any anatomical site; 48% develop in the glans,

21% prepuce, both (9%), coronal sulcus 6%, shaft <2%.

Bladder/renal cancer

(Buntinx, 1997)(273)

This was a systematic review of studies of the diagnostic value of macroscopic haematuria in diagnosing urological cancers in primary care. Studies were sought using Medline and FAMLI databases. 14 studies were selected, but none had been undertaken in primary care, most being based on chart reviews in hospital settings of referred patients. The findings are summarised in Table 2.

Table 2 Pooled sensitivity of macroscopic haematuria for the diagnosis of urological cancers.(273)

	No of studies	Pooled sensitivity	95% CI
Bladder			
All	7	0.83	0.80-0.85
<40 yrs only	4	0.82	0.74-0.88
Ureter			
All	4	0.66	0.53-0.77
Painless	2	0.55	0.45-0.65
With pain	1	0.20	0.07-0.34
Kidney			
All	3	0.48	0.36-0.60

Penile cancer

(Micali et al, 2004)(2)

In this review, a Medline search and meeting abstract books were searched to identify articles on penile cancer. Relatively few studies reported the clinical findings at presentation, but on the basis of the studies identified, the clinical features of squamous carcinoma of the penis were described as either small ulcers that both enlarge superficially and infiltrate deeper tissues, or as circumscribed areas of warty growth that subsequently progress to a mass or nodule and undergo necrosis or ulceration. In both cases, erythema, induration, bleeding and secondary infection are reported as common findings. The majority of cases occur on the glans, foreskin. And/or coronary sulcus, and initially may be asymptomatic or more often cause itching, burning or pain. The development of penile cancer has been reported as following the occurrence of several predisposing factors, including leukoplakia, genital lichen sclerosus, human papillomavirus, and chronic balanitis.

Primary studies

Prostate cancer

(Haid et al, 1994)(274)

This study involved 99 men who had undergone transrectal ultrasound (TRUS) at a US hospital. The records were reviewed to extract information on findings from digital rectal examination (DRE), prostate biopsy reports, and PSA levels. With biopsy as the gold standard, 32 (32.3%) of the 99 had carcinomas.

Among those with carcinoma, 24 (77.4%) (of 31 with data) had a palpable nodule on rectal examination, the mean PSA was 32.5, and 15/31 had an abnormality on transrectal ultrasound (48.4%). Among those who did not have carcinomas, 52/64 had a palpable

nodule (81.2%), the mean PSA was 8.4, and 26/65 had an abnormality on ultrasound (40.0%).

For DRE sensitivity was 77.4% while specificity was 18.8%. The positive predictive value (PPV) amounted to 31.6% and negative predictive value (NPV) totalled 63.2%. Whereas TRUS sensitivity was 98% while specificity was 60%. The PPV amounted to 36.6% and NVP totalled 70.9%. Finally PSE sensitivity was 93.3% while specificity was 21.2%. The PPV amounted to 40% and NVP totalled 84.6%.

(Brett, 1998)(275)

A consecutive series of 241 men aged 50–79 attending a solo general practice in Perth, Western Australia, in 1996 were invited to take part in the study. Of these, 211 gave consent, and were offered both digital rectal examination and PSA tests. A prostate was regarded as abnormal on examination if there was evidence of nodularity, induration, asymmetry or absence of median sulcus. 199 (91.0%) were found to have a normal prostate, and 19 (9.0%) abnormal. The PSA test was regarded as normal if results were in the 0-4ng/ml range. 191 (90.5%) were in the normal range, and 20 (9.5%) were abnormal.

Of the 211 patients, 182 were normal on both tests, 29 having an abnormal finding on one or other test. From the 29, 11 biopsies were performed, with prostate cancer detected in three (27.3%). Twelve patients opted for various reasons not to undergo biopsy (eight had had biopsies in the past), and six were not biopsied because of poor health.

Table 3 Summary findings of DRE and PSA test in 211 males aged 50-79 consulting one general practitioner.(275)

Age (yrs)	Number	Normal DRE	Abnormal DRE	Normal PSA	Abnormal PSA
50-59	88	88	0	86	2
60-69	68	63	5	60	8
70-79	55	41	14	45	10
All	211	192	19	191	20

(Mansson et al, 1999)(149)

This study was a retrospective case series, the cases being patients identified from a cancer registry and from one district in Sweden (Kungsbacka). The medical records of all patients were reviewed for information about initial symptoms, diagnostic procedures, outcome of diagnostic procedures, level of care, and doctor's delay. The study collected information about new cases of prostate cancer presenting 1980-1984. There were 86 cases, an age standardized incidence of 103/100,000 per year. The symptoms at presentation are shown in *Table 4*.

Table 4 Initial symptoms of prostate cancer reported at the first visit and all the symptoms presented at the first visit.(149)

	Initial symptom observed by patient			Symptoms presented at first consultation		
Symptoms	GP	Other	Total (%)	GP	Other	Total (%)
Urgency	10	1	13	5	1	7
Nocturia	8	2	12	5	0	6
Skeletal or abdominal pain	6	0	7	14	1	17
Urinary tract infection	5	0	6	4	0	5
Other isolated local symptoms[1]	7	5	14	6	2	9
2 or more local symptoms	16	11	31	31	16	55
General symptoms[2]	3	1	5	7	2	10
No symptoms (routine examination)	8	3	13	8	3	13
Total	63	23	101	-	-	-

1-urinary retention, incontinence, macroscopic haematuria, starting problems, poor stream, terminal dribbling

2-weight loss, dyspnoea, tiredness, vertigo, fever

(Gjengsto et al, 2004)(172)

This study was undertaken in a early prostate cancer clinic in Norway, and included 872 patients referred by their general practitioner between 1997 and 2000. A total of 360 (41.3%) were diagnosed as having prostate cancer on biopsy. The median age was 63.7 years (range 40-86 years). Of the 373 patients who had consulted their general practitioner because of lower urinary tract symptoms, 34.3% were found to have cancer. Among the 462 patients who consulted without urological symptoms, the frequency of cancer was higher – 51% for those undergoing a health check, 41.9% for those with non- urological disease and 42.1% among those concerned about having cancer. The general practitioner gave a raised PSA as the reason for referral in 647 cases (222 or 34.3% had cancer), elevated PSA and suspicious DRE in 185 (125 or 67.6% had cancer), and suspicious DRE alone 24 (7 or 29.2% had cancer). Of those found to have cancer, 79.2% had no family history; 11.7% had a first-degree relative history, 6.4% a second-degree relative history, and 1.9% a first and second degree relative history.

Bladder/renal cancer

(Summerton et al, 2002)(276)

The patients in this case series were 363 people referred to an open access haematuria clinic in the UK. Patients were aged between 18 and 80, and the final diagnosis was established by cystoscopy and radiological assessment, supplemented by review of the records to check for any changes in diagnoses over time. Information was collected prospectively about clinical features and comorbidities at first clinic attendance. Cases were classified into urological and non-urological cancers, and urological and non-cancerous/normal groups. The associations between clinical features and diagnoses were explored using a variety of statistical techniques, including logistic regression.

172 patients had macroscopic haematuria and 186 microscopic haematuria. Of the 363 referred patients, no abnormality was detected in 260, 42 had benign prostatic disorders, 12 had strictures or stenoses, 13 had calculi, and 36 had urological cancers (28 of which were bladder cancers, two prostate cancers, five renal cancers, and one had both renal and bladder tumours). In multivariate analysis, the variables tending to be associated with urological cancer were older age, male sex, macroscopic haematuria (especially if a single episode), poor stream, history of urinary tract infection and smoking.

Table 5 Log-likelihood ratios for normal conditions versus urological cancer (N=296).(276)

Variable	Normal conditions (%) N=260	Cancer (%) N=36	Log likelihood ratios
Age in years			
<= 45	55 (22.1)	1 (2.8)	-.21
46-59	69 (27.3)	6 (16.7)	-.05
60-74	90 (35.6)	15 (41.7)	0.02
75+	38 (15.0)	14 (38.9)	1.0
Sex			
Male	126 (48.5)	28 (77.8)	0.05
Female	134 (51.5)	8 (22.2)	-.08
Type of haematuria			
microscopic	159 (61.9)	3 (8.6)	-2.0
macroscopic	98 (38.1)	32 (91.4)	0.9
Timing of macroscopic blood			
Beginning	12 (13.0)	7 (21.9)	0.5
Throughout	25 (27.2)	13 (40.6)	0.4
End	14 (15.2)	3 (9.4)	-0.5
Unsure	41 (44.6)	9 (28.1)	-0.5
Number of episodes			
0	61 (23.5)	2 (5.6)	-1.4
1	59 (22.7)	15 (41.7)	0.6
2	65 (25.0)	5 (13.9)	-0.6
3+	75 (28.8)	14 (38.9)	0.3
History of UTI			
0	195 (75.0)	29 (80.6)	0.1
1	28 (10.8)	7 (19.4)	0.6
2+	37 (14.2)	0 (0)	-2.4
Nocturia			
0-1	157 (60.4)	18 (50.0)	-0.2
2-4	88 (33.8)	15 (41.7)	0.2
5+	15 (5.8)	3 (8.3)	0.4
Hesitancy			
No	231 (88.8)	24 (68.6)	-0.3
Yes	29 (11.2)	11 (31.4)	1.0
Poor stream			
No	221 (85.0)	25 (71.4)	-0.2
Yes	39 (15.0)	10 (28.6)	0.7
Urgency			

Variable	Normal conditions (%) N=260	Cancer (%) N=36	Log likelihood ratios
No	171 (65.8)	21 (60.0)	-0.1
Yes	89 (34.2)	14 (40.0)	0.2

(Bruyninckx et al, 2003)(277)

The study was undertaken in a network of Belgian general practices and included all patients attending with macroscopic haematuria during 1993-1994. 83 general practitioners took part. Patients were followed up for 18 months to determine the final diagnosis.

409 patients attended with macroscopic haematuria and 126 patients were diagnosed during the same period as having urological cancer. The mean age of patients with macroscopic haematuria was 57 years, but the age of those with cancer was 72 years. 13% of those with haematuria were younger than 40 years and 53% older than 60 years.

In 87 patients (70 males, 17 females) bladder cancer was detected, and in 39 (23 males, 15 females, one sex unknown) other urological cancers were detected. 75 of the 126 patients reported macroscopic haematuria in the weeks before diagnosis, giving a sensitivity for a diagnosis of any urological cancer of 59.5% (95% CI 50.4-68.1%). The PPV of macroscopic haematuria for the diagnosis of urological cancer was 10.3% (95% CI 7.6-13.7%). The occurrence of haematuria with dysuria or increased frequency of micturition did not change the likelihood of cancer (see Table 6).

Table 6 Probability (expressed as a percentage) of urological cancer for macroscopic haematuria and additional signs and symptoms.(277)

	Haematuria and symptom			
	Present		Absent	
	All ages	Men >60 yrs	All ages	Men >60 yrs
Pain	5.3	17.8	10.9	18.9
	(2.7-9.8)	(8.5-32.6)	(7.3-16.0)	(11.9-28.6)
Increased frequency	7.2	22.6	13.4	22.0
	(3.8-12.8)	(10.3-41.5)	(9.4-18.7)	(14.9-31.2)
Dysuria	5.6	24.1	23.6	21.6
	(2.6-11.0)	(11-43.9)	(17.1-31.5)	(14.6-30.6)
Nocturia	6.3	12.5	11.2	23.3
	(2.4-14.8)	(3.3-33.5)	(8.1-15.2)	(16.3-32.1)
Weight loss	10.0	33.3	8.3	18.2
	(0.5-45.9)	(1.8-87.5)	(5.8-11.5)	(12.4-26.0)
Fatigue	20.8	30.0	8.9	20.8
	(11.0-35.4)	(12.8-54.3)	(6.2-12.4)	(14.2-29.4)

Risk Factors

(Morganstern,1998)(278)

This review provides a summary of risk factors for urological cancers. Age is the principal risk factor for prostate cancer. Risk factors for the development of bladder cancer in addition to age include cigarette smoking, and occupational exposure among dye, rubber, textile and leather workers. The risk of bladder cancer with tobacco appears to be dose-dependent and partly reversible with smoking cessation, although the risk associated with occupational exposures appear to be relatively long lasting.

Most cases of renal cell carcinoma are sporadic, although a small proportion are familial and related to mutations on chromosome 3p and Von Hippel- Lindau disease. There is a moderate, dose-dependent risk associated with cigarette smoking; Increased risk is also associated with excess body weight, hypertension and/or antihypertensives, increased parity, and a variety of occupational exposures including asbestos, petroleum products, and dry cleaning solvents. Acquired cystic kidney disease with renal insufficiency also poses a risk.

(Zeegers at el, 2003)(279)

This review sought to determine the risk of prostate cancer among relatives of affected patients. Studies published up to 2002 were included, following a search in various bibliographic databases, and a random effects meta- regression model was used to undertake a meta-analysis.

33 studies were included. From the pooled findings, the relative risk among first-degree family members was 2.53 (95% CI 2.24-2.85). The risk for second-degree relatives was only slightly elevated (1.68, 95% CI 1.07-2.64). Among first-degree family members, the risk increased with the number of affected relatives and decreased with increasing age of the affected relative.

(Huyghe et al, 2003)(280)

Following a Medline search for articles published 1980 to 2002, 30 studies were included to identify trends in the incidence of testicular cancer. A trend towards an increased rate over the last 30 years was observed in the majority of industrialized countries, including North America, Europe and Oceania. There were marked differences between nearby countries, for example 2.5/100,000 in Finland and 9.2/100,000 in Denmark, as well as among regions in the same country. From the limited information available about incidence in ethnic groups, the incidence among white men in the US has increased, but this is not the case among black Americans. Worldwide, only Maori were found to have an incidence as high as that among white males.

14.2 Investigations

14.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

14.2.2 Evidence Question:

In patients attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

14.2.3 Evidence Statements:

The PSA test is moderately sensitive and specific. (III)

Other than tests of microscopic haematuria, currently available urine tests for tumour markers are insufficiently sensitive for use in primary care. (III)

Secondary studies

Prostate cancer

(Watson et al, 2002)(281)

This guidance was published by the NHS Cancer Screening programme, and intended as advice for primary care professionals. It made clear that the PSA test is not diagnostic, and abnormal results require further investigation before a diagnosis is reached. It pointed out that 20% of men with clinically significant prostate cancer will have a normal PSA. It was advised that before having a PSA test, men should not have

a) an active urinary tract infection,
b) ejaculated in the previous 48 hours,
c) exercised vigorously in the previous 48 hours, or
d) had a prostate biopsy in the pervious 6 weeks. If practical, a PSA should be done before a DRE or delayed until a week after the DRE. Age-specific cut-off values recommended by the Prostate Cancer Risk Management Programme were given as follows:

- aged 50-59 years ≥ 3.0 ng/ml
- aged 60-69 years ≥ 4.0 ng/ml
- aged 70 years and over > 5.0 ng/ml

(Price et al, 2001)(282)

This study reported a comprehensive review of factors that influence the use of PSA in screening programmes. It identified nine studies that had investigated the effect of prior DRE on PSA levels. In the majority of studies DRE was followed by a small but statistically significant increase in PSA. In most cases this increase is not clinically significant, but in a small number the increase would have clinical significance. The review concluded that serum for PSA testing should be drawn before DRE, but if such an examination has already been performed, PSA testing should ideally be delayed for one week. The review also recommended use of age-related reference ranges to determine decision points for total PSA in men younger than 60 years as this will increase cancer detection in those likely to benefit from treatment.

(Roddam et al, 2004)(283)

In this modelling study, the impact of biased and nonequimolar assays on the decision to recommend prostate biopsy was investigated. Small deviations in bias and nonequimolarity were found to lead to significant increases in the number of false-positive biopsy recommendations, highlighting the importance of using a calibrated, unbiased equimolar assay to measure serum PSA values.

(Garnick, 1996)(284)

This review was one of a series concerned with aspects of prostate cancer. Articles published 1992-1996 were sought in a search of Medline. A largely qualitative analysis of the identified articles was undertaken.

Most of the initial screening studies that had assessed an abnormal PSA had used 4.0ng/ml as the upper limit of normal. Several studies considered methods of refining interpretation of the PSA test. The PSA density refers to a numerical ratio determined by dividing the PSA serum value by the volume of the prostate gland as determined by transrectal ultrasonography. This gives the PSA value per gram of prostate, and densities of 0.15 or more may strongly indicate the presence of cancer. However, estimation of the volume of the prostate gland is subject to error. Prostate-specific antigen velocity refers to the rate of change in the PSA value over time. A value that continues to increase over time may signal cancer. Two studies of the value of PSA velocity were included in the review, and they indicated that a change of more than 0.75ng/ml per year should be regarded with a high degree of suspicion. Recent studies have also suggested that the upper-limit of normal PSA value varies by age, being lower in younger than older men. Some preliminary studies have been undertaken of the potential role of the relative percentage of free PSA and PSA bound to serum proteins.

(Selley et al, 1997)(285)

This was a systematic review of the diagnosis, management and screening of early localised prostate cancer. PSA is a protease produced almost exclusively by prostatic epithelium. The normal range is between 0-4ng/ml, although some men with cancer have values in the normal range, and high values can be caused by conditions other than cancer. Reports of PSA sensitivity range from 57-99%, and specificity from 59-97%. The gold standard test used in studies of PSA testing is prostate biopsy, but in the primary studies not all men with elevated results would have undergone biopsy. Therefore, the true number of cancers cannot be accurately determined. The review found that evidence to support use of PSA density was equivocal, and that further research was needed into the role of PSA velocity, free and bound PSA and age-specific reference ranges for PSA normal values.

Bladder/renal cancer

(Lokeshwar and Soloway, 2001)(286)

In this systematic review, Pubmed was used to identify relevant articles. The tests included were urine cytology, haematuria detected by dipstick, and tests currently undergoing evaluation, including human complement tests, nuclear mitotic apparatus protein testing, cytology plus immunofluorescence, telomerase testing and the hyaluronic acid and hyaluronidase test.

Urine cytology was reported to have a sensitivity of 35-40% (range between studies 16-60%) for detecting bladder cancer. Haematuria can be caused by many conditions other than cancer, and therefore the specificity for cancer is low, but the sensitivity was reported to be 67-90%. There is insufficient evidence available to determine which of the other tests, or which combination of tests, can be recommended as non-invasive methods of detecting bladder cancers.

14.3 Delay and Diagnostic Difficulties

14.3.1 Key Clinical Question:

What influence do age, gender, social class and ethnicity have on the differential delay at presentation?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a woman/man who presents with urological symptoms/signs may or may not need urgent referral with suspected cancer?

14.3.2 Evidence Question:

In people attending primary care services with symptoms or signs that might be explained by urological cancer, which psychosocial and socio- demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with urological symptoms/signs may or may not need urgent referral with suspected cancer?

14.3.3 Evidence Statements:

Delay

This is little or no evidence on factors associated with delay in the diagnosis of testicular or penile cancer. (III)

The occurrence of macroscopic haematuria is associated with shorter patient delay in seeking advice. (III)

The occurrence of haematuria is associated with shorter delay by doctors. (III)

Diagnostic Difficulties

No evidence could be identified in order to create evidence statements.

Delay

Introduction

Most of the evidence found related to bladder cancer. Based on the few studies identified, it appeared that there was no relationship between patient delay and age, gender, level of education, perceived seriousness of initial symptoms, or civil status. The type of symptom appeared to be the most important factor in determining patient delay, with haematuria as the main symptom that prompted the patient to seek urgent medical advice.

Doctor delay appeared to be longer for women than for men. Doctor delay was also greatly influenced by the nature of the presenting symptoms, with shortest delay for patients presenting with haematuria and pain than with haematuria only, and longest when urgency was the only symptom. Patient age also appeared to influence doctor delay, with younger patients being diagnosed significantly earlier than those aged 70 years and above.

The effect that delay in diagnosis may have on overall survival is an area of interest for researchers. Patients whose cancers are diagnosed early do not appear to have a clear survival advantage.

Secondary studies

No papers were identified

Primary studies

Testicular cancer

(Khadra et al, 2002)(287)

The aims of this UK study were to investigate the level of awareness of testicular cancer and practice of testicular self examination (TSE) in general practitioners' male attendees, and to see if awareness of TSE was related to age, marital status, education, ethnicity, social class, knowing someone with testicular cancer, having attended a men's health clinic and having heard of a testicular cancer awareness campaign.

The authors recruited men from two UK general practices, one inner city and one suburban. Questionnaires were issued to consecutively attending male patients (N = 202) between the ages of 18 and 50 years.

Although 91% of men claimed to be aware of testicular cancer, only 26% knew both the age group most affected (25–34 years) and that testicular cancer can be curable if detected early.

Forty-nine per cent of responders had carried out TSE in the past year, but only 22% did so according to recommendations, i.e. feeling for lumps on a monthly basis. TSE was associated with age >35 years, white ethnicity, having correct knowledge of testicular cancer, knowing someone with testicular cancer, having attended a men's health clinic and having heard of a testicular cancer awareness campaign.

TSE was suggested by the media to 56% of those who examined themselves and by a nurse or general practitioner to only 16%. Forty-eight per cent of those carrying out TSE had received written instructions, and 10% had received a testicular examination by their general practitioner. Only 3% had attended a men's health clinic in the past. Of those 103

responders not carrying out TSE, 71% said they did not know what to do, 27% said they were too busy and 2% were afraid they might discover a lump. Eighty-five per cent (169/199) of the men were keen to find out more about TSE and 67% (136/202) would attend a men's health clinic if one were set up in their general practitioners surgery.

Bladder cancer

(Mansson et al, 1993)(288)

This Swedish study was undertaken to investigate various factors that may play a role in patient and doctor delays in the diagnosis of bladder cancer.

The authors examined the clinical records of all patients with a diagnosis of bladder cancer as gathered from a regional tumour registry. Variables extracted from the records included onset date and specific pattern of symptoms, date and place of first medical consultation, referral patterns, investigations, and date of diagnosis, amongst others.

A questionnaire was sent to patients to explore how seriously the patients viewed their first symptoms of bladder cancer, their experiences of previous serious or protracted illness, and their habitual perception of bodily changes and level of general education. Patient delay was defined as the time lag from the patient's first awareness of symptoms to the first medical consultation, and doctor delay as the interval from that consultation to establishment of correct diagnosis. In cases referred for further investigation, two phases of doctor delay were distinguished, viz. time from first consultation to first referral letter (time lag *A*) and from first referral to diagnosis (time lag *B*). The date of diagnosis was defined as the date of a first positive pathologic report.

The clinical records of 343 patients were examined, and 203 patients completed the questionnaire (88.6% of those eligible). Macroscopic haematuria was the commonest symptom bringing the patient to the doctor. Urgency was more common in advanced than in superficial cancer (51% vs.34%, P<0.002). No correlation was found between presence of haematuria and tumour category.

161 (67%) patients initially consulted a in primary care (mostly a general practitioner) and 51 (15%) a private practice (mostly a general practitioner or gynaecologist). The remaining 118 patients presented at a hospital. Three patients (1%) never sought medical advice and were diagnosed at post- mortem examination.

The median patient delay was 15 days (mean 141, range 0-2,857). There was no relationship between this delay and age or gender.

The type of symptom was an important factor in patient delay. Haematuria prompted the patient to seek medical advice more quickly than either urgency or pain (median 5 vs. 45 and 38 days respectively, P<0.001). Although the difference was not statistically significant, median patient delay was longer in patients with advanced cancer than in those with superficial tumour.

Amongst the responders to the questionnaire, no correlation was demonstrable between patient delay and level of education, perceived seriousness of initial symptoms, or civil status.

The median doctor delay was 62 days overall. It was longer for women than for men (76 vs. 59 days, P<0.05). The health service first consulted was a major factor in doctor delay (P<0.001), delay varying from a median of 78 days for patients initially seen in a primary care unit to a median of 21 days when the patient directly attended a department of urology, but the longer median delay was not due to delayed referral to a specialist, since in the total series doctor delay phase *A* was only six days, whereas phase *B* was 47 days (indicating considerable waiting time in the referral system).

The use of urine cytology and intravenous urography in general or private practice was associated with some, but not significant, shortening of doctor delay. The nature of the presenting symptoms influenced doctor delay, with delay being shorter with haematuria plus pain than with haematuria only, and longest when urgency was the only symptom (median 44,

53 and 114 days, P<0.001).

Patient age was associated with doctor delay. The median delay was less in patients younger than 70 years than in older patients, viz. 54 and 69 days (P<0.01).

(Wallace et al, 2002)(289)

The aim of this UK study was to assess the effect on survival of delays in the diagnosis and treatment of bladder cancer (dividing the delay from onset of symptoms to first treatment into several components, comprising patient delay, general practitioner delay, and two or more periods of hospital delay. The authors sought to collect data prospectively on all newly diagnosed cases of urothelial cancer (N=1,537) in the West Midlands from January 1991 to June 1992. The data collected included the dates of onset of symptoms, first referral by the general practitioner, first hospital appointment and first definitive treatment. Clinical details collected included the presence or absence of haematuria (macroscopic or microscopic), the number, size and type of tumours, and the findings on bimanual examination. Details of patient characteristics were also collected. In addition, patients were asked to complete a questionnaire on their smoking and occupational history.

Delay times were calculated as follows: date of onset of symptoms to date of first referral by a general practitioner (delay 1); date of general practitioner referral to date of first attendance at hospital (delay 2); date of first hospital attendance to date of first treatment by TURBT (delay 3); date of general practitioner referral to date of first treatment (hospital delay = delay 2 + 3); date of onset of symptoms to date of first treatment (total delay = delay 1 + 2 + 3). The date of first definitive treatment was the date of the diagnostic TURBT.

The median (IQR) Delay 1 was 14 (0–61) days. Patients with a longer delay were more likely to present with a higher stage tumour (P=0.04). Patients with an unknown haematuria status were more likely to have a shorter delay (P<0.001). No other patient or tumour characteristics showed a significant difference above or below the median delay. Delay 1 had a significant effect on survival; patients with a delay of <14 days to referral had an improved survival of 5% at 5-years compared with those who had a delay of >14 days (P=0.02). Adjusting for tumour stage, there was a trend for patients with a shorter Delay 1 to have a better survival (P=0.06).

The median Delay 2 was 28 (7–61) days. Patients known to have had macroscopic haematuria (N=1032) were more likely to have a shorter delay than those known to have had microscopic haematuria (N=70); patients with an unknown haematuria status were more likely to have a longer delay (P<0.001). There were no other significant differences in patient or tumour characteristics above or below the median delay. Patients who had a shorter Delay 2 had a significantly worse survival (P=0.001). Survival by Delay 2 after adjusting for tumour stage similarly showed that patients with a shorter Delay 2 had significantly worse survival (P=0.001).

The median total delay was 110 (62–209) days. Longer delays were significantly associated with women (P=0.05), younger patients (P=0.03), non- smokers (P=0.04) and patients with a low risk of occupational exposure (P=0.04). No other patient or tumour characteristics showed significant differences above or below the median delay. The total delay had no effect on survival (P=0.17); this was also true after adjusting for tumour stage (P=0.43).

For prognostic factors, there was no survival difference for sex (P=0.92), haematuria (P=0.39) and number of tumours (P=0.13), both in the log-rank analysis and Cox regression models.

(Mommsen et al, 1983)(290)

The purpose of this Danish study was to elucidate causes of delay in the diagnosis of bladder cancer.

The authors interviewed patients (N=212) with newly diagnosed bladder tumour admitted consecutively to a department of oncology and radiotherapy during a three year period beginning in 1977. The interview concerned symptoms, some demographic variables and the time intervals under study (phases A, B, and C). Phase A covered the interval between

onset of the presenting symptom and the consultation with the general practitioner. Phase B was the interval between this consultation and the patient's first examination at the local hospital. Phase C was the interval between the hospital examination and initiation of definitive treatment.

The presenting symptom was haematuria, which commonly was painless, in 79% of the patients. The interval from onset of symptoms until treatment averaged 28 weeks (median = 15 weeks). The general practitioner delay comprised half of the total delay.

Half of the patients consulted their general practitioner within a week after onset of the presenting symptom. A higher percentage of men than of women delayed 13 weeks or more.

Fewer women than men (62% and 82%) were referred to hospital within 12 weeks of the index consultation with the general practitioner (χ^2 = 8.97; d.f.=1; P <0.005). Of the patients with haematuria, 13% of the men but 35% of the women were referred to hospital after 13 weeks or more (χ^2 =9.70; d.f.=1; P<0.005). Cystitis as the presenting symptom was associated with later referral to hospital than haematuria; this was most pronounced for men (χ^2=12.56; d.f.=1; P<0.005).

(Wallace et al, 1999)(291)

The authors of this UK study examined the relationship between delay in presentation of patients with bladder cancer and tumour stage and material deprivation.

Data on delay periods to treatment, tumour characteristics, occupation and postcodes were collected for patients with urothelial cancer presenting to a Regional Cancer Intelligence Unit. The Townsend material deprivation score was derived from the patient's postcode (the score assesses four variables measuring unemployment, overcrowding, wealth and income).

A delay of < two weeks in referral to hospital was associated with a 6% improvement in survival (P = 0.018); shorter delays to hospital appointment correlated inversely with survival (P< 0.001). The overall delay time and delay to hospital admission did not correlate with survival. The deprivation scores showed no correlation with delay times, smoking or T-category of tumour. Material deprivation was correlated with low tumour grade (P = 0.004) and better survival (P = 0.02).

15 Haematological cancers

General recommendations

1 A patient who presents with symptoms suggesting haematological cancer should be referred to a team specialising in the management of haematological cancer, depending on local arrangements. D

2 Primary healthcare professionals should be aware that haematological cancers can present with a variety of symptoms that may have a number of different clinical explanations. D

3 Combinations of the following symptoms and signs may suggest haematological cancer and warrant full examination, further investigation (including a blood count and film) and possible referral:
- fatigue
- drenching night sweats
- fever
- weight loss
- generalised itching
- breathlessness
- bruising
- bleeding
- recurrent infections
- bone pain
- alcohol-induced pain

- abdominal pain
- lymphadenopathy
- splenomegaly.

The urgency of referral depends on the severity of the symptoms and signs, and findings of investigations. C

Specific Recommendations

4 In patients with a blood count or blood film reported as acute leukaemia, an immediate referral should be made. D

5 In patients with persistent unexplained splenomegaly, an urgent referral should be made. C

Investigations

6 Investigation of patients with persistent unexplained fatigue should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or Creactive protein (according to local policy), and repeated at least once if the patient's condition remains unexplained and does not improve. [B(DS)]

7 Investigation of patients with unexplained lymphadenopathy should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [B(DS)]

8 Any of the following additional features of lymphadenopathy should trigger further investigation and/or referral:
- persistence for 6 weeks or more
- lymph nodes increasing in size
- lymph nodes greater than 2 cm in size
- widespread nature
- associated splenomegaly, night sweats or weight loss. [C(DS)]

9 Investigation of a patient with unexplained bruising, bleeding, and purpura or symptoms suggesting anaemia should include a full blood count, blood film, clotting screen and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [B(DS)]

10 A patient with bone pain that is persistent and unexplained should be investigated with full blood count and X-ray, urea and electrolytes, liver and bone profile, PSA test (in males) and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy). [C(DS)]

11 In patients with spinal cord compression or renal failure suspected of being caused by myeloma, an immediate referral should be made. C

Introduction

Epidemiology

Haematological cancers (cancer of blood cells) account for an estimated 7% of all cancers in the UK. However, the incidence continues to rise, with a 3-5% increase between 1984 and 1993.

The haematological cancers considered in the guideline can be divided into three main diseases, the leukaemia's, the lymphomas and myelomas.(292) Figures provided by the Office for National Statistics and Cancer Intelligence and Surveillance Unit suggest that 39 new cases are reported per 100,000 population per annum.(292) It is possible that the figures are higher, as this number is only of registered cases.

Multiple myeloma

Multiple myeloma is a neoplastic monoclonal proliferation of bone marrow plasma cells. The

aetiology is unknown. Plasma cells are responsible for immunoglobulin production, and in myeloma they may produce a single monoclonal immunoglobulin (around 1% of cases are non-secretory). In about 15% of cases the paraprotein is absent, with the production of light chains only which are excreted in the urine (Bence Jones proteinuria). It accounts for less than 1% of cancers in most countries despite being on the increase worldwide.

In 2001 there were 2,859 new registrations of cases of multiple myeloma,

1,528 in males and 1,331 in females. Trends in mortality have been similar to those in incidence rates, demonstrating a general increase with age.

Figure 11 2001 Registrations of multiple myeloma in England and Wales. (77)

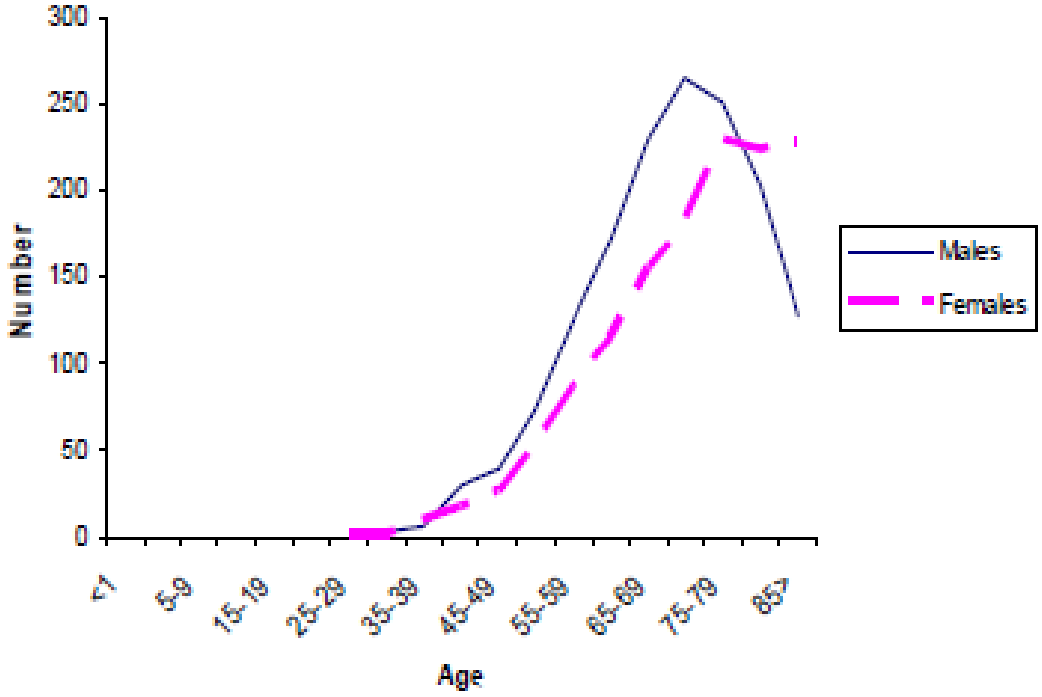
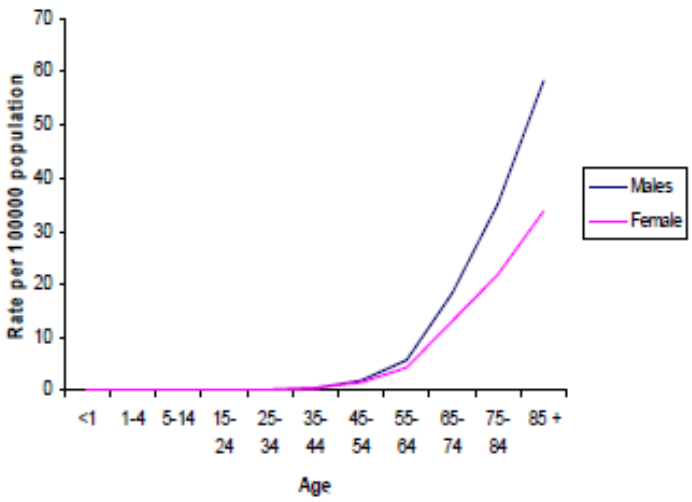


Figure 12 2002 mortality rates from multiple myeloma in England and Wales. (78)



Leukaemia

As a group the leukaemia's account for approximately 3% of cancer incidence worldwide and 2.5% of cancers in England and Wales, with males having a generally higher incidence rate than females.

The incidence of the leukaemia's in England and Wales in 1994 was as follows:

- Acute myeloid leukaemia (AML): approximately one third of cases.
- Chronic lymphoid leukaemia (CLL): approximately one third of cases.
- Chronic myeloid leukaemia (CML): just over one tenth.
- Acute lymphoblastic leukaemia (ALL): just over one tenth.
- Monocytic leukaemia and other specified: each only 1%
- Other or unspecified leukaemia: 9%

In 2001 in England and Wales, there were 5,598 new cases of leukaemia, 2,439 females and 3,159 in males (Figure 130).

In England and Wales in 2002 there were 3900 deaths from leukaemia (2,100 in males and 1,811 in females) (See Figure 14).

Figure 13 2001 Registrations of all leukaemias in England and Wales. (77)

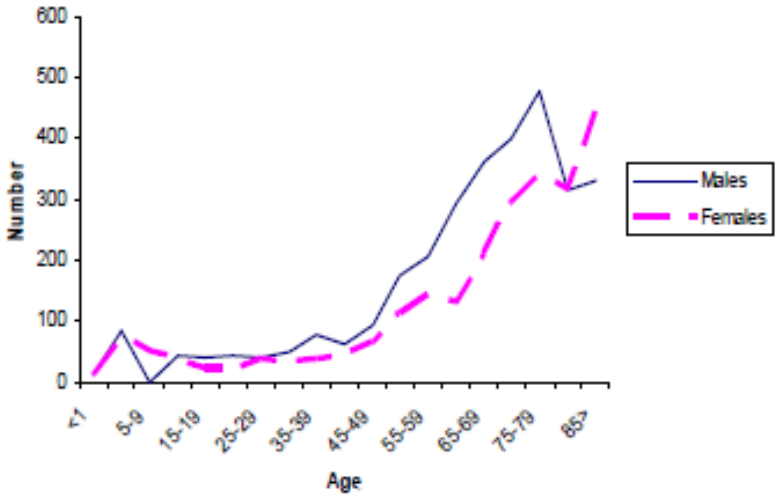
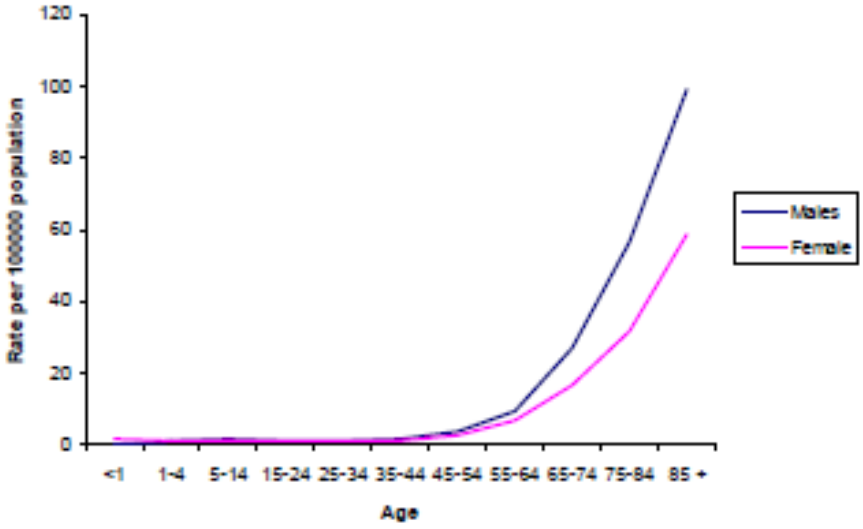


Figure 14 2002 mortality rates from all leukaemias in England and Wales. (78)



Lymphomas. (Hodgkin's Lyphoma and Non-Hodgkin's Lymphoma)

The lymphomas are malignancies of the lymph nodes and other lymphoid tissues. They are classified into Hodgkin's lymphoma and the non-Hodgkin's lymphomas.

Hodgkin's lymphoma

The incidence of Hodgkin's lymphoma in England and Wales decreased from 1970 until the end of the 1980s when it began to levels began to stabilise in both males and females. Incidence in both sexes increases sharply from age five until peaking around the age of 20 when there is a steady decline until age 50. In 2001 the recorded registrations of newly diagnosed Hodgkin's lymphoma were 1,176, of which 507 cases were in females and 669 in males. (See Figure 15)

Mortality from Hodgkin's lymphoma increases with age. There were 489 deaths (286 in males and 203 in females) in 2002 in England and Wales (Figure 1633).

Figure 15 2001 Registrations of Hodgkin's lymphoma in England and Wales. (78)

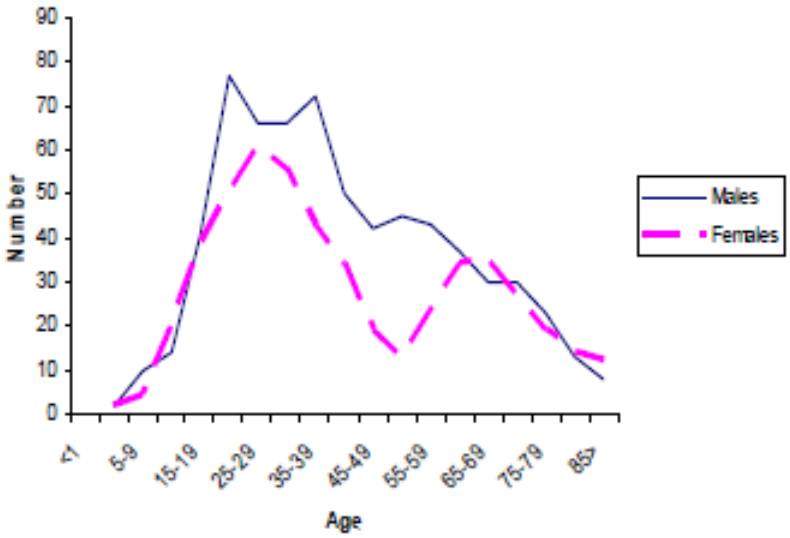
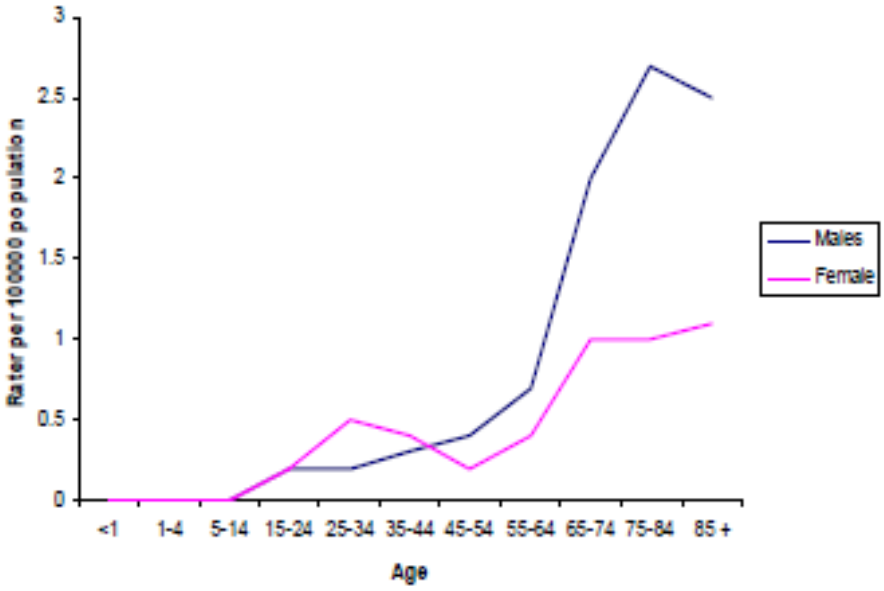


Figure 16 2002 mortality rates from Hodgkin's lymphoma in England and Wales. (78)



Non-Hodgkin's lymphoma

Just over half of cases occur in those aged 60-79. The number of newly diagnosed cases of non-Hodgkin's lymphoma in 2001 was 7794, 4,146 in males and 3,648 in females (see Figure 17).

Mortality rates increase as steeply as incidence rates in both sexes, including the most significant rise being in those aged 75 and over. In England and Wales in 2002, there were 3,217 deaths from non-Hodgkin's lymphoma, 2,250 in males and 1,967 in males (Figure 18).

Figure 17 2001 Registrations of Non-Hodgkin's lymphoma in England and Wales. (77)

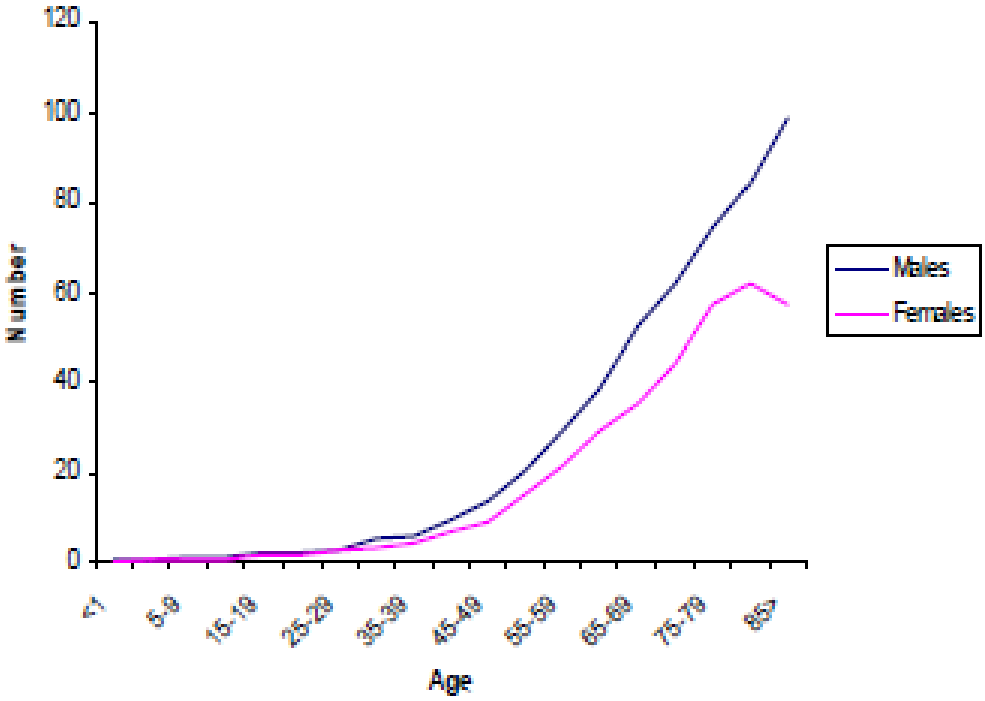
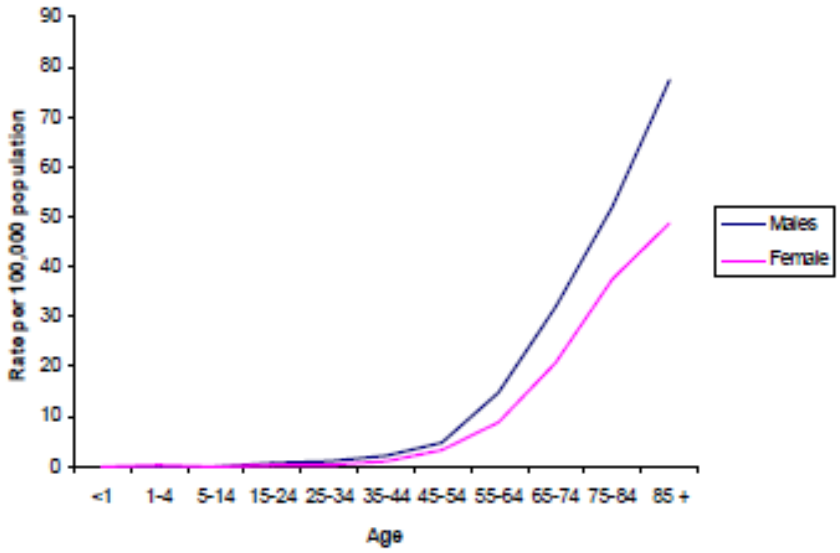


Figure 18 2002 Mortality rates from Non-Hodgkin's lymphoma in England and Wales. (78)



Review of cancer referral audits

The review identified 26 relevant audits. The proportion of two week wait referrals found to be in accordance with the symptoms listed in the guidelines (Department of Health, 2000) ranged from 74% to 100% (eight audits). The proportion of patients referred under the two week wait system who were found to have cancer ranged from 28% to 45% (six audits). The proportion of patients with cancer who had been referred via the two week wait system ranged from 0% to 25%.

15.1 Signs and Symptoms

15.1.1 Key Clinical Question:

How common are haematological cancers in certain population groups, characterised by age, sex, and different ethnic groups?

Which symptoms, signs and other features raise a suspicion of cancer, and those that make cancer less likely as a diagnosis?

Does family history discriminate patients who should be referred? What is the influence of co-morbidity on suspicion and referral?

15.1.2 Evidence Question:

In people attending primary care services, which symptoms and signs and other features including family history when compared with the "gold standard" are predictive of a diagnosis of haematological cancers and which symptoms and signs are not?

15.1.3 Evidence Statement:

Fatigue may be a presenting symptom of haematological cancers, but there is insufficient evidence to distinguish fatigue due to haematological cancers from other causes of fatigue (III).

Although lymphadenopathy is a common sign in patients in primary care, lymphoma is an uncommon cause. In one US series of 249 patients in primary care presenting with lymphadenopathy, one (0.4%) had Hodgkin's disease and one adenocarcinoma (III).

There is insufficient evidence from primary care studies of the significance of fever in

identifying patients who might have haematological cancers (III).

There is insufficient evidence from primary care studies of the significance of bruising, bleeding or anaemia in identifying patients who might have haematological cancers (III).

Bone pain is a common presenting symptom in people with myeloma, in one study the proportion being 72.6% of patients (III).

Risk factors associated with haematological malignancies include exposure to chemicals used in the rubber industry, Epstein-Barr virus, and socio-economic factors. However, these factors are not helpful in making decisions about referral in patients who present with suggestive symptoms, signs or laboratory test results (III).

The incidence of Hodgkin's lymphoma has a peak at 20-25 years of age, and another peak at 75-79 years (III).

The incidence of non-Hodgkin's lymphoma rise from around 45 years of age (III).

The incidence of multiple myeloma rises from aged 50, and is almost nil below aged 35 years (III).

The incidence of the acute leukaemias has a peak aged 5-9, then increases from aged 49. Chronic myeloid leukaemia is seen in childhood but is rare, chronic lymphocytic leukaemia does not occur in childhood, is uncommon in early adult life and is seen overwhelmingly in late life. (III).

Only a small number of studies of patients with haematological cancers presenting in primary care were identified, and the findings of the review that follows must therefore be interpreted with caution. The principal signs and symptoms identified in the papers included fatigue and lymphadenopathy. We also sought studies of prolonged fever, anaemia, bleeding and bruising, among patients in primary care, but found little or no relevant evidence.

Secondary studies

Fatigue

(Servaes et al, 2002)(293)

This article reviewed studies of the relationship between cancer and fatigue. Two Medline searches were undertaken for the period July 1980-2001. A total of 181 articles were identified through two searches. Of those, 127 were excluded (review articles, editorials/comments/practical guidelines, small sample size, published in a language other than English or Dutch), leaving 54 to be reviewed. In most articles, fatigue was investigated among patients who were undergoing treatment for cancer rather than at the time of initial diagnosis. Information on the relationship between fatigue and haematological cancer was scarce. No articles were based on data from a primary care setting. The reviewers reported that the identified studies seldom properly investigated the relationship between fatigue and disease and treatment- related characteristics. Relationships between fatigue and psychological, social, behavioural and physical factors were identified in several studies. Most studies however, focused on the depression-fatigue association. Seven studies investigated fatigue during treatment with chemotherapy.

In seven of ten relevant studies, severity of fatigue appeared to be unrelated to cancer diagnosis, cancer stage at diagnosis, size of original tumour, number of nodes involved and presence and site of metastases. However, significant associations were found between fatigue and particular types of cancer in three studies. In a sample of radiotherapy patients, patients with lung cancer reported the most fatigue compared to those with head and neck, gastrointestinal, gynaecological, lung, breast, urogenital and haematological malignancies. Those with cancer in the head and neck region reported the least fatigue. In another study, patients with small cell lung cancer were found to report less fatigue in contrast to patients with cholangiocarcinoma or pancreatic cancer, breast cancer, or a lymphoma

during a cycle of chemotherapy owing to feeling better more quickly after the administration of chemotherapy.

Thirteen studies indicated a strong correlation between fatigue and psychological distress such as depression, somatisation and anxiety. However, all these patients had advanced disease and most had multiple physical problems and a short prognosis. Finally, in three studies, although correlations between fatigue and depression were moderate, depression scores did not change while fatigue scores rose over the course of radiotherapy and hormonal therapy.

Prevalence estimates of fatigue during treatment for cancer ranged from 25 to 75% in different samples of cancer patients, measured with different questionnaires. In studies that included a control group of healthy subjects, patients with cancer reported more frequent and severe fatigue. In nine of the ten studies, no significant relationships were demonstrated between demographic variables and fatigue. Psychological distress, quality of sleep and a few other variables (pain, therapy side-effects, and physical activity) were found to be related to fatigue.

Primary studies

Lymphadenopathy

(Fijten and Blijham, 1988)(294)

This Dutch study investigated the probability of malignancy in patients presenting with unexplained lymphadenopathy in primary care. Clinical characteristics that may be discriminatory for malignancy were also investigated. The study was a retrospective case series that involved 82 patients who had undergone biopsy for unexplained lymphadenopathy between 1982 and 1984.

The possibility of malignant disease was considered to be the main justification for referral. Early referral (defined as taking place within four weeks after the first contact between patient and family physician) with a biopsy positive for malignancy was considered to be a true-positive test result. A referral later than four weeks was considered as physician delay (false- negative). Cytologic or histologic examination was used as the 'gold standard' for malignant and benign lymphadenopathy.

The 82 patients who underwent lymph node aspiration or biopsy represented about 3% of all 2256 patients presenting with this problem in family practice during the time period and catchment area of the study. Of these 82 patients, 9 had a malignancy, a prior probability of 1.1 percent (29/2256) and a posterior probability after referral of 11.0 percent (29/256). Diagnoses included 14 malignant lymphomas, 15 metastases, 37 reactive lymph nodes without specific diagnosis, and 16 benign causes.

The ability of the family physician to refer malignant cases within four weeks after initial consultation (sensitivity of referral) was 80 to 90 percent; 91 to 98 percent of benign cases were not referred (specificity of referral). An increased likelihood of malignancy was associated with age over 40 years (4%) and supraclavicular lymphadenopathy (50%). The incidence of malignancy in patients presenting with unexplained lymphadenopathy to the family physicians was very low (1-2%).

Of 29 patients with malignant disease, 26 had been referred within four weeks for a sensitivity of 90%. A physician delay exceeding four weeks occurred in three cases, all with a diagnosis of malignant lymphoma. A total of 36 patients were referred within four weeks but turned out to have benign lymphadenopathy, for a specificity of 98%.

Table 7 Patient Characteristics and Diagnostic Outcome in Unexplained Lymphadenopathy (Fijten and Blijham, 1988(294))

	Malignant Lymphadenopathy		
	Yes	No	P Value
Age (years)			
>40	20	7	<0.1
<40	9	46	
Sex			
Female	12	31	NS
Male	17	22	
Weight Loss			
>10 percent	7	3	<0.1
<10 percent	20	37	
Nodal Pain			
Yes	8	11	NS
No	20	32	
Duration of Symptoms			
<4 weeks	15	28	NS
> 4 weeks	14	24	
Number of enlarged nodes			
1	17	28	NS
>1	12	24	
Localization of nodes			
Supraclavicular	13	2	<0.1
Other neck	9	25	NS
Axillary	4	16	NS
Inguinal	7	13	NS
Erythrocyte sedimentation rate			
>30 mm/h	7	3	=.1
<30 mm/h	22	38	
White cell count			
>10 x 10^9/L	4	4	=.1
<10 x 10^9/L	25	34	

X^2 test with Yates' correction; NS- not significant

Table 8 Sensitivity and Specificity of Early Referral for Unexplained Lymphadenopathy (Fijten and Blijham, 1988(294))

Referral	**Malignant Causes**	
	Present	**Absent**
Within four weeks	26	36
After four weeks or not at all	3	2,491
Sensitivity for malignant lymphadenopathy: 90% *Specificity for malignant lymphadenopathy: 98%*		

Only age over 40 years and the presence of an enlarged supraclavicular node were clearly related to an increased likelihood of malignancy; borderline significance was obtained for an increased sedimentation rate and weight loss.

In an unselected population in primary care, about 20% of patients with unexplained lymphadenopathy are older than 40 years. In primary care, patients 40 years of age and older with unexplained lymphadenopathy have about a 4% risk of cancer versus a 0.4%

risk in patients younger than 40 years old.

(Allhiser et al, 1981)(295)

In this retrospective case series, 80 cases of lymphadenopathy were identified and reviewed in a primary care setting (the Cedar Rapids Family Practice Residency Program). Several clinical parameters important to the evaluation of lymphadenopathy were incompletely recorded in the medical notes. Isolated cervical nodes accounted for 44% of all cases, while 24% had enlarged nodes in more than one anatomic region. The most frequently performed laboratory test was a full blood count (34%) and the most frequent positive test was a throat culture (30%). 20% of patients received antibiotics.

56 cases (70%) were discovered by patients and 15 (19%) by the physician (previously unknown to the patient). It was unclear from the medical records who had first noted the node enlargement in the other nine cases (11%). Of those discovered by the patient, the duration of swelling by the time of first visit ranged from one day to six months, with one third reporting swelling of less than one week. 37 patients (46%) reported pain and 35 (44%) denied it. No mention of pain was found in the charts of eight patients (10%).

Table 9 Location of Enlarged Nodes (Allhiser et al, 1981(295))

Location	Number	1.1.1 Percent
Cervical	35	44
Inguinal	13	16
Submandibular	9	11
Axillary	3	4
Occipital	1	1
More than one location	19	24

Seven patients (9%) had nodes measuring less than 0.5 cm, 14 patients (18%) had nodes measuring less than 0.5 cm, 14 patients (18%) had nodes 0.5-1cm, and 36 (45%) had nodes recorded as greater than 1cm.

Table 10 Combination of Node Enlargements (Allhiser et al, 1981(295))

Combination	Number
Cervical, Axillary, Inguinal	7
Cervical, Submandibular	3
Cervical, Occipital	2
Cervical, Axillary	2
Cervical, Subclavian	1
Cervical, Axillary, Submandibular	1
Cervical, Sublingual, Axillary, Inguinal	1
Occipital, Axillary, Inguinal	1
Submandibular, Axillary, Inguinal	1
Total	19

Table 11 Laboratory Work-Up (Allhiser et al, 1981(295))

	Number done	Number Abnormal	Number Repeated
Complete Blood Count	27	1	1
Sedimentation Rate	15	0	2
Chest X-ray Film	14	0	
Monospot	13	1	2
Throat Culture	10	3	
PPD	8	1	
Chemistry Panel	4	0	
Urinalysis	4	0	
Biopsy	4	0*	
Other Cultures	2	0	
Total	101	6	5
*All benign			

As with many retrospective studies, incomplete recording of details in medical records was a problem. For example, liver or spleen enlargement was apparently not assessed in 44 (55%) cases, and thyroid size was not mentioned in 55 (69%) cases.

(Williamson, 1985)(296)

In this case series, the primary care charts of 249 US patients with enlarged lymph nodes presenting between 1978 and 1983 were reviewed to provide a primary care database for evaluating lymphadenopathy. The patients included in the study were those whose diagnoses were coded ‘enlarged lymph nodes, not infected’, and ‘lymphadenitis, acute’ by the consulting physician. The mean age indicated from the 249 charts was 24 years; 26% were aged less than 15 years. Females accounted for 58% of the subjects. For those seen for enlarged lymph nodes, 51% were seen once, 23% twice, and 26% seen three times.

A firm diagnosis was made in only 36% of patients despite an average of 1.7 visits and two laboratory tests per patient tested. Lymph node biopsies were performed in only 3% of patients. No patient was found to have a prolonged, disabling illness without a prompt diagnosis. The data suggested that in patients without associated signs or symptoms, a period of observation was safe and likely to save unnecessary expense and biopsy.

Of the patients whose charts were reviewed, 18% had associated upper respiratory tract infection, 8% had infected or inflamed tissue near the node site (dermatitis, cuts, cellulitis, abscess) and 5% had insect bites. No potentially serious diseases presented with lymphadenopathy alone; all had associated signs or symptoms that led to a diagnosis. Older persons were more likely to have serious disease associated with enlarged nodes.

Table 12 Laboratory Work on 249 Patients with Lymphadenopathy (Williamson, 1985(296))

Laboratory Test	Number (%)	1.1.2 Number Positive (%)
None	128(51)	0
Complete Blood Count	81(33)	3(3.7)
Throat Culture	40(16)	6(15)
Chest roentgenogram	29(12)	3(10)
Tuberculin	28(12)	3(10)

Monospot	25(10)	1(4)
Automated chemistry	9(4)	0
Biopsy of node	8(3)	3(38)
Culture, gonorrhoea	8(3)	2(25)
Serum test for Syphilis	6(2)	1(16)
Sedimentation rate	5(2)	0
Histoplasma titre	2(1)	0
Toxoplasma titre	2(1)	0
Febrile agglutinins	2(1)	0

15.2 Investigations

15.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

15.2.2 Evidence Question:

In people attending primary care services with symptoms and signs that might be associated with haematological cancers, which investigations when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

15.2.3 Evidence Statements:

Biopsy is the definitive investigation of lymphadenopathy, although this is not usually undertaken in primary care. An abnormal chest x-ray may be associated with a diagnosis of tumour in cases of lymphadenopathy (III).

A blood film detects the white cell abnormalities of leukaemia (III).

Haemoglobin and blood film tests are common triggers for referral of patients with suspected haematological malignancies (III).

Primary studies

(Lee et al, 1980)(297)

The authors undertook a retrospective study of all patients who had isolated lymph node biopsies over a five-year period in a large county hospital. Data regarding age, sex, and site of node removed were obtained. A total of 551 (60%) of the nodes removed were benign lesions, 263 (28%) were carcinomas, and 111 (12%) were malignant lymphomas. Of the peripheral lymph node biopsies, isolated axillary lymphadenopathy had the highest likelihood (23%) of having lymphomatous involvement; and second highest was the neck area (18%). About 8% of the supraclavicular or groin node biopsies were lymphomatous. The possibility that a peripheral lymphadenopathy was benign decreased with the patient's age (for patients younger than age 30, 77-85% of the lesions were benign, 2-8% carcinomatous, and 13-23% lymphomatous; for patients 51-80 years old, 35-41% had benign lesions, 32-47% carcinomas, and 11-33% lymphomas). For patients younger than 30 years old, peripheral lymphadenopathies were more likely to be lymphoma than carcinomas (mean 15% vs. 6%); among patients older than 51 years, carcinomas were more common than lymphomas (mean 44% vs. 16%). Patient gender did not influence the likelihood of benign or malignant diagnosis. 4% of isolated abdominal lymph node biopsies, 1% of intrathoracic nodes, and 15% of peripheral lymph nodes contained lymphoma.

(Slap et al, 1984)(298)

The authors developed a predictive (discrimination) model to differentiate patients whose biopsy results did not lead to treatment from those whose biopsy results did lead to treatment (for granulomatous or malignant nodes – Hodgkin's disease and non-Hodgkin's lymphoma, and metastatic solid tumour). Medical records and histopathology slides of patients who underwent biopsies of enlarged peripheral lymph nodes at the Hospital of the University of Pennsylvania between 1953 and 1983, or at the Children's Hospital of Philadelphia between 1969 and 1983, were reviewed and pathological diagnosis was compared with 22 clinical findings. Patients were excluded from the study if a previous biopsy had revealed histopathology, if there was no palpable peripheral lymphadenopathy, or if the pathology slides were unavailable for review. The authors retrospectively validated the model with a second sample of patients who had also undergone biopsies.

The following four clinical findings were associated with granuloma or tumour at P<0.05: abnormal chest x-ray, lymph node size on physical examination greater than 2cm in diameter, history of night sweats, and history of weight loss. A history of recent ENT symptoms (ear ache, coryza, or sore throat) was the only variable associated with the absence of granuloma or tumour at P<0.05. A haemoglobin value of 10.0g/dl or less was associated with granuloma or tumour at P=0.08. Three of the variables (haemoglobin, night sweats, and weight loss) did not contribute significantly to discrimination. The model developed with the other three variables (chest x-ray, lymph node size, and history of recent ENT symptoms) classified correctly 95-97% of patients, with a sensitivity and positive predictive value of 95% and a specificity and negative predictive value of 96%. Chest x-ray was found to have the greatest impact on the discriminant score. The diagnostic performance of the model was significantly better than that of chance alone (P=0.001).

(Montserrat et al, 1991)(299)

This study sought to describe presenting features and prognosis of a case series of 117 previously untreated younger patients with chronic lymphocytic leukaemia (CLL) from 14 different Spanish institutions. The mean age of patients was 44.5 years; SD, 4.8; range, 19-49; male-female ratio, 2.08). Blood lymphocyte counts and lymphocyte doubling time were treated as reliable predictors of patient outcome.

The number of CLL cases increased with age: one patient was less than 20 years old; one was between 20 and 30 years old; 16 were between 30 and 40 years old; and 99 (85%) were between 41 and 49 years old. The presenting features of both the younger age group (less than 50 years of age) and the older age group (50 or more years of age) were used for comparative purposes. In the younger age group there was a significant predominance of males (2.08 vs. 1.21; P<0.25), and the haemoglobin level was slightly, albeit significantly, increased (13.47 ± 2.70g/dL vs. 12.84 ± 2.77g/dL; P<0.5). No differences were found in the initial lymphocyte and platelet counts. Blood lymphocyte counts and doubling time were useful in predicting the outcome of the disease in younger patients. The increased male/female ratio in the younger group (2.08) was an unexpected finding.

(Nasuti et al, 2000)(300)

The utilisation and efficacy of lymph node fine needle aspiration was evaluated over a five-year period for 387 cases. A total of 365 FNA specimens from an equal number of cases were performed on palpable and non-palpable masses clinically believed to be lymph nodes and an additional 22 cases of extranodal lymphoreticular tumours were reviewed over a five- year period from February 1993 to February 1998.

Approximately half (N=182) were diagnosed as either metastatic carcinoma or melanoma; in 54 cases (30%) excisional biopsy or tissue study was performed to confirm the diagnosis; there was only one false-positive diagnosis of a metastatic squamous carcinoma (from a submandibular lymph node). 61 lymphoma cases successfully diagnosed via lymphnode FNA with no false positives. Concurrent flow cytometry was utilised in 51% (N=31) of the 61 cases and supported the cytologic diagnosis of lymphoma in 27 of the 31 cases (87%). A benign or reactive lymph node process was also diagnosed by FNA alone or in combination with flow cytometry in 48 cases with only five false negatives, which included four cases of

mantle cell lymphoma and one case of melanoma.

(Pangalis et al, 1993)(301)

The aim of this study was to determine whether a patient presenting with an enlarged lymph node was within or outside the normal limits. The exact cause of abnormal enlargement was subsequently investigated to establish the cause of lymphadenopathy. The vast majority of pathological lymph node enlargement < 1cm^2 in this Greek hospital based study had a non-specific aetiology (118 of 186 patients [63.4%]). Among the specific causes, toxoplasmosis, infectious mononucleosis and tuberculosis were the most frequently encountered. A lymph node size of 2.25cm^2 (1.5 X 1.5cm) was reported as discriminating between malignant or granulomatous lymphadenopathies from other lymphadenopathies (RR = 13.0). Based on this observation, patients with a lymph node size < 1cm^2 could be simply observed, after the exclusion of toxoplasmosis and/or infectious mononucleosis, except when there is other evidence of an underlying systemic disease.

Data from the hospital unit suggested that splenomegaly coexists with lymphadenopathy in a small proportion of patients (10 of 220 or 4.5%). The presence of lymphadenopathy and splenomegaly is compatible with infectious mononucleosis (splenomegaly in 50% of the patients), Hodgkin's disease, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, and other leukaemias. Lymph node biopsy was necessary for establishing the diagnosis in 74 out of 220 patients (33.6%).

(Schmidt et al, 1985)(302)

A Danish team investigated the clinical diagnosis in all 88 cases of monoclonal gammopathy, detected by general practitioners in one district during a three-year period, 1979 to 1981. The cases were all serum protein electrophoresis tests requested by general practitioners in a county with 482 000 inhabitants that had been performed in one of two departments of clinical chemistry. The follow up observation period was 18-54 months. Malignant monoclonal gammopathy accounted for 15%, non-haematologic cancers 5%, and a benign disorder was found in 80%. These results indicated that the finding of a monoclonal gammopathy in general practice deserves attention, but it is not automatically accompanied by a grave prognosis.

A classification of disorders modified from Kyle (1), was used to divide the monoclonal gammopathys into malignant monoclonal gammopathy (MMG) and monoclonal gammopathy of undetermined significance (MGUS).

In the three years of the study, close to 10,000 serum protein electrophoresis investigations were requested from general practice, 88 cases of monoclonal gammopathy being found (i.e. in less than 1% of the serum protein electrophoresis performed). No person had primary amyloidosis or heavy- chain disease. Monoclonal gammopathy was most often found in patients between 60 and 80 years of age. There were 13 (15%) people with malignant monoclonal gammopathy and 75 (85%) monoclonal gammopathy of undetermined significance. Only one of 13 persons below the age of 50 years with a monoclonal gammopathy had a malignant disease. Malignant monoclonal gammopathy was more common in the older group (19% of cases of gammopathy). Less than 0.2% (13 out of 10,000) of those in whom a serum protein electrophoresis was requested had malignant monoclonal gammopathy.

(Wright et al, 1992)(303)

In this case series involving 226 patients newly referred in a one year period to the haematology department at Leeds General Infirmary, the records were reviewed to investigate sources and types of referral. General practitioners initiated 126 (56%) of all referrals, consultants in other hospital departments referred 68 (30%), and 25 (11%) were cross boundary referrals from hospitals outside the district. Haematology medical staff initiated 4 (1.8%) referrals i.e. telephoning general practitioners and suggesting that the patient be referred following an abnormal full blood count (FBC). Abnormal full blood counts or blood film findings prompted most general practitioner referrals (71 out of 126, i.e. 56%); the haematologist often enclosed a written report suggesting referral. Three patients (1.3%) were transferred from private practice.

The results indicated that general practitioners initiated over half of all referrals, often prompted by written comments from a haematologist on a full blood count advising them that further tests were required. Most general practitioner requests were made with a request for a diagnosis. Hospital initiated referrals were more likely to have a final diagnosis of a malignant haematological disease, whereas those from general practice tended to have benign or self-limiting conditions. Of those referred, 91% of patients had an abnormality.

The most common abnormality leading to referral was lymphadenopathy [24 (11%)] followed by an iron deficient full blood count report [20 (9%)], easy bruising [19 (8%)], neutropenia [14 (6%)], and a full blood count report suggesting a myeloprofilerative disorder [14 (6%)]. Reasons for referral differed depending on the source. General practitioners initiated all the referrals for suspected iron-deficiency, and 19/24 (79%) of referrals with lymphadenopathy. In contrast, hospital consultants referred most cases of thrombocytopenia for investigation, all cases of paraprotein for further investigation, and all cases of lymphoma proven by histology before referral.

General practitioners referred 95% (21/22) of cases subsequently diagnosed as being iron deficient (17% of all general practitioner referrals). No haematological abnormality was found in 13% of general practitioner referrals requiring follow-up, compared with 5% of hospital referrals. Post-viral fatigue syndrome was exclusively a final diagnosis of general practitioner referred patients.

It was departmental policy for a member of the medical staff to telephone general practitioners with the results of any full blood count that required further investigation or action. Such personal contact, as well as initiating referrals, sometimes prevented inappropriate referral, particularly if the general practitioner (or another hospital department) could undertake further investigations. The value of telephone contact in enhancing the outpatient service was emphasised. The generally high quality and appropriateness of the referrals may be inferred from the low numbers of patients transferred to the care of other departments (6%).

15.3 Delay and Diagnostic Difficulties

15.3.1 Key Clinical Questions:

What influence do age, gender, social class and ethnicity have on the differential delay at presentation?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with haematological symptoms/signs relevant to the head and/or neck may or may not need urgent referral with suspected cancer?

15.3.2 Evidence Questions:

In people attending primary care services with symptoms or signs that might be explained by haematological cancer, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with haematological symptoms/signs may or may not need urgent referral with suspected cancer?

15.3.3 Evidence Statements:

Delay

Only limited evidence is available about the factors leading to delay in presentation and referral in the case of lymphoma.

Most delay is due to delay in presentation by patients (III)

The impact of delay on survival is unclear (III)

Diagnostic Difficulties

We did not identify any evidence to address this question

Delay

Secondary studies

No relevant secondary studies were identified.

Primary studies

(Norum, 1995)(304)

A retrospective study was undertaken of the hospital records of 50 patients treated for primary Hodgkin's lymphoma in Northern Norway between 1985 and 1993. Diagnostic delay was related to clinical stage, age, sex, relapse or death, and was defined as the time period between the patient's first symptoms of lymphoma and the histological or cytological diagnosis of Hodgkin's lymphoma. Little information was available about the proportion of delay accounted for by doctors and patients separately.

There was no correlation between delay in diagnosis and age, sex, symptoms, or stage of disease. The diagnostic delay disease did not seem to have any significant influence on stage distribution, relapse rate or short-term survival. Those dying of disease had had a short delay, suggesting that the aggressiveness of the tumour was the important parameter. All six patients dying of Hodgkin's lymphoma had a diagnostic delay of six months or less (median 3.2 months). The same tendency was revealed for relapse and diagnostic delay. Nine of ten relapsing patients had a delay of six months or less. There was no statistical correlation between delay in diagnosis and age, sex, or symptoms. There was no improvement in diagnostic delay during the study period (1985-93).

In comparison with the other pathological subgroups, the lymphocyte predominant Hodgkin's lymphoma sub group experienced a significant delay (P+0.038). The median delay was four months (range 0-48 months) in lymphocyte predominant Hodgkin's lymphoma compared to four months (range 0-27months) in the other subgroups. The median age at diagnosis was 41 years (range 15-70 years). The cases of lymphocyte predominant Hodgkin's lymphoma had usually presented in stage one and two, located in lymph nodes without affecting adjacent structures, a factor which may have explained prolonged delay.

(Summerfield et al, 2000)(305)

Delays in the diagnosis and treatment of lymphoma in district hospitals in the northern region of the UK were audited in order to assess the appropriateness of the target that all new patients with suspected cancer be seen by a specialist within two weeks of a referral by their general practitioner. Delays were monitored at different stages of the process of diagnosis and initial treatment of lymphoma. Sources of delay were analysed in all 89 consecutive cases presenting to hospitals in 1997-1999.

Delay was divided into those generated by the patient, those from first seeking medical advice to the time of a diagnostic biopsy (diagnostic delay) and those from diagnostic biopsy to the start of treatment (treatment delay). The numbers of patients entered from each institution were: 19 (North Tyneside), 20 (Bishop Auckland and Gateshead) and 30 (Sunderland). Diagnostic delay was evaluated in 88, treatment delay in 87 and patient delay in only 76, as a result of failure to record the date of onset of symptoms in the case records. Delays at different stages were found not to differ significantly between different institutions, but the

number of cases from each institution was relatively small.

The results of the audit showed that during the period of study, delay from general practitioner referral to hospital appointment averaged 3.9± 1.2 (mean ± SE) weeks. Delay between hospital appointment and biopsy was 4.7 ± 1.0 (mean ± SE) weeks (N=87), and delay from biopsy to local histology report 1.2 ± 0.1 (mean ± SE weeks (N=83), and then from local histology to review panel report 3.1 ± 0.6 (mean ± SE) weeks (N=48). In addition a delay from diagnostic biopsy to bone marrow examination was recorded of 2.8 ± 0.3 (mean ± SE) weeks (N=70), furthered by delay from diagnostic biopsy to CT scan 2.8 ± 0.41 weeks (N=85).

The major delays were not, however, those between referral and initial hospital appointment but those introduced by patients themselves (mean 3.9 months), and between first medical contact and diagnostic biopsy (mean 2.8 months). This suggested that significant reductions in diagnostic delay can best be achieved by increased patient education about the early signs of lymphoma and by a locally agreed rapid referral process from general practitioner to hospital with subsequent fast tracking of diagnostic biopsies.

Many patients with aggressive high grade non-Hodgkin's lymphoma had short survival despite minimal delay in diagnosis or starting treatment. Survival may be related to the aggressiveness and inherent resistance to treatment of lymphoma rather than to diagnostic delay. There is little published evidence that delay reduces survival duration or cure rate, although in aggressive high- grade non-Hodgkin's lymphoma this would seem likely to be the case. Delays in the diagnosis and treatment of lymphoma could damage patient confidence and reduce satisfaction with the outcome of treatment.

15.4 Support and Information needs

15.4.1 Key Clinical Question:

What are the support and information needs of patients who are being referred for suspected cancer? Are the needs different in different groups of patients?

15.4.2 Evidence Question:

What are the support and information needs of patients who are being referred for suspected haematological cancer? Are the needs different in different age, sex, ethnic and cultural groups of patients?

15.4.3 Evidence Statement:

There was insufficient evidence on which to base an evidence statement.

General advice about the support and information needs of patients being referred with suspected cancer can be found in Chapter 7.

Primary studies

(Persson et al, 2001)(306)

This study investigated the quality of life of patients with acute leukaemia and malignant lymphoma at the start of treatment and over two years. Questionnaire responses were compared with patients' statements in open- ended interviews. A consecutive sample of patients with acute leukaemia and highly malignant lymphoma, undergoing chemotherapy (N=16) between 1993 and 1995, were included from the starting treatment and over the first two years. A consecutive sample of 16 patients were asked to complete a battery of instruments that included the Quality of Life Questionnaire (QLQ-C30) and a sense of coherence scale, at intervals during the first two years of care. At the start of treatment, the quality of life score in the total sample indicated decreased functioning in all aspects and the presence of all symptoms. Role functioning, social functioning and global quality of life

were affected most, and fatigue, dyspnoea and sleep disturbance were the most troublesome symptoms.

At the start of treatment: Respondents with acute leukaemia were significantly more affected with regard to social functioning (P=0.04) and global quality of life (P=0.01) than respondents with highly malignant lymphoma. Men were significantly more emotionally affected (P=0.02) than women. Younger people had more dyspnoea than older people (P<0.05).

Development over the two years: Throughout the study period, patients with acute leukaemia were significantly more affected in their role (P<0.05) and social (P<0.01) functioning than patients with highly malignant lymphoma. No significant differences were observed concerning the severity of problems experienced in the comparison groups of men and women or different ages.

16 Skin cancer

1 A patient presenting with skin lesions suggestive of skin cancer or in whom a biopsy has been confirmed should be referred to a team specialising in skin cancer. D

2 All primary healthcare professionals should be aware of the 7-point weighted checklist (see recommendation 1.10.8) for assessment of pigmented skin lesions. C

3 All primary healthcare professionals who perform minor surgery should have received appropriate accredited training in relevant aspects of skin surgery including cryotherapy, curettage, and incisional and excisional biopsy techniques, and should undertake appropriate continuing professional development. D

4 Patients with persistent or slowly evolving unresponsive skin conditions in which the diagnosis is uncertain and cancer is a possibility should be referred to a dermatologist. D

5 All excised skin specimens should be sent for pathological examination. [C(DS)]

6 On making a referral of a patient in whom an excised lesion has been diagnosed as malignant, a copy of the pathology report should be sent with the referral correspondence, as there may be details (such as tumour thickness, excision margin) that will specifically influence future management. D

Specific recommendations

Melanoma

7 Change is a key element in diagnosing malignant melanoma. For low-suspicion lesions, careful monitoring for change should be undertaken using the 7-point checklist (see recommendation 1.10.8) for 8 weeks. Measurement should be made with photographs and a marker scale and/or ruler. D

8 All primary healthcare professionals should use the weighted 7-point checklist in the assessment of pigmented lesions to determine referral:
Major features of the lesions:
- change in size
- irregular shape
- irregular colour.

Minor features of the lesions:
- largest diameter 7 mm or more
- inflammation
- oozing
- change in sensation.

Suspicion is greater for lesions scoring 3 points or more (based on major features scoring 2 points each and minor features scoring 1 point each). However, if there are strong concerns about cancer, any one feature is adequate to prompt urgent referral. C

9 In patients with a lesion suspected to be melanoma (see recommendation 1.10.8), an urgent referral to a dermatologist or other suitable specialist with experience of melanoma diagnosis should be made, and excision in primary care should be avoided. C

Squamous cell carincomas

10 Squamous cell carcinomas present as keratinizing or crusted tumours that may ulcerate. Non-healing lesions larger than 1 cm with significant induration on palpation, commonly on face, scalp or back of hand with a documented expansion over 8 weeks, may be squamous cell carcinomas and an urgent referral should be made. C

11 Squamous cell carcinomas are common in patients on immunosuppressive treatment, but may be atypical and aggressive. In patients who have had an organ transplant who develop new or growing cutaneous lesions, an urgent referral should be made. C

12 In any patient with histological diagnosis of a squamous cell carcinoma made in primary care, an urgent referral should be made. C

Basal cell carcinomas

13 Basal cell carcinomas are slow growing, usually without significant expansion over 2 months, and usually occur on the face. Where there is a suspicion that the patient has a basal cell carcinoma, a nonurgent referral should be made. C

Investigations

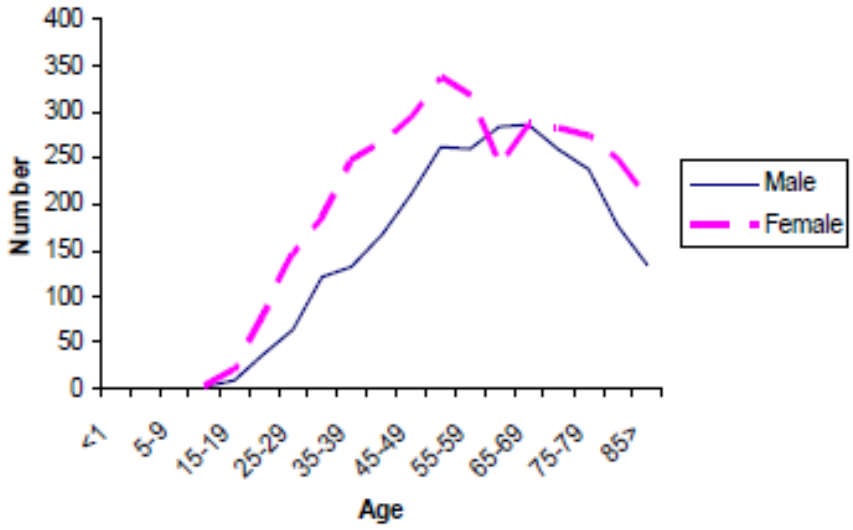
14 All pigmented lesions that are not viewed as suspicious of melanoma but are excised should have a lateral excision margin of 2 mm of clinically normal skin and cut to include subcutaneous fat in depth. [B(DS)]

Introduction

Melanoma

There were 6,062 recorded cases of malignant melanoma in England and Wales in 2001. Of these 3,424 were in females and 2,638 in males. The incidence of melanoma increases with age in both males and females rising steadily in both sexes from age 15 years onwards.

Figure 19 Newly diagnosed cases of skin melanoma in 2001 in England and Wales. (77)

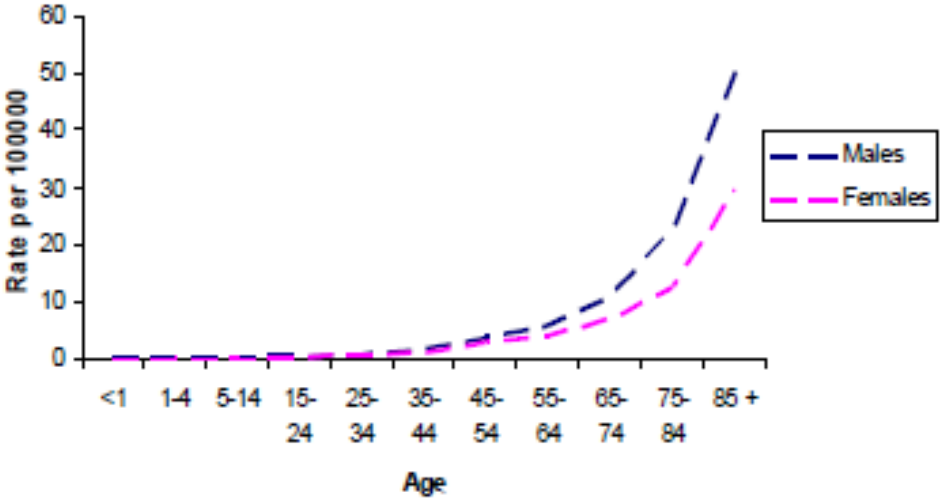


Mortality

The age specific mortality rates for melanoma of the skin are similar for both men and women, and numbers mirror the increase in incidence with increase in age. There were a total of 1,480

deaths from malignant melanoma in England and Wales in 2002, of which 784 were males and 696 females (see Figure 20).

Figure 20 Mortality figures from skin melanoma for 2002 in England and Wales. (78)



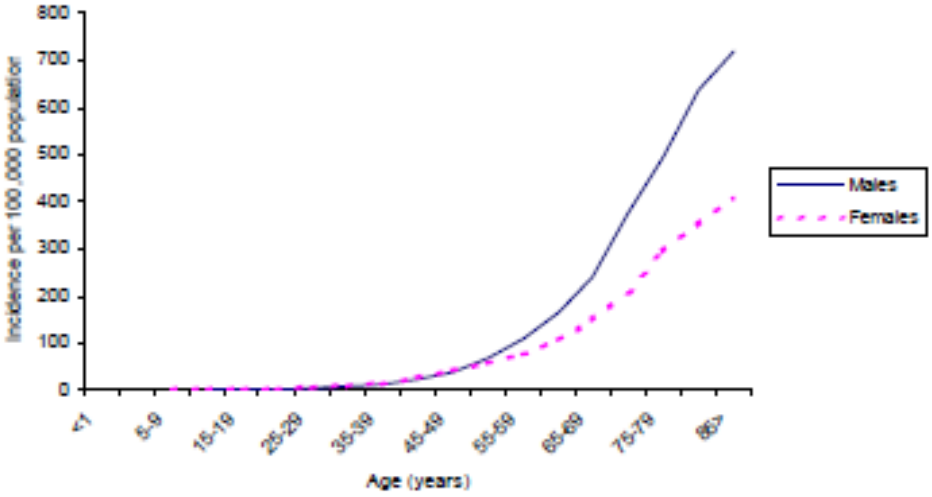
Non-Melanoma (basal and squamous cell carcinoma)

Incidence

Non-melanoma skin cancers are the most common cancer occurring in the UK (http://www.cancerresearchuk.org). There were an estimated 59,000 cases diagnosed in 1999 across the UK, but the true figure may be higher because of under-reporting of cases. Basal cell carcinoma (BCC) is now thought to be the most common of all human malignancies closely followed by squamous cell carcinoma (SCC) (307).

Incidence rates increase with age in males and females, and in 1994 incidence reached 718 in males and 407 in females per 100,000 population in those aged 85 years and over.

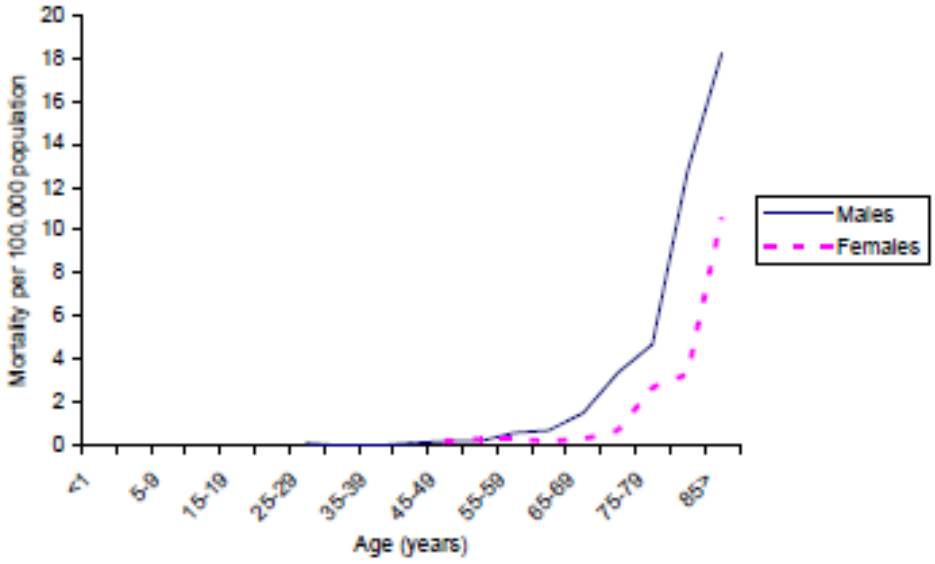
Figure 21 Incidence rates per 100 000 population for non-melanoma skin cancer, England and Wales, 1994(17)



Mortality

The provisional mortality rates for 1999 show that mortality from non- melanoma skin carcinoma remains low in those less than 50 years of age. Mortality in males increases steadily from age 60 years onwards peaking at 18/100,000 population in those aged 85 years or over. Female mortality rates begin to rise steeply from age 70 years and peak at 7/100,000 population in the same age group. In 2002, there were 259 deaths among men from non- melanoma skin cancers and 187 in women.

Figure 22 Mortality per 100 000 population from non-melanoma skin, England and Wales, 1999 (provisional)(17)



16.1 Symptoms and Signs

16.1.1 Key Clinical Questions:

How common are skin cancers in certain population groups? Which symptoms, signs and other features raise a suspicion of skin cancers (melanoma and basal cell carcinoma [BCC], squamous cell carcinoma [SCC]), and those that make cancer less likely as a diagnosis? Does family history discriminate patients who should be referred?

16.1.2 Evidence Question:

In people attending primary care services with dermatological problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer; and which symptoms and signs are not?

16.1.3 Evidence Statements:

The incidence of melanoma is rare below aged 15 years, and increases with age. The incidence has been increasing over the last 20 years. (III)

The incidence of non-melanoma skin cancers increases with age, and has been increasing over the past 20 years. (III)

Melanoma

Features of skin lesions associated with melanoma include: increase in size, change in shape, change in colour, size >5-7 mm, irregular outline, ulceration, inflammation and bleeding. (III)

The evidence about the use of checklists such as the ABCD or seven-point checklists is limited. (III)

There is insufficient evidence about the effectiveness of educational interventions to improve the ability of general practitioners to identify melanoma. (III)

Several factors are associated with melanoma, but the level of risk conferred by these factors is insufficient to discriminate between those who should or should not be suspected of having melanomas. (III)

Non melanoma (basal or squamous cell carcinomas)

Squamous cell carcinomas present as keratinizing or crusted tumours that may ulcerate. (III)

Basal cell carcinomas may be nodular, cystic or ulcerated. (III)

The risk of squamous cell carcinomas is increased in people who are immunosuppressed. (III)

Several other factors increase the risk of squamous cell carcinoma, but insufficiently to distinguish those patients who should be suspected of having these tumours. (III)

Several factors, including immunosuppression, have been associated with basal cell carcinoma. (III)

Guidelines

Melanoma

(SIGN, Cutaneous melanoma: A National Clinical Guideline, 2003)(308)

The SIGN guidelines were developed following a detailed literature review and included the following recommendations:
Clinicians should be familiar with the seven point or the ABCDE checklist for assessing lesions. (D)
Clinicians using hand held dermatoscopy should be appropriately trained. (D) Health professionals should be encouraged to examine patients' skin during other clinical examinations. (D)
Patients with suspicious pigmented lesions should be seen at a specialist clinic in a time commensurate with the level of concern indicated by the general practitioner referral letter. (recommended best practice)
Emphasis should be given to the recognition of early melanoma by both patients and health professionals. (recommended best practice)
Targeted education can enhance professionals' ability to diagnose melanoma. (recommended best practice)
Healthcare professionals and members of the public should be aware of the risk factors for melanoma. (B).
Individuals identified as being at higher risk should be:
advised about appropriate methods of sun protection educated about the diagnostic features of cutaneous melanoma encouraged to perform self-examination of the skin. (C)
Brochures and leaflets should be used to deliver preventive information on melanoma to the general public. (D)
Leaflets and brochures used in melanoma prevention work should be non- alarmist. (recommended best practice)
If computer-based learning programmes are used they should be interactive in nature. (recommended best practice)

(Australian Cancer Network, 1999)(309)

These guidelines for melanoma were based on a systematic review of evidence that was considered by a multidisciplinary panel. The recommendations relating to clinical diagnosis were:
Good lighting and magnification is recommended when lesions are examined. All clinicians should be trained in the recognition of early melanoma.

A good clinical history of the change in the lesion (if any), a past history of skin lesions, and a family history of melanoma should be obtained.
A family history is defined as melanoma in a direct-line family member – grandparent, parent, sibling or child of the patient.
Lesions which are suspicious or cannot be diagnosed after a period of observation should be biopsied, or the patient referred for a specialist opinion.
High risk individuals should be advised of the specific changes which suggest melanoma and encouraged to perform self-examination.

(Roberts et al, 2002)(310)

These guidelines for melanoma were produced jointly by the British Association of Dermatologists and the Melanoma Study Group. The seven- point checklist was recommended for both patient and general practitioner education. Lesions with any of the three major features (change in shape, irregular shape, irregular colour) or three of the minor features (largest diameter 7mm or more, inflammation, oozing, change in sensation) are suspicious of melanoma, and should ideally be seen by specialists (that is, clinicians routinely treating large numbers of patients with pigmented lesions). Specific recommendations were:

Patients with lesions suspicious of melanoma should be referred urgently to a dermatologist or surgeon/plastic surgeon with an interest in pigmented lesions.

These specialists should ensure that a system is in place to enable patients with suspicious lesions to be seen within two weeks of receipt of the referral letter.

All patients who have had lesions removed by their general practitioner that are subsequently reported as melanoma should be referred immediately to specialists.
(Grade C, level III)

Squamous Cell Carcinoma

(Motley et al, 2002)(311)

These British Association of Dermatologists/British Association of Plastic Surgeons guidelines addressed squamous cell carcinoma. Squamous cell carcinoma was defined as a malignant skin tumour of keratinizing cells of the epidermis or its appendages, which is locally invasive and has the potential to metastasize. The guidelines state it usually presents as an indurated nodular keratinizing or crusted tumour that may ulcerate, or may present as an ulcer without evidence of keratinization.

Other forms of squamous cell carcinoma include (a) actinic and radiation keratoses, which are scaly erythematous papules or plaques on sun damaged or irradiated skin that may develop into invasive squamous cell carcinoma; (b) pre-invasive carcinoma (carcinoma in situ): (i) Bowen's disease, which is crusted, keratotic or a velvety erythrematius plaque; (ii) erythroplasia of Queyrat, which appears on the glans penis as a red, velvety patch; (iii) erythroplakia and malignant leukoplakia, on mucous membranes other than the glans penis; (c) verrucous carcinoma, a warty tumour that occurs most often on the hands, feet, anogenital area and oral cavity; (d) keratoacanthoma.

Basal Cell Carcinoma

(Telfer et al, 1999)(312)

These guidelines were produced on behalf of the British Association of Dermatologists, and dealt with basal cell carcinoma. Basal cell carcinoma was defined as a slow-growing, locally invasive malignant epidermal skin tumour, which occurs most commonly in caucasians. Metastasis is extremely rare, and morbidity is related to local tissue destruction, particularly on the head and

neck. The clinical appearances are diverse, and include nodular, cystic, ulcerated ('rodent ulcer'), superficial, morphoeic (sclerosing), keratotic and pigmented variants.

Primary studies

Melanoma

(Elwood et al, 1998)(313)

This article was a report from a larger case control study of risk factors. Information on all histologically confirmed cases of newly diagnosed cutaneous malignant melanoma was obtained from treatment centres and cancer registries in four provinces of Canada. Identified patients were interviewed about initial presentation and symptoms. In total, 801 patients aged 20 to 79 years were approached for interview, and 665 (83%) were successfully interviewed. Of these, 14 had acral lentiginous melanoma and were excluded from the report, leaving 651 patients who had cutaneous melanomas.

Population matched controls were selected for all cases. The interviewer was unaware of the case or control status of the interviewee. Pathological slides were obtained and reviewed by one of two pathologists, although slides could not be obtained for 121 patients (20%). The original pathology report was used for these patients.

Of the 651 patients, 60% were female. The mean age of the sample was 49.7 years (range 21 to 79 years). 415 patients (64%) had superficial spreading melanoma, 128 (20%) had nodular melanoma, 52 (8%) had unclassified or borderline melanoma and 56 (9%) had lentigo maligna melanoma. Most patients (65%) reported one or more of a set of four symptoms related to an existing mole or pigmented spot:

Each of the 651 patients presenting with melanoma were asked to describe, without prompting, the first indications of their disease, the results are shown in Table 13.

Table 13 First symptoms of melanoma(313)

Major symptom group	
Enlargement, colour change, pain or bleeding	N=425 (65%)
Suspicious lesion, no other detail	N=154 (24%)
New mole	N=50 (8%)
Miscellaneous	N=22 (3%)
Frequency of 'classic' symptoms	
Enlargement	N=282 (43%)
Colour change	N=209 (32%)
Pain	N=144 (22%)
Bleeding	N=102 (16%)

(Brady et al, 2000)(314)

This case series included 471 newly diagnosed patients with cutaneous melanoma presenting to a US specialist cancer centre between July 1995 and May 1998. Patients with an unknown primary site, noncutaneous melanoma, distant metastases or recurrent disease were excluded. All patients were asked to complete a questionnaire at their first visit to the cancer centre. Information regarding the Breslow thickness of the melanoma was available in 454 patients.

There were approximately equal numbers of males and females, but females were younger than males (51 years vs. 55 years, P<0.01). Most of the patients were Caucasian (N=456 of 471 patients; 97%) and most patients presented with American Joint Committee on Cancer Stage I and Stage II disease.

Most patients presented with melanoma > 0.75mm in Breslow thickness (62%; N=283 patients). The remaining patients (38%) had thin melanomas (≥0.75mm; N=122 patients) or in situ disease (N=49 patients). The majority of patients detected their own melanomas (N=270; 57%). Patterns of detection were influenced by patient gender. Females were more likely to self-detect than males (69% vs. 47%; P<0.0001). Physicians detected the melanoma in 16% of patients (N=74), followed by spouse in 11% (N=51). Physicians were three times more likely to detect thin lesions (≤0.75 mm) compared with nonphysician detectors (95% confidence interval [95% CI] 2.1, 6.5; P=0.0001). Physician detection occurred in only four of 84 males under age 0 years compared with 43 of 166 males age ≥ 50 years (P<0.0001). Patients who reported a family history of melanoma had a 2.7 fold increased likelihood of presenting with a thin lesion (95% CI, 1.6, 4.7; P=0.003). Family history information was available for 451 patients. Of these, 84 patients (19%) reported a family history of melanoma, and 366 patients (81%) reported no first or second degree relative with the disease.

Despite a trend towards thinner melanomas in females, the difference in the median Breslow thickness between females and males was not significantly different (1.10 mm vs. 1.13 mm; P=0.07). There was no significant association between tumour thickness and age, gender or lesion visibility.

(Schwartz et al, 2002)(315)

In this US case series, 1515 consecutive patients presenting to a US cancer centre between January 1998 and December 1999 with in situ or invasive cutaneous melanomas were questioned about their signs and symptoms. All histology slides were reviewed by a skin pathologist to confirm the diagnosis of primary cutaneous melanoma.

The mean age at diagnosis of the first primary melanoma was 52.6 years. The majority of patients (72%) were between the ages of 21 and 65, 26% being older than 65 years, and only 2% younger than 21 years. Females (48.9 years) were younger than males (56.1 years) at diagnosis of their first primaries (P<0.001). Physician detected lesions were thinner (0.40mm) than either self-detected (1.17 mm; P<0.001) or spouse-detected (1.00 mm; P<0.001) lesions. In males the Breslow depth of self-detected lesions (1.42 mm) was greater than that of the lesions detected by either the spouse (1.04 mm; P<0.005) or physician (0.42 mm; P<0.001). In females, the mean Breslow depth of self-detected lesions (0.98 mm) was greater than physician detected lesions (0.35 mm; P<0.001) but was not significantly different from spouse-detected lesions (0.72 mm; P=0.2).

The most common changes noted by patients were the colour, size, and/or shape/elevation of a lesion. Less common changes included ulceration, bleeding, tenderness, and itching. Mean Breslow depths associated with a change in colour (1.15 mm), size (1.33 mm), shape/elevation (1.47 mm) and itching (1.70 mm) were less than mean Breslow depths associated with ulceration (2.69 mm), bleeding (2.63 mm) and tenderness (2.44 mm; all P<0.005).

(Sober et al,198)(316)

The study included a total of 598 patients attending two US hospitals. A questionnaire was administered by a trained interviewer to evaluate the frequency with which signs and symptoms were associated with melanoma. All patients in this sample had clinical stage 1 cutaneous melanoma. They were seen either with the primary tumour intact or within 30 days of its removal. The frequency of each sign and symptom was cross tabulated with four thickness ranges: <0.85 mm, 0.85 mm, 0.85 to 1.69 mm, 1.70 to 3.64 mm, and ≥ 3.65 mm.

For thin lesions (<0.85 mm) increase in size was noted in more than half and was the most frequent

sign or symptom present for 'thin' tumours. This was closely followed by colour change, which was present in half. Bleeding, ulceration and tenderness were infrequently seen (present in five to 13%). Conversely, increase in height was the most frequent feature noted with the thickest tumours (≥ 3.65 mm), observed by more than 80% of patients. Bleeding and ulceration were reported in more than half. There was a direct relationship between increase in height and increasing tumour thickness. Itching of the lesion occurred in 20-46% of patients.

(Wick et al,1980)(317)

The clinical characteristics of the primary tumour in 786 US patients with histologically confirmed superficial spreading melanoma were investigated in this case series from five US hospitals.

The most useful features for early diagnosis were change in size and change in colour, present in 71% and 55% respectively of patients with level II lesions. Increase in height of lesion correlated with more advanced disease. Ulceration and bleeding were predominantly found in advanced primary lesions and were judged of limited use in early recognition. The data revealed that primary lesions were of substantial size and generally much larger than acquired naevi (<7mm) from which they must be differentiated. The results suggested that site was not a major determinant for the presentation of early lesions. There was however a higher proportion of level II lesions (42%) on the head and neck. Conversely, a higher percentage of deeper lesions were encountered on the foot. Characteristic features of early (II, III) lesions associated with tumour growth were colouration and size. The features characteristic of advanced lesions were tenderness, ulceration and bleeding. Elevation became common at level III and above.

(Cassileth,1987)(318)

In this case series, a retrospective analysis of the charts of 568 patients treated between 1972 and 1981 for superficial spreading melanomas was undertaken. The sample was composed of patients who had attended a single specialist US centre, and only data for patients over 17 years of age and with no prior primary melanomas were included. Information was recorded routinely for all patients by clinic nurses using a structured interview guide during the patient's first clinic visit. Patients were asked about the presence of each of seven symptoms (size, elevation, colour, bleeding, ulceration, itching and tenderness) plus other features. Information was recorded about the type, number and duration of individual symptoms noticed by the patient; catalyst symptoms or the particular event that preceded the patient's request for medical attention; and location, thickness and level of the melanoma.

Forty-eight percent of patients who met the eligibility criteria were men. Forty- six percent of patients reported the simultaneous occurrence of more than one catalyst symptom; 35% reported experiencing one catalyst symptom only; and 19% claimed that they had noticed no changes in existing lesions. The most common catalyst symptom pattern, a combination of size, elevation and colour was reported by 60 patients, who were diagnosed an average of 11.2 months after observing this combination. The mean tumour thickness at diagnosis for this group of patients was 1.26 mm (± 1.8 mm). The second most common catalyst symptom, bleeding, was reported by 49 patients, who were diagnosed after an average of 2.3 months. A total of 75 different catalyst symptoms or symptom combinations were described.

Patients who sought medical attention in response to bleeding alone (N=49) had thicker lesions (mean 1.77 mm) than did the 45 patients who sought medical attention in response to changes in both size and colour (mean 0.54 mm). A total of 109 patients, 19% of the sample, could not identify any change in an existing lesion. The average lesion thickness for these 109 patients was 0.93 mm (± 1.4 mm) compared with the average lesion thickness of 1.37 (± 1.8 mm) for all other patients ($P<0.01$).

Symptom/Sign Checklists for Melanoma

Two checklists have been developed as diagnostic aids to assist identification of melanoma lesions

from the presenting features indicative of malignancy.

The seven point checklist(310) recommended criteria used to evaluate lesions suggestive of melanoma. The checklist specifies major and minor features, they are; major features: change in size, irregular shape and irregular colour; minor features: largest diameter 7mm or more, inflammation, oozing and change in sensation. The checklist was developed mainly for use by primary care physicians to facilitate referral decisions. In a revision of the list, 'irregular shape' was replaced by 'change in shape'. The major criteria are therefore change in size, shape and colour. The minor criteria are inflammation, crusting or bleeding, sensory change and a diameter greater than or equal to
7mm.

Table 14 ABCD(E) System for clinical diagnosis of malignant melanoma(319)

A Asymmetry
B Border irregularity
C Colour variegation
D Diameter of 6mm or more
E Elevation*

*often excluded

The ABCD method(319) developed in the USA is another tool for diagnosing malignant melanoma. The system was expanded into ABCDE list to include an 'E' which has been used to indicate either 'elevation' or 'evolutionary change'. Many benign naevi however, may be elevated. Asymmetry refers to one half of the lesion not matching the other. Border irregularity describes edges that are ragged, notched or blurred. Colour irregularity involves pigmentation that is not uniform; shades of tan, brown and black are present with dashes of red, white or blue; and a diameter of at least 6 mm is also classified as important.

(Whited, 1998)(319)

This was a systematic review of the accuracy of skin examination for melanoma using the ABCD(E) and revised seven point checklists. A literature search was performed using MEDLINE for the years 1966 through 1996 to identify relevant retrospective and prospective studies.

Evidence contained in the articles were evaluated and included if they had been given a quality rating of C or above. Twelve studies were included in total. Two studies reported information about the sensitivity for the ABCD checklist, in one it was 92%; (CI 95%, 82%-96%), and in the other 100% (95% CI 54%-100%); one study reported specificity to be 98% (95% CI, 95%-99%). The revised seven point checklist has been reported to have a sensitivity of 79% (95% CI, 70%-85%) to 100% (95% CI 94%-100%) and specificity of 30% (95% CI, 21%-39%) to 37% (95% CI, 21%-39%). Physicians' global assessments for detecting the presence or absence of melanoma were estimated to have a specificity of 96% to 99%, while sensitivity ranges widely from 50% to 97%. Non-dermatologists' examinations were less sensitive than those performed by dermatologists.

(Osborne, 1999)(320)

The aim of the study was to investigate possible predictor variables for false negative gradings using the seven point checklist in a population (107) of patients with histologically confirmed malignant melanomas presenting in Leicestershire between 1982 and 1996. The case notes of the included patients were examined retrospectively. False negatives were defined as those patients in whom another diagnosis was made or in whom there was evidence in the case notes that the diagnosis

was thought not to be malignant melanoma. Demographic data were recorded together with clinical diagnosis, clinical features of each lesion according to the revised seven point checklist, and site of the lesion.

No clinical diagnosis had been given in the records for 43 of the 778 lesions,

599 were suspected of being melanoma, and 136 had not been suspected on clinical grounds. The clinical false negative diagnosis rate was 18.5% and the diagnostic sensitivity 81.5%. There were 476 females and 257 males, giving a ratio of 65% females. Sex had no effect on false negative rate; the proportion of females in the diagnosed group being 66% and the non-diagnosed group 60% (=0.20). The false negative rate varied markedly with site and was lowest for the trunk and leg (12 and 13%), but was 21% for the arm. More rarely occurring sites gave higher false negative rates from 31% to 42%. Comparing the false negative rate on the trunk (the lowest rate) with the other sites, the odds ratio for the face was 3.4 (P=0.0007), head and neck 5.1 (P<0.0001), arm 2.0 (P=0.02), leg 1.0 (P=0.6), sole 3.4 (P=0.06) and subungual 5.5 (P=0.007).

The false negative clinical diagnosis rate varied markedly with the presence of features of the seven point checklist (P<0.00001). It was lower if major features were present (8-18%), and greater if the minor features were present (13-35%). Major features associated with a particularly low rate were irregular shape and irregular pigmentation, 8 and 10%, respectively. Clinical features of lesions associated with a higher false negative rate were lack of irregular pigmentation and shape, altered sensation, the presence of inflammation and size < 7mm.

The multivariate logistic regression of all parameters showed that the relationships of false negative rate and melanoma site, irregular pigmentation, irregular shape, sensation, inflammation and diameter >6 mm were significant and independent. For the individual sites, results of univariate and multivariate analysis were similar, although the adjusted odds ratio and its significance, for the face compared with the trunk increased markedly on multivariate analysis. The results suggested that the face is a particularly difficult site. All of the clinical features except surface oozing/crusting/bleeding retained significance on multiple regression.

Risk Factors

Melanoma

(SIGN, 2003)(308)

The SIGN guidelines involved a systematic literature search that included assessment of risk factors. The findings were presented in a table, reproduced here. In the table, odds ratios are given, based on the findings of one or more primary studies, odds ratios being the odds in favour of exposure to a risk factor in people with melanoma to the odds in favour of exposure to the same risk factor among people who have not developed melanoma. The SIGN guideline observed that the odds ratios for someone who has skin that does not tan easily (1.98) is modest in comparison with the ten fold or greater risk of developing lung cancer in someone who smokes cigarettes compared to a person who has never smoked.

SIGN recommended that:

Genetic testing in familial or sporadic melanoma is not appropriate in a routine clinical setting and should only be undertaken in the context of appropriate research studies (D).
The SIGN guidelines cited a consensus document, which estimated that one to two percent of melanomas were attributable to the inheritance of melanoma susceptibility genes.

'Members of such families are at significantly increased risk of developing melanomas. Many more melanoma patients have only one relative who also has melanoma. An intensive search for putative melanoma susceptibility genes has identified mutations in the CDKN2A gene in 20-30% of melanoma prone families in Scotland, reflecting rates reported in other parts of the world. Current

expert consensus recommends that genetic testing in familial or sporadic melanoma is not appropriate in a routine clinical setting and should only be undertaken in the context of appropriate research studies and when appropriate counselling services are available.'(308)

Table 15 Established Risk Factors for cutaneous melanomas(308)

Risk Factor	OR	Information
11-50 common moles >2mm	1.7 – 1.9	The risk of melanoma rises with the number of common moles.
51 – 100 common moles >2mm	3.2 - 3.7	
>100 common moles >2mm	7.6 – 7.7	
Family history of melanoma	1.8	Melanoma in a first degree family member (parent, sibling or child of the patient.
Previous history of melanoma		Standardised incidence ratio range 4.5 – 25.6
Presence of 1-4 atypical moles	1.6 – 7.3	Atypical moles: ill-defined or irregular border; irregular pigmentation; diameter >5mm; erythaema (blanchable in lesion or edge); accentuated skin markings.
Red or light-coloured hair	1.4 – 3.5	
Presence of actinic lentigines	1.9 – 3.5	Actinic lentigines: flat, brown skin lesions associated with acute and chronic sun exposure. No direct malignant potential.
Giant congenital melanocytic naevi ≥20cm in diameter		Relative risk range 239-1, 224 for extracutaneous as well as cutaneous melanoma.
Unusually high sun exposure	2.6	
Reported growth of a mole	2.3	
Skin that does not tan easily	1.98	
Light coloured eyes	1.55 – 1.60	
Light coloured skin	1.40 – 1.42	
Affluence		Relative risk approximately 3.0 for people residing in areas defined as Carstairs deprivation category 1 (least deprived) compared to Carstairs category 7 (most deprived).

Non-melanoma skin cancers

Basal cell carcinoma

Secondary studies

(Wong et al, 1989)(321)

This authoritative review concluded that exposure to ultraviolet radiation was the main causative factor in the pathogenesis of basal cell carcinoma. However, the precise relationship between risk of basal cell carcinoma and the amount, timing and pattern of exposure to ultraviolet radiation were unclear. The magnitude of the risk associated with increased exposure seemed to be insufficient to explain why particular people get these tumours whereas others did not. Several studies showed an association between cumulative ultraviolet exposure and risk of basal cell carcinoma, although the magnitude of risk conferred was small, with odds ratios in the region of 1.0 to 1.5. Other studies failed to find a significant association between estimated cumulative sun exposure in adulthood and the presence of basal cell carcinoma.

Skin type 1 (always burns, never tans), red or blonde hair and blue or green eyes have been shown to be risk factors for the development of basal cell carcinoma with an estimated odds ratio of 1.6. Development of basal cell carcinoma was reported to be more frequent after freckling in childhood and also after frequent or severe sunburn in childhood. This was in contrast to a story of sunburn as an adult, which does not seem to be associated with the development of basal cell carcinoma. Recreational sun exposure in childhood was identified as an important risk factor.

A positive family history of skin cancer seemed to be a predictor of development of basal cell carcinoma with an odds ratio estimated at 2.2. Several genetic conditions associated with the risk of developing basal cell carcinoma were albinism, xeroderma pigmentosa, and Bazex's syndrome. Gorlin's syndrome (the naevoid basal cell carcinoma syndrome) is a rare autosomal dominant condition in which patients develop multiple basal cell carcinomas and have other abnormalities including spine and rib anomalies, cataracts, and pitting of the palms and soles of the feet. Patients on immunosuppressive treatment also had an increased risk of basal cell carcinoma. The risk of developing a squamous cell carcinoma was increased slightly after a basal cell carcinoma, with a 6% risk at three years.

(Telfer et al, 1999)(312)

The British Association of Dermatologists guidelines stated that the most significant aetiological factor was chronic exposure to ultraviolet light, and consequently the head and neck were the most frequently affected sites. It mainly affects Caucasians, and increasing age, male sex, and a tendency to freckles were also identified as known risk factors.

Squamous cell carcinoma

Secondary studies

(Hawrot et al, 2003)(322)

This authoritative review described several risk factors. Patients with psoriasis treated with psoralens and ultraviolet A light (PUVA) were show to have an increased risk of squamous cell carcinoma that was associated with the number of treatments and the intensity of therapy. Long term follow-up studies of patients who underwent treatment with high doses of PUVA showed a relative risk of four to six compared with individuals not exposed to such treatments. PUVA effects appeared to be dose related and although lesions may occur as early as five years after therapy, the strongest correlation was seen in the second decade after therapy completion.

The incidence rate of cutaneous squamous cell carcinomas was increased in organ transplant recipients. Patients with transplants were at a three to four fold increased risk of systemic and cutaneous. An increased incidence rate of squamous cell carcinomas after transplantation was associated with time after transplantation, decreasing latitude and older age as well as childhood, duration of immunosuppression, intensity of immunosuppression, and history of skin cancer before

transplantation.

In some studies the relative risk of squamous cell carcinomas was found to be approximately three times higher in people born in geographic areas receiving high amounts of ultraviolet radiation than in residents who moved to such areas only in adulthood; two to five times higher in those with very light skin colour, hazel or blue eyes and blonde or red hair; five times higher in individuals with exclusively outdoor occupations and three to eight times higher in people with severe versus no solar elastosis, freckling and facial telangiectasias. Although fair skinned caucasians, especially men in their 60s and 70s are at highest risk for cutaneous squamous cell carcinomas, other racial and ethnic types with intermediate skin types may be susceptible given predisposing environmental conditions.

Human papilloma virus (HPV) types 5, 16 and 18 were positively associated with squamous cell carcinomas. HPV types 16 and 18 were shown to produce cell line immortalization and tumour development in situ. The authors also considered that arsenic induces tumour formation. Therefore, metal ore workers and those with substantial exposure to insecticide were at risk. The carcinogenic effects of arsenic seemed to be dose dependent and may indicate internal malignant disease, especially if the skin tumour was in a non-exposed area.

Organ transplant recipients were at significantly increased risk for cutaneous squamous cell carcinomas and other cutaneous lesions. Persons infected with HIV showed a slightly higher incidence rate of cutaneous squamous cell carcinomas at relatively earlier ages than nonimmunosuppressed individuals although this finding was not confirmed. Individuals with chronically injured or inflamed skin with longstanding ulcers, sinus tracts, osteomyelitis, radiation dermatitis or burn scars were also at increased risk.

(Motley et al, 2002)(311)

Squamous cell carcinoma was usually related to chronic ultraviolet light exposure and was therefore especially common in sun damaged fair skinned individuals, in albinos and in those with xeroderma pigmentosum. It may develop de novo, as a result of previous exposure to ionising radiation or arsenic, within chronic wounds, scars, burns, ulcers or sinus tracts and from pre-existing lesions such as Bowen's disease (intraepidermal squamous cell carcinoma). Individuals with impaired immune function, for example those receiving immunosuppressive drugs following allogeneic organ transplantation or those with lymphoma or leukaemia, showed increased risk of this tumour; some squamous cell carcinomas are associated with human papillomavirus infection. There was good evidence linking squamous cell carcinomas with chronic actinic damage and to support the use of sun avoidance, protective clothing and effective sunblocks in the prevention of actinic keratoses and squamous cell carcinomas; this was particularly important for patients receiving long-term immunosuppressive medication.

16.1 Investigations

16.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

16.2 Evidence Question:

In people attending primary care services with dermatological symptoms, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

16.3 Evidence Statements:

Biopsy with histological examination is the standard investigation in people presenting with skins

lesions that may be cancer. (III)

In comparison with specialists, a greater proportion of lesions excised by general practitioners are incompletely excised, and general practitioners are less able to predict malignancy. (III)

The investigation considered in this paper was excision biopsy, a procedure often undertaken in primary care.

Guidelines

(Department of Health, 2000)(2)

The Department of Health guidelines stated: '*It is not recommended that patients with suspected melanoma are biopsied in a general practice setting. Patients should be referred with the lesion intact to the local specialist.*'

(SIGN, 2003)(308)

The SIGN guideline included the following recommendations:
GPs should refer urgently all patients in whom melanoma is a strong possibility rather than carry out a biopsy in primary care. (recommended best practice).

The local availability of fast-track services for patients in whom melanoma is suspected should be advertised widely to general practitioners. (recommended best practice).

A suspected melanoma should be excised with a 2mm margin and a cuff of fat. (D)
If complete excision cannot be performed as a primary procedure a full thickness incisional or punch biopsy of the most suspicious area is advised. (D)
A superficial shave biopsy is inappropriate for suspicious pigmented lesions. (C)

Primary studies

Nine articles were identified that reported studies of aspects of excision biopsy by general practitioners. Many of these were prompted by the general practitioner contract introduced in 1990, which included financial incentives for general practitioners to undertake minor surgical procedures. The 'gold standard' in all the studies was histological diagnosis.

(Bricknell, 1993)(323)

This study reviewed histopathology reports at one UK hospital with an aim of to examine the difference between skin biopsies of pigmented skin lesions taken by general practitioners and those taken by hospital specialists. It included 1205 biopsies involving 1000 patients, 15 of those patients had melanomas. General practitioners had undertaken 55% of the biopsies on the 1000 identified patients.

Features recorded on pathology forms included size increase (general practitioner 15.0%, specialists 25.1%), bleeding 13.6% vs. 6.6%, colour change 4.8% vs. 11.7% (all $P<0.001$). Hospital specialists excised significantly more lesions that had increased in size ($P < 0.001$) or changed in colour ($P < 0.001$). General practitioners excised more lesions that had bled ($P < 0.001$). Hospital specialists excised more of the 15 melanomas diagnosed (80%) ($P < 0.05$), and general practitioners excised more squamous papillomas ($P < 0.01$).

Of the melanomas excised, 40% were not suspected by the clinician. Although the study found that general practitioners were able to detect the majority of suspicious lesions, it concluded that all specimen's should be submitted for histopathological diagnosis due to the uncertainty of clinical diagnosis. Additionally the paper commented that in order for general practitioners to carry out this minor operation, training is required in technical and diagnostic aspects of skin biopsy.

(Cox 1992)(324)

In this study, the findings of skin biopsies by general practitioners and examined at one UK hospital were reported. Of the total of 1017 biopsies, 56 (5.5%) were for malignant lesions. Of 21 basal cell carcinomas, nine had been considered by the general practitioner to be malignant. Six of the 21 had been inadequately excised. None of the four melanomas had been suspected, although they had been adequately excised. Additionally 21 squamous cell carcinomas were excised. Excision was adequate in eight, and the diagnosis had been suspected in only one.

(Khorshid, 1998)(325)

This study involved a survey of 819 pathology reports and interviews of 55 UK general practitioners who had submitted samples for analysis. 819 melanoma biopsies were identified, of which 59 were excised by the general practitioner. Various specialists excised the remaining melanomas. 15% of general practitioner excisions compared to 36% of non-general practitioner excisions were complete and adequate (P<0.001). General practitioners made an accurate clinical diagnosis in only 17% of cases.

(Herd, 1992)(326)

This UK retrospective case-control study included 42 biopsies performed by general practitioners which were found to be melanoma, compared to 84 randomly selected biopsies carried out in hospitals. The Breslow thickness of lesions was not significantly different. Ten of the general practitioner excisions were incomplete compared with only three incomplete in the hospital sample (P<0.001).

Only six (15%) of the 40 general practitioner request forms mentioned the possibility of melanoma. Six had been excised for cosmetic reasons alone. The other reasons were change in size (N=25), and patient worry about malignancy (N=16).

(Hillan, 1991)(327)

This study reviewed 149 specimens referred by UK general practitioners to one hospital laboratory. The specimens included one melanoma, and two basal cell carcinomas. No squamous cell carcinomas were identified. 10% of the general practitioner specimens and 11% of a comparison group of specimens referred from the hospital were inadequately excised.

(Lowy, 1997)(328)

This study reviewed pathology specimens before and after the introduction of a policy of referring all removed tissue in the UK in order to examine whether histological examination of all tissue removed by general practitioners in minor surgery increases the rate of detection of clinically important skin lesions. A random sample of specimens sent by 257 general practices referring to 19 pathology laboratories was undertaken.

During the intervention period 5723 specimens were sent, compared with 4430 during the control period. The referral rate increased by an estimated 1.34 specimens per 1000 patient years (95% confidence interval 0.93 to 1.76, P < 0.0001). During the control period general practitioners sent 204 specimens (188 non-melanoma and 16 melanoma), compared with 188 specimens sent during the intervention period (173 non-melanomas and 15 melanomas).

This multi-centre study that showed no increase in detection of malignancy through a policy of referring all general practitioner skin excisions for histological examination.

(McWilliam, 1991)(329)

This study reported a retrospective analysis of histology records at one UK hospital, and included 292 skin biopsy specimens by general practitioners and 324 by general and plastic surgeons. General practitioner cases included six (2%) basal cell carcinomas, five (1%) squamous cell carcinomas, and one (0.3%) melanoma. 36% of all general practitioner's samples compared with 16% of surgeons' samples were incompletely excised. Agreement between clinical and pathological diagnosis in malignant cases was 29% for general practitioners and 90% for surgeons.

(O'Cathain, 1992)(330)

This study reported a UK prospective comparison of patients undergoing minor surgery in general practice and at one hospital. A total of 161 patients were compared, 67 of those in general practice and 94 in hospital. 9.8% of general practitioner cases and 1.2% of hospital cases were malignancies diagnosed as benign. 4.9% of general practitioner cases compared to 0% of hospital cases had not been adequately excised.

(Williams, 1991)(331)

This retrospective review of pathology records in one UK hospital evaluated 571 skin biopsy specimens from general practitioners. 26 (4.6%) biopsies were malignant (14 basal cell carcinomas, eight squamous cell carcinomas, four melanomas). The study did not assess completeness of excision

The articles generally indicated that a greater proportion of skin lesions performed by general practitioners had been inadequately excised in comparison with specialists, and that general practitioners were less able than specialists to predict malignancy among the lesions they excise. A small proportion of lesions excised by general practitioners turned out to be malignant (basal cell carcinomas, squamous cell carcinomas and melanomas). Mandatory referral of excised specimens for pathological examination has been recommended in joint guidelines of the Royal Colleges of General Practitioners and the General Medical Services Committee with the support of the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh, and the Joint Committee of Postgraduate Training for General Practice and other organisations,(332) but the value of this policy was been questioned by Lowy et al (1997).(328) The guidelines stated:
'Occasionally malignant lesions will be encountered which were not diagnosed clinically. All lesions removed by minor surgery should be sent for histological examination. There should be a written procedure in the practice which ensures that the pathology report is seen either by the general practitioner operator, or by the patient's own general practitioner if different, and that any necessary action is initialled in writing.'

The joint guidelines also promoted training for general practitioners, audit of minor surgery, adequate staffing, premises, equipment, sterilization, and attention to the hepatitis status of the general practitioner and staff. General practitioners who complied with these guidelines would be eligible for inclusion in the minor surgery list.

16.3 Delay and Diagnostic Difficulties

16.3.1 Key Clinical Questions:

In people attending primary care services with skin cancer symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a patient who presents with dermatological symptoms/signs may or may not need urgent referral with suspected cancer?

16.3.2 Evidence Questions:

In people attending primary care services with skin cancer symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a patient who presents with dermatological symptoms/signs may or may not need urgent referral with suspected cancer?

16.3.3 Evidence Statements:

Delay in the detection of melanoma may be associated with patients' lack of awareness of the significance of signs of the condition (III).

Other factors may also influence patient delay in melanoma, including the site of the lesion, educational level, and anxiety. (III)

In countries that do not have primary care gatekeeping, delay is less when specialists make the diagnosis. (III)

Misdiagnosis on inspection of skin lesions by clinicians can lead to delay in diagnosis in some patients. (III)

Delay

Introduction

A summary of the available evidence on diagnostic delays for skin cancers is presented below. Although a large number of studies explored delays in diagnosis of melanomas, no relevant studies were identified that addressed diagnostic delays for both basal cell carcinomas and squamous cell carcinomas.

Therefore, all of the studies included in this review were surveys of patients with cutaneous melanoma. Most explored not only the relationship between patient/doctor characteristics and delays in diagnosis, but also the relationship of these characteristics and tumour thickness. It is of note that in the case of cutaneous melanomas, longer delays in diagnosis did not necessarily mean a worse prognosis. The relationship between diagnostic delay and tumour thickness was far from linear, probably indicating that melanoma thickness was not only a product of the delay in diagnosis but also of the biological aggressiveness of the tumour.

Approximately 70% of cutaneous melanomas were detected by the patients themselves. Longer medical delays and greater tumour thickness at diagnosis appeared to occur more frequently in men, the elderly, poorly educated individuals, residents of rural areas, and people with little knowledge about melanocytic tumours. Common reasons given by patients for failing to seek medical advice were absence of systemic signs, absence of awareness of the urgency, fear and anxiety.

Malignant melanoma was misdiagnosed in approximately one in every six affected patients. Dermatologists appeared to have shorter diagnostic delays than general practitioners. Tumour thickness tended to be lower in melanomas diagnosed by dermatologists, and also in melanomas diagnosed coincidentally by any physician. The fact that most of the studies described took place in non-UK health care systems, where access to specialists was not dependent upon a previous referral by the patient's general practitioner, limited the extrapolation of these findings to the NHS.

Melanoma

Secondary studies

(Silfen et al, 2002)(333)

In this authoritative review, the authors investigated the role of the physician and the patients in diagnostic delay of melanoma.

- Physicians

  Tumour characteristics had an important effect, a shorter medical delay occurring for nodular and lentigo melanoma than for acrolentiginous melanoma. Longer diagnostic delays were also associated with tumours deriving from nevi compared with de novo melanomas.
- Patients
  In one case-control study, monthly skin self-examination was associated with a 63% reduction in mortality from melanoma.

Primary studies

(Betti et al, 2003)(334)

The aim of the study was to investigate factors related to early detection of melanoma and factors associated with delay. Consecutive patients referred to an Italian hospital with cutaneous melanoma between September 1994 and December 2000 were interviewed by a trained dermatologist. The questionnaire included demographic, tumour and behavioural data. All patients had histologically confirmed melanoma. Patients who were not able to respond accurately to the questionnaire were not included in the study. 216 out of the 270 patients approached were enrolled in the study. Mean patient delay was 6.11 months (range ± 9.75 months), and mean medical delay was 1.53 months (range ± 5.34 months). There were no differences among causes of patient delay and mean age, anatomic site of lesions, level of education, knowledge of the problem, civil status or pigmentation. 51% of the patients delayed the consultation of a physician because of anxiety, fear, or lack of no time or being too busy. They tended to have a longer patient delay and a higher Breslow thickness (0.99 ± 1.41) ($P < 0.001$).

22 cases (10.19%) were observed in which the practitioner or the specialist delayed diagnosis or treatment. No correlation between physician delay and anatomic location of the lesion was observed. Pigmentation of the lesion significantly delayed the time of diagnosis by the physician (4 ± 9 months vs. 1.34 ± 5 months for the pigmented melanomas) ($P < 0.04$).

(Brochez et al, 2001)(335)

The aim of this study was to describe the diagnostic pathway for cutaneous melanoma in a Belgian community, to quantify both patient and physician delay and to define factors related to it. Patients were recruited both from a university hospital setting and from practices (population based melanoma register). All patients with a diagnosis of cutaneous melanoma between January 1995 and December 1999 were included, and asked to complete in a questionnaire about delay in diagnosis.

131 questionnaires were completed. The time from the first noticing a new or changing lesion to consultation with a physician (patient delay) was a mean of 169 days (median, 61 days). Worried patients tended to have a longer patient delay, although the difference did not reach statistical significance. There was no difference in patient delay for lesions difficult to self-examine compared with lesions more easily self-examined such as head and neck, chest, abdomen, arms, extensor side of the legs. Colour change and itch were associated with longer patient delay (median 64 days vs. 24 days if no colour change, $P < 0.05$; and 137.5 days vs. 29 days if no itch, $P < 0.01$). Patient delay was not influenced by age, gender or socio-economic factors.

General practitioners and dermatologists were the physicians most frequently involved in the first medical encounter about a lesion (55 and 33% of all cases, respectively). Of the physicians

who first observed the lesion, 34 of the 43 dermatologists suspected the lesion immediately, compared with 38 of 72 general practitioners (x^2 = 7.95, P = 0.005). There were significant differences in the time to excision if the physician took immediate action, referred the patient or took no immediate action.

(Oliveria et al, 1999)(336)

The purpose of this large population-based case control study was to examine the relationship between patients' knowledge and awareness of the signs and symptoms of melanoma and delay in seeking medical attention for suspicious lesions. The study included 650 Caucasian residents of Connecticut 18 years of age or older with cutaneous melanoma newly diagnosed between 1987 to 1989, who were part of a population-based control study. Patients who had their melanoma identified by a physician during a visit for an unrelated condition were excluded (N= 395). Cases were identified from pathology reports and hospital tumour registry logs (N= 255, participation rate = 75%). Personal interviews were conducted to obtain information on patient's knowledge of melanoma signs and symptoms, skin awareness, and delay in seeking medical attention.

The mean delay time for patients seeking medical attention was two months with a range from 0.5 to 22 months. Overall, the results revealed an inverse relationship between both knowledge and awareness and delay in seeking medical attention for melanoma. The odds ratios for knowledge of melanoma characteristics and delay ranged from 0.42 to 0.81 after controlling for age, gender, prior history of cancer, and skin self-examination. Patients who were aware of skin changes and or abnormalities had a reduced likelihood of delay in melanoma diagnosis after adjusting for age, gender, prior history of cancer, and skin self-examination practices (OR = 0.30, 95% CI = 0.12 – 0.71). The findings suggested that knowledge of two or more signs or symptoms of melanoma reduces the likelihood of a delayed diagnosis (OR = 0.34, 95% CI = 0.13-0.88).

Skin awareness was associated with a reduced thickness (OR = 0.50, 95% CI = 0.28-0.89). Increased knowledge of melanoma signs and symptoms also decreased the likelihood of being diagnosed with a thick tumour (≥ 0.75 mm). The odds ratio ranged from 0.69 to 0.95 for the knowledge variables (except for larger diameter and abnormal shape, odds ratios = 1.17 and 1.14 respectively).

(Carli et al, 2003)(337)

The aim of this study was to investigate patterns of detection and variables associated with early diagnosis of melanoma in a population at intermediate melanoma risk. The study included 816 patients with cutaneous melanoma diagnosed in 2001, in 11 Italian clinical centres.

The patients, all caucasians with newly diagnosed lesions, were included in the study at the first visit after surgery, when the diagnosis of melanoma was histologically confirmed.

Each patient received a questionnaire about first identification of the lesion, the interval before diagnosis by a dermatologist or another specialist (patient's delay), and the interval before the lesion was removed (physician's delay). Patients were also asked about their knowledge of the criteria for early diagnosis of melanoma, their skin self-examination habits, and periodic medical consultation aimed to screen for melanoma. The main outcome measure was the relationship between patterns of detection and patients' and physicians' delays with melanoma thickness.

The mean (± SD) age of patients was 53.8 (± 14.8) years for men and 49.6 (±15.7) years for women.

Patterns of melanoma detection

Most patients self-detected melanoma. Their spouse detected 12.5% of the lesions, while physicians first detected 38.7% of the lesions. The percentage of melanomas detected by a spouse differed according to sex (18.5% in male patients *vs.* 6.4% in female patients; x^2 test, P = .000).

More than half of the subjects (68.9%) waited no more than three months before obtaining a diagnosis. The main reasons for longer waiting were the feeling that it was not important (56%), fear about a possible diagnosis of cancer (10.1%), lack of time (7.3%), and the mistaken opinion that to remove a naevus is dangerous (5.6%). Fifty-two patients (21%) reported waiting more than three months because another physician, seldom the family physician, did not think it was really a lesion suggestive of being a melanoma.

Effects on mean thickness

A lower mean thickness was significantly associated with female sex, high educational level, and the habit of performing skin self-examination. Age older than 60 years was associated with a higher mean thickness, compared with age younger than 40 years. Paradoxically, a lower mean thickness was found in those patients who waited more than one month before surgery once a definite diagnosis of a lesion suggestive of a melanoma was established (adjusted mean thickness, 0.74 vs. 0.89 mm).

Association with diagnosis of thin lesions

A statistically significant association with early diagnosis was found for female sex (odds ratio [OR] for a lesion >1mm in thickness, 0.70; 95% confidence interval [CI], 0.50-0.97), higher educational level (OR, 0.44; 95% CI, 0.24-0.79), and the habit of performing skin self-examination (OR, 0.65; 95% CI, 0.45-0.93). The association with age was of borderline statistical significance.

(Montella et al, 2002)(338)

The study's aims were to test the relationship between tumour thickness and social and clinical variables (including diagnosis/treatment delay), and the relationship between delay and clinical variables. The authors undertook a retrospective study of 530 consecutive patients who underwent surgery for histologically confirmed melanoma between January 1996 and December 2000 at a single Italian hospital. Patients with an unknown primary site and metastatic tumour were excluded.

Data obtained at interview included: age, education, occupational status, diagnosis mode (symptomatic, asymptomatic, or incidental), visibility of tumour, and first symptom. Medical records were also inspected to extract information on some patient characteristics.

The most frequently reported symptoms were a lesion with increasing size (50.8%), bleeding (17.8%), colour change (15.2%), and itching (12.0%).

Breslow thickness

A larger proportion of females (72.1%) compared with males (64.4%) had a Breslow tumour thickness < 1.5 mm (OR = 1.8, 95% CI = 1.2-2.8, P = 0.005). A significant risk of having a Breslow tumour thickness ≥ 1.5 mm was noted in patients who had a low level of education (OR 3.0, 95% CI 1.9-5.0, p =0.0001) or who were unemployed (OR = 1.7, 95% CI = 1.1-2.8, P = 0.001). A significant risk of Breslow tumour thickness ≥ 1.5 mm was reported for patients who were examined by a physician other than a dermatologist (OR =1.8, 95% CI = 1.2-2.8).

Patient delay

A greater than three month delay was observed for anatomic locations visible to patients (OR = 1.7, 95% CI = 1.1-2.6, P = 0.02). Anatomic site of the primary lesion was also related to patient delay: patients who had the primary lesion on an extremity were more likely to delay > three months (OR = 1.6, 95% CI = 1.1-2.5, P = 0.02), especially females (OR = 2.2, 95% CI = 1.3-3.7, no P value given).

Medical delay

A significant association was observed between medical delay and the physician who made the diagnosis: a delay > three months carried a higher risk (OR = 2.0, 95% CI = 1.2-3.4, P = 0.01) in patients examined by a dermatologist. A medical delay of one to three months for patients with a primary lesion on an extremity was associated with an increased risk of melanoma (OR = 1.8, 95% CI = 1.0-2.9, P = 0.03).

None of the other variables studied (gender, age at diagnosis, education, and occupational status) were significantly associated with either patient or medical delay.

(Blum et al, 1999)(339)

This study included all patients (N= 429) with histologically confirmed cutaneous melanoma who had undergone surgical treatment at a Swiss hospital between 1993 and 1996. Patients were interviewed using a standardised questionnaire, the information obtained being merged with thedata on tumour characteristics and case history contained in the medical records. Delay in melanoma diagnosis was defined as the time period between a patient's first observation of a suspicious skin lesion and definite tumour treatment.

429 patients were interviewed (184 men, 245 women), median age 52 years. The melanoma was detected in 67% of women and 45% of men by the patients themselves (inter-gender comparison: P < 0.0001). The tumour was detected in about 50% of the remaining patients by a physician. Earlier diagnosis and treatment of melanoma were not significantly related to prognostic tumour parameters such as Breslow thickness or Clark's level of invasion. Women were significantly more aware than men of the possible benefit of early treatment (P= 0.004). However, increased melanoma awareness was not associated with an earlier visit to a physician. Patients who detected the lesions themselves sought medical attention later than patients in whom attention had been called to their skin changes by other persons (median 122 vs. 59 days), and therefore were treated significantly later (P < 0.01). A misdiagnosis by the first physician visited was reported by 18% of patients, and 60% of these physicians were dermatologists. Misdiagnosis increased the period of time between first observation and treatment (median 122 vs. 31 days, P < 0.0001) as well as between the first visit to a doctor and treatment (median 61 vs. 28 days, P < 0.0001). When more than one physician omitted the diagnosis of melanoma (in 8% of all patients), there was a significant additional delay in treatment (median 303 vs. 89 days, P < 0.001).

Multiple regression analysis revealed the following factors to be significantly related to delay in melanoma diagnosis: denial of melanoma diagnosis by the first physician visited (P < 0.001, regression coefficient = 0.192), invasive melanoma of the head and neck (P < 0.05, regression coefficient = 0.134), self detection of melanoma *vs.* detection by other persons (P < 0.05, regression coefficient = 0.129), and patient's knowledge about the induction of skin cancer by sun exposure (P < 0.05, regression coefficient = - 0.107). No correlation was found between delay in diagnosis/treatment and gender, age, Breslow tumour thickness, Clark's level of invasion and histological type of melanoma.

(Richard et al, 2000a)(340)

This paper evaluated the role of a patient in contributing to delay in diagnosis of skin cancer. Consecutive patients referred for cutaneous melanoma to 18 French dermatological departments of the public hospital system participated in the study conducted between 1995 and 1996. Inclusion criteria were: at least 12 years of age, histological confirmation of diagnosis of melanoma, and interview within 12 weeks after melanoma resection. Patients were included only when the report forms were completed, when a histological slide was available, and when two experts confirmed the diagnosis. A total of 645 were entered by the centres, but only the 590 fulfilled all these criteria and included in the analysis.

All patients were examined and interviewed by a specially trained dermatologist in each centre. The questionnaire addressed patients' characteristics such as age, sex, residence, social level, and

education level, amongst others.

42.4% of the sample were males and 57.6% females. Tumour thickness in coincidentally diagnosed melanoma was significantly lower than in self- diagnosed melanoma (median 0.93 mm vs. 1.30 mm, P < 0.001). Median tumour thickness was significantly lower when the lesion was first detected by the patient than when it was detected by the family (1.22 mm vs. 1.40 mm, P< 0.001, Kruskal-Wallis test).

Reasons for delay according to the patient Patients delayed presentation to a physician beyond two months in 48.1% of cases. The reasons given were: innocent appearance of the lesion together with the absence of systemic signs in 39.3%, absence of awareness about the urgency in 34.8%, occupational reasons in 20.4%, familial reasons in 16.9%, fear of diagnosis in 9.4%, passivity until family urged consultation in 5.5%, negligence in 4.5%, and absence of pain in 1.0%.

Comparison of the self-detected and the coincidentally diagnosed melanoma

Melanomas were more often self-detected by women than by men: 74.1% vs. 66.8%, respectively (x^2 test, P = 0.053). The patients with a self-detected melanoma had a significantly higher educational level than the patient with a coincidentally diagnosed melanoma (53.1% vs. 65.7%, x^2 test, P = 0.03). The patients with a coincidentally diagnosed melanoma lived more frequently in the countryside than the patient with a self-detected melanoma (29.6% vs. 20.3%, x^2 test, P = 0.02). Previous history of melanoma was more frequent in the patients with a coincidentally diagnosed melanoma than in the patients with a self-detected melanoma (27.9% vs. 16.5%, P < 0.001). The degree of awareness about skin, sun, and cancer was higher in patients who later detected their melanoma themselves than in those whose tumour was coincidentally detected.

Univariate analysis showed that people older than 65 years sought medical attention more quickly than people younger than 50 years (P = 0.003), but they tended to develop thicker tumours (P = 0.51). Gender did not influence significantly any component of the delays, although Breslow thickness was higher in men than women (P < 0.001). Delays did not differ in patients with high and low level of education, although those with low education level had thicker tumours (P < 0.001). There was no difference in the socioeconomic profile of the patients in regard to delays or Breslow thickness. Delays or tumour thickness were not influenced by marital status. People living in the countryside, although seeking medical attention more rapidly (P = 0.003), developed thicker tumours (P = 0.045). Awareness and information about melanoma did not have any significant impact on patient delay. Tumour thickness was significantly thinner when the patient had already heard about melanoma and was previously aware of the early signs of melanoma.

In a multivariate analysis, none of the candidate variables related to patient delay significantly predicted independently patient delay in multivariate analysis. In a stepwise multiple linear regression using all variables influencing tumour thickness, three variables were predictive of a high Breslow: ulceration, the fact that the patient said that raising was the reason for consultation, and nodular histological type.

(Richard et al, 2000b)(341)

The purpose of the study was to assess all doctor-related components in the delay before melanoma resection. Consecutive patients referred for cutaneous melanoma to 18 French dermatological departments of the public hospital system participated in the study conducted between 1995 and 1996.

Inclusion criteria were: at least 12 years of age, histological confirmation of diagnosis of melanoma, and interview within 12 weeks after melanoma resection. Patients were accepted only when the report forms were completed, when a histological slide was available, and when two experts confirmed the diagnosis. A total of 645 were entered by the centres, but only the 590 who fulfilled all these criteria were included in the analysis.

All patients were examined and interviewed by a specially trained dermatologist in each centre. The questionnaire investigated patient characteristics and habits, tumour clinical features, circumstances of melanoma detection, causes of delay in diagnosis, and doctors attitudes before removal. Physician delay was defined as the interval between the date the lesion was first examined by a physician and the date when a physician first proposed resection.

The median delay before the doctor proposed tumour resection was 0 (mean 103, range 0-5,783) days. For comparison, the median delay under patient responsibility was 912 (mean 3,829, range 0-25,261) days.

The first advice from the first doctor was considered to be appropriate in 85.8% of cases.

The delay to propose resection was much longer when the attitude of the first physician was inappropriate than when removal was proposed at the first visit (median 109 days vs. 0 days, P< 0.001). Although there was a higher tumour thickness when the attitude was inappropriate (median 1.40 vs. 1.15 mm, mean 3.15 vs. 2.00 mm), the difference was not significant (P = 0.99).

Tumour thickness was significantly lower when first seen by a dermatologist than by another physician (median 0.94 mm vs. 1.50 mm, mean 1.88 mm vs. 2.82 mm, respectively; P< 0.001). The delay to propose removal was significantly shorter when the first physician was a dermatologist than when he or she was a general practitioner or another specialist (median 0 vs. 25 days, mean 60 vs. 153 days, respectively; P < 0.001).

In self-detected tumours, doctors proposed removal significantly later for acrolentiginous melanoma, amelanotic melanomas, and melanomas of the hand and foot than for other tumours.

In a stepwise multiple linear regression, the most predictive factors influencing physician delay were histoclinical type and the ability of the first physician seen to recognise melanoma. The shorter delays were observed with lentigo melanoma and melanomas first seen by dermatologists. In a stepwise logistic regression, the factor most predictive of a long physician delay (> 30 days) remained the specialty of the first physician (other physicians vs. dermatologists; coefficient 2.27, SE 0.32, OR 9.7, 95% CI 5.16-18.2, P<0.001).

(Schmid-Wendtner et al, 2002)(342)

The aim of the study was to investigate the extent and consequence of patient and professional delay in diagnosis and treatment of cutaneous melanoma. Between 1999 and 2001, 233 patients with histologically confirmed primary cutaneous melanoma diagnosed and treated at a German university hospital, were within three months of diagnosis. The interview investigated melanoma-associated symptoms, the site and features of the cutaneous melanoma, time intervals, and reasons for delay in diagnosis.

Patients with knowledge about melanoma presented with a median tumour thickness of 0.7 mm, whereas patients without knowledge had a median tumour thickness of 2.1 mm (P < 0.0001). Knowledge about melanoma was associated with the educational status of patients. More than 90% of patients with a high or medium educational status had knowledge about melanoma, and less than 10% had no knowledge about melanoma (P < 0.001). In contrast, only 71% of patients with low educational status were knowledgeable about melanoma.

Medical attention was sought within 1 month of noticing the appearance of a new lesion or the onset of changes in a pre-existing lesion by 15.5% of patients. Longer periods of patient delay were not associated with greater tumour thickness. The majority of patients asked about the reasons for delay had initially thought that the pigmented lesion was benign or not important (63.5%). A smaller group of patients did not delay the consultation of a physician (12.0%), 9.9% of patients were afraid of the physician's diagnosis, 8.1% of patients could not detect the lesions themselves because of its anatomical site, and 6.9% mentioned that they were too busy to consult a physician. In 3% of patients the reasons for delay remained unclear.

(Cassileth et al, 1988)(343)

In this study, consecutive patients with cutaneous malignant melanoma referred to two US hospital-based melanoma clinics by community physicians between 1984 and 1986 participated in the study. Patients were white and over the age of 18.

The authors conducted interviews with all the patients (N = 275) and also the physicians (N = 437) whom they had consulted regarding their suspicious lesions before their eventual referral to a melanoma centre. Histology data were obtained for all patients.

A mean of six months elapsed (median one month) between the time that patients first noticed a new mark or a change in an existing lesion and the time that they became suspicious about it. The particular characteristics of lesions noted by patients did not influence length of time to suspicion. A mean of 2.6 additional months elapsed following suspicion until patients sought medical attention. The median delay during this period was one month. No lesion signs or characteristics were related to how quickly patients sought medical attention. The most common reason given by patients to explain this delay was that the lesion “did not represent an urgent problem”.

For the entire subject population, the mean time from the initial physician visit to the diagnosis of malignant melanoma was 3.9 months. Time from initial physician visit to diagnosis was shorter only for lesions with pigmentation (P =0.002). No other lesion characteristic was associated with length of delay from initial visit to diagnosis.

Physicians alerted primarily by the lesion’s pigmentation and/or by its diameter or border, recalled having assessed the lesion clinically as a melanoma in 74% of patients. There was a significant relationship between correct identification of melanoma and physicians’ specialty (chi square, P <0.05). Surgeons and dermatologists were more likely than other physicians to have identified the lesion correctly. The relationship between self-rated knowledge and correct identification of melanoma did not achieve statistical significance.

Physicians’ actions in response to this initial evaluation were associated with type of specialty practice (chi square, P < 0.001). Internists were most likely to make an immediate referral to a melanoma clinic, and surgeons were least likely to do so. Lesion characteristics were not associated with melanoma referral. Half of physicians interviewed reported that they did not examine the patient’s entire cutaneous surface. 52% of patients were seen by more than one physician prior to melanoma clinic referral. Patients who saw more than one physician were diagnosed as having melanoma a mean of 6.8 months after becoming suspicious about their lesions, compared to 4.1 months for patients who saw only one physician prior to melanoma clinic referral (Mann- Whitney U test, P= 0.006). Further, the interval from the initial physician appointment to diagnosis was greater for patients seen by more than one physician (5.8 months) than for patients seen by only one physician (1.8 months; P < 0.0001 by Mann-Whitney U test).

Of all the demographic variables analysed (sex, occupation, education, marital status, health insurance, and age), only sex was significantly associated with delay. Men waited an average of 1.9 months and women an average of 3.3 months before seeing a physician after becoming suspicious about their lesions (P < 0.005 with the Mann-Whitney U test). Neither patients’ self-rated awareness of body changes nor their scores on the preoccupation with appearance test were associated with any component of delay, with tumour thickness, or with level of invasion.

(Rampen et al, 1989)(344)

The aim of the study was to relate possible delay factors to the most important prognostic features at the time of diagnosis (the clinical stage of the disease for all patients, and the maximal tumour thickness). The study comprised consecutive patients (N = 284) with cutaneous melanoma presenting with primaries or metastases to 12 Dutch hospitals. Patients with non-invasive (Clark level 1) melanoma, patients who refused taking part in the study, and patients who were mentally

unsuitable for the enquiry were excluded (N = 16).

All patients were interviewed shortly after diagnosis using a detailed questionnaire about the patient's history, tumour characteristics, treatment particulars, and pathology.

The interval between the onset of signs and the first visit to a doctor tended to increase with age (P = 0.055). Females presented with less advanced disease than males, particularly in stage I disease (P = 0.004). Visibility of the primary lesion had no impact on the stage of the disease. The average interval between the appearance of the first signs and doctor's consultation was similar in males and females. For both sexes, the interval was considerably longer for the easily visible melanomas than for the more hidden ones (P <0.001, adjusted for sex). If patients suspected they had cancer, this tended to have a favourable impact on the stage of the disease (for the microstage P =0.079, for the clinical stage P = 0.049). There was no evidence that patients in the higher socio-economic class have a better knowledge of the malignant nature of their disease (P = 0.076). Even if patients were aware of the possible malignant character of the growth, they often displayed a delay of more than one month before they consulted a doctor (54% of cases, N = 63). The reasons given for this delay were a feeling that the situation was not pressing in 41, lack of time in 24, fear of cancer in 15, aversion of going to the doctor in ten, and miscellaneous reasons in nine patients (many patients gave more than one reason).

Patients who had waited until their symptoms became severe enough to seek medical care by themselves, had a more advanced clinical stage of the disease than those who had been persuaded by someone else to go to the doctor, or than those whose melanoma had been discovered by chance (P =0.018). Patients who presented their melanoma secondary to another reason for visiting the doctor had a more favourable clinical stage and the primary melanomas were considerably thinner (P < 0.001).

When doctors found a primary melanoma by chance, the microstage appeared to be much more favourable than when patients themselves had noticed a suspicious lesion (P < 0.001). Patients with amelanotic melanomas had more unfavourable microstages than those with melanotic primaries (P <0.006). Melanoma suspicion was highest for melanotic and lowest for amelanotic tumours (P = 0.049).

Basal and squamous cell carcinomas

No suitable studies were identified

Melanoma

One systematic review of studies comparing the diagnostic performance of general practitioners and dermatologists in diagnosing melanoma was identified, and two additional primary studies that had not been included in the review were also assessed. No studies addressed the difficulties in diagnosis of basal cell carcinomas or squamous cell carcinomas.

Diagnostic difficulties

Secondary studies

(Chen, 2001)(345)

This systematic review was undertaken in order to compare the diagnostic accuracy and biopsy or referral accuracy of dermatologists and primary care physicians. Studies that presented sufficient data to determine the sensitivity and specificity of dermatologists' or primary care physicians ability to correctly diagnose lesions suggestive of melanoma and to perform biopsies on or refer patients with such lesions. Studies published between January 1966 and October 1999 in MEDLINE, EMBASE and CancerLit databases were retrieved.

Two reviewers independently abstracted data on the sensitivity and specificity of the dermatologists and primary care physicians for diagnostic and biopsy or referral accuracy. Strict criteria for inclusion were applied to ensure results were comparable across studies. Thirty-two studies met the inclusion criteria. Ten of these were prospective, of which nine provided data for diagnostic accuracy and only one reported data for biopsy or referral accuracy. The nine prospective studies provided data from 583 dermatologists and 2314 primary care physicians for a comparison of melanoma diagnostic accuracy. Five of the nine prospective studies (plus an additional one) provided data for the biopsy or referral accuracy analysis. These studies included data on 106 dermatologists and 886 primary care physicians. Two of the studies used histopathologic analysis as the gold standard to define whether the biopsy or referral decision was correct, whereas another four used an expert panel of physicians.

The study designs differed considerably and were either prospective assessments or retrospective histopathologic reviews. Some studies permitted the physicians to give a list of differential diagnoses. Other researchers accepted only one diagnosis or only considered the first diagnosis if a list was given. For diagnostic accuracy, sensitivity for dermatologists was 0.81 to 1.00 for diagnostic accuracy (calculated from six studies) and 0.42 to 1.00 (from nine studies) for primary care physicians. None of the studies reported specificity for dermatologists. One study reported specificity for primary care physicians (0.98). For biopsy or referral accuracy, sensitivity ranged from 0.82 to 1.00 (from five studies) for dermatologists and 0.70 to 0.88 (from six studies) for primary care physicians. The range of specificity was 0.70 to 0.89 (from three studies) for dermatologists and 0.70 to 0.87 (from four studies) for primary care physicians.

Most of the studies included in the review evaluated only diagnostic accuracy and not biopsy or referral and did not report either sensitivity or specificity, and did not have an adequate sample size or describe the lesions shown to subjects.

Primary studies

(Brochez, 2001)(346)

This study was not included in the review (Chen, 2001(345)). It aimed to compare the diagnostic abilities of general practitioners and dermatologists in Belgium concerning pigmented skin lesions in general and melanoma in particular. The study design was a 'before and after' evaluation of a health education programme for general practitioners. A test set of 13 pigmented skin lesions on 35 mm colour slides as presented to 160 participating general practitioners and 60 dermatologists during a monthly educational course.

An invitation was addressed to 67 educational groups (representing 1956 general practitioners). Eight groups (160 general practitioners) accepted the invitation. The 160 general practitioners participating in the study represented 8% of all general practitioners in East-Flanders and 1% nationwide. Sixty dermatologists attending a monthly educational course were given the same test. The participating dermatologists represented about 7% of all those in the country.

The frequency of melanomas encountered was one in seven years for the general practitioners and one in eight months for dermatologists. Consultations for advice about pigmented lesions were encountered once in 30 days by general practitioners and once per day by dermatologists.

Sensitivity of general practitioners before the course in diagnosing melanoma from the slides was 72%, and 84% afterwards (dermatologists 91%). Specificity among general practitioners was 71% before and 70% after, and 95% among dermatologists. The positive predictive value (PPV) of general practitioners before was 61%, and 63% after (dermatologists 92%). The negative predictive value was 80% before and 87% after among general practitioners (dermatologists 95%).

(Girgis et al 1996)(347)

Questionnaires were sent to 141 randomly selected family physicians in one region in Australia to

investigate their beliefs and practices in relation to skin cancer prevention, early detection and management. A total of 97 (69%) responded. Compared with family physicians throughout Australia, the survey had significantly fewer family physicians aged less than 30 years, and a significantly higher proportion aged 40 to 49 years.

Ninety-one percent of family physicians (N=86) indicated that they thought skin examinations were very or extremely worthwhile in the early detection of melanoma and other skin cancers. The three issues in which they felt most confident were performing a surgical excision (72%), diagnosing a basal cell carcinoma (71%), and advising patients on signs of skin cancer (69%). A total of 65% (53) of family physicians considered that they currently detected 90 to 100% of their patients with melanoma. Family physicians indicated that the factors most likely to encourage them to offer screening were patients being more informed about its benefits (82%; N=79), patients initiating the procedure (64%; N=62), having instructions about the signs to look for (61%; N=59), having long consultation times and a reduced patient workload (59%; N=57), and having consistent information about who needs screening and how often (57%; N=55). The factors that were most likely to discourage family physicians from screening their patients included lack of time (32%; N=31), forgetting (26%; N=25), lack of financial incentive (20%; N=19), not being familiar with the patients' screening history (14%; N=14) and inability to convince patients who refuse (13%; N=13).

17 Head and Neck cancer

General recommendations

1 A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements. D

2 Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after 6 weeks, an urgent referral should be made. D

3 Primary healthcare professionals should advise all patients, including those with dentures, to have regular dental checkups. D

Specific recommendations

4 A patient who presents with unexplained red and white patches (including suspected lichen planus) of the oral mucosa that are:

- painful, or
- swollen, or
- bleeding
- an urgent referral should be made.

A non-urgent referral should be made in the absence of these features. If oral lichen planus is confirmed, the patient should be monitored for oral cancer as part of routine dental examination[14]. C

5 In patients with unexplained ulceration of the oral mucosa or mass persisting for more than 3 weeks, an urgent referral should be made. C

6 In adult patients with unexplained tooth mobility persisting for more than 3 weeks, an urgent referral to a dentist should be made. C

[14] See: National Institute for Clinical Excellence (2004) Dental recall: recall interval between routine dental examinations. *NICE Clinical Guideline* No. 19. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG019

7 In any patient with hoarseness persisting for more than 3 weeks, particularly smokers aged 50 years and older and heavy drinkers, an urgent referral for a chest X-ray should be made. Patients with positive findings should be referred urgently to a team specialising in the management of lung cancer. Patients with a negative finding should be urgently referred to a team specialising in head and neck cancer. C

8 In patients with an unexplained lump in the neck which has recently appeared or a lump which has not been diagnosed before that has changed over a period of 3 to 6 weeks, an urgent referral should be made. C

9 In patients with an unexplained persistent swelling in the parotid or submandibular gland, an urgent referral should be made. D

10 In patients with unexplained persistent sore or painful throat, an urgent referral should be made. D

11 In patients with unilateral unexplained pain in the head and neck area for more than 4 weeks, associated with otalgia (ear ache) but with normal otoscopy, an urgent referral should be made. D

Investigations

12 With the exception of persistent hoarseness (see recommendation 1.11.7), investigations for head and neck cancer in primary care are not recommended as they can delay referral. D

Thyroid cancers

13 In patients presenting with symptoms of tracheal compression including stridor due to thyroid swelling, immediate referral should be made. D

14 In patients presenting with a thyroid swelling associated with any of the following, an urgent referral should be made:

- a solitary nodule increasing in size
- a history of neck irradiation
- a family history of an endocrine tumour
- unexplained hoarseness or voice changes
- cervical lymphadenopathy
- very young (pre-pubertal) patients
- patients aged 65 years and older. D

15 In patients with a thyroid swelling without stridor or any of the features indicated in recommendation 1.11.14, the primary healthcare professional should request thyroid function tests. Patients with hyper- or hypothyroidism and an associated goitre are very unlikely to have thyroid cancer and could be referred, non-urgently, to an endocrinologist. Those with goitre and normal thyroid function tests who do not have any of the features indicated in recommendation 1.11.14 should be referred nonurgently. D

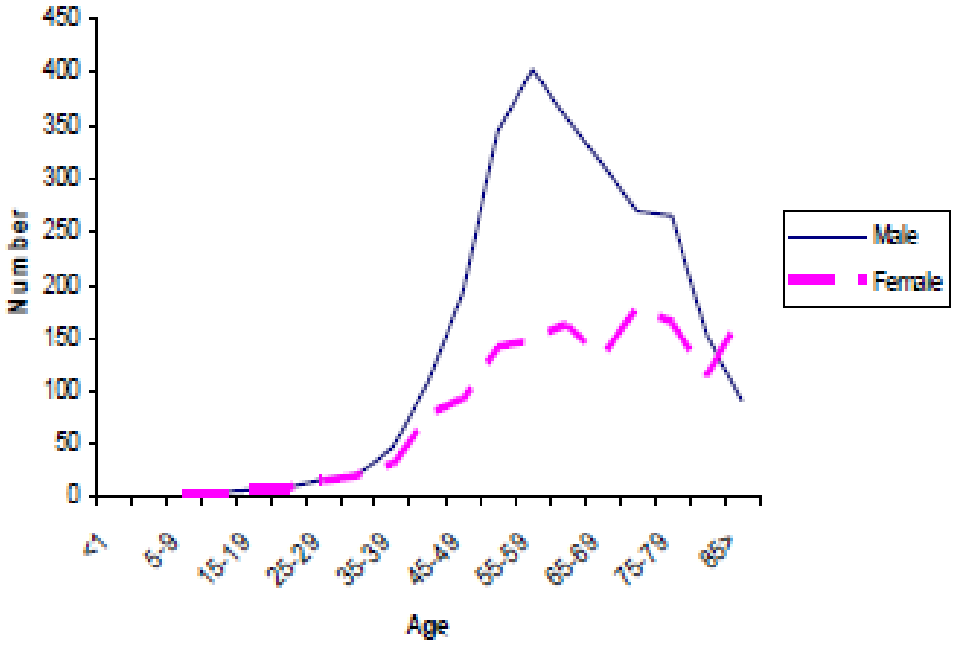
16 Initiation of other investigations by the primary healthcare professional, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and is not recommended. D

Introduction

Incidence

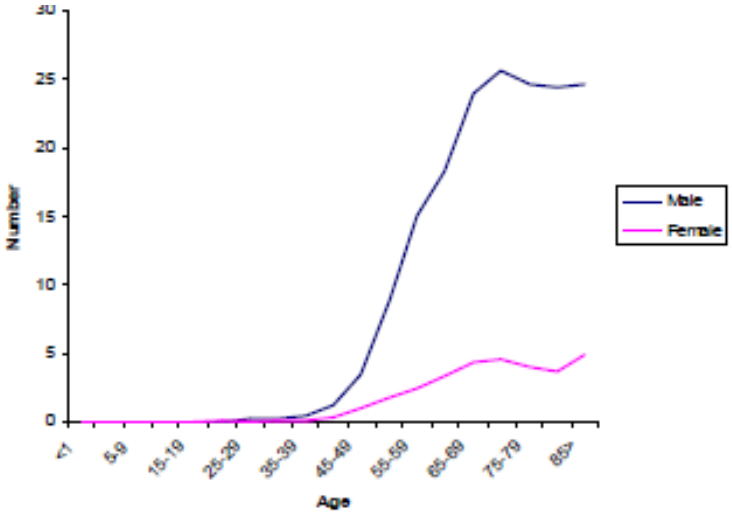
In both males and females the incidence of lip, mouth and pharyngeal cancer increases with age, although the incidence in males is almost double that in females. There were a total of 4,067 newly registered cases of lip, mouth and pharyngeal cancer in 2001. Of those 2,606 were in males and 1,461 in females.

Figure 23 2001 Registrations of lip, mouth and pharynx in England and Wales. (77)



Cancer of the larynx is more common in men and rare below the age of 45 years. There were a total of 1,477 newly registered cases of laryngeal cancer in males and 328 in females in 2001. Age distribution of incidence is shown below in Figure 24.

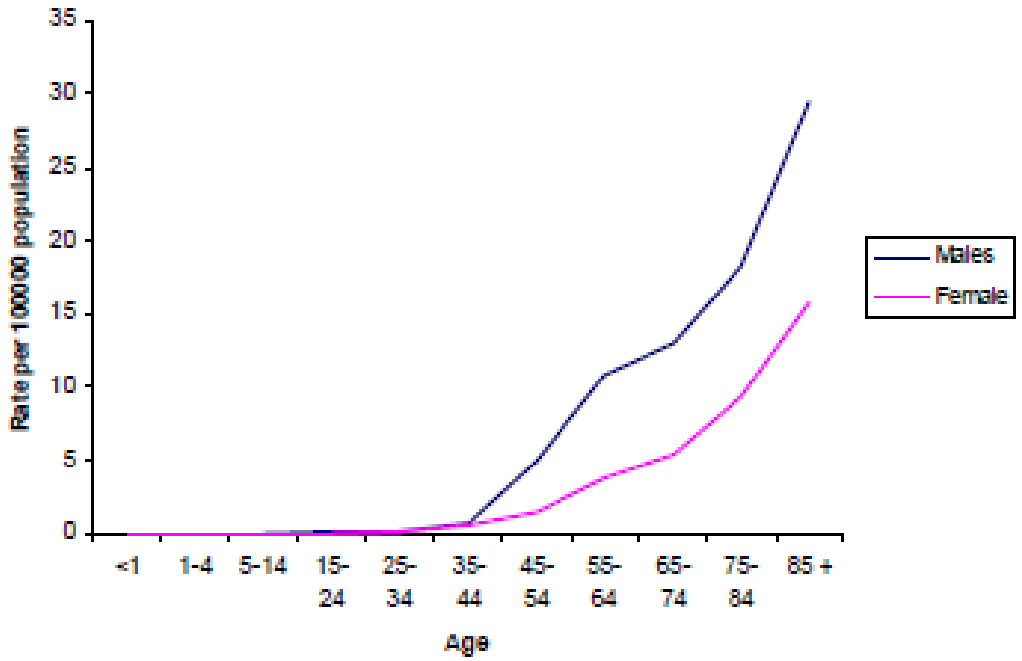
Figure 24 2001 Registrations of cancer of the larynx in England and Wales. (77)



Mortality

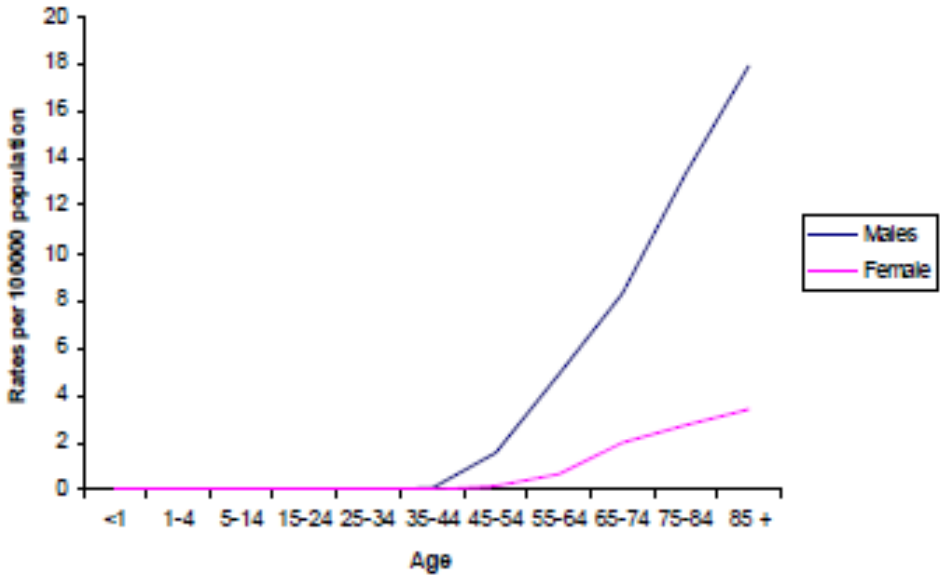
Mortality rates from lip, mouth and pharyngeal cancers increase steeply in those aged 45 years and over. There were 1,091 deaths per in males and 600 in females in 2002.

Figure 25 2002 Mortality rates from lip, mouth and pharyngeal cancer in England and Wales. (78).



Mortality from laryngeal cancer rises with age. There were 508 deaths in males and 123 in females from laryngeal cancer in 2002.

Figure 26 2002 Mortality rates of cancer of the larynx in England and Wales. (78)



Thyroid cancers

In 2001, 316 males and 862 females were newly diagnosed with thyroid cancer in England and Wales. In 2002, 100 males and 179 females died of thyroid cancer.

Review of cancer referral audits

The review identified 30 relevant clinical audits (CRD, 2004) (for information about the review, see the methods chapter of the guideline). The proportion of two week referrals found to be in accordance with the guidelines ranged from 57% to 86% (six audits). The proportion of two week referrals found to have cancer ranged from 4% to 18% (13 audits). The proportion of two week referrals considered appropriate by the consultant ranged from 36% to 76% (six audits). The percentage of cancer patients who had been referred under the two week system ranged from 0% to 25% (four audits).

17.1 Signs and symptoms

17.1.1 Key Clinical Questions:

How common is the disease in certain population groups, such as age, sex, different ethnic groups?

Which symptoms, signs and other features raise a suspicion of cancer, and those that make cancer less likely as a diagnosis?

Does family history discriminate patients who should be referred? What is the influence of co-morbidity on suspicion and referral?

17.1.2 Evidence Question:

In people attending primary care services, which symptoms and signs and other features including family history when compared with the "gold standard" are predictive of a diagnosis of head and neck cancer; and which symptoms and signs are not?

17.1.3 Evidence Statement:

The incidence of laryngeal cancer rises with age (III)

Squamous cell carcinoma, the most frequent cancer in the head and neck, is independently associated with tobacco and excessive drinking of alcohol. (III)

3.3% of 300 consecutive patients seen in Hoarse Voice Clinic with persistent hoarseness (>/= four weeks) were found to have laryngeal cancer (III)

Secondary studies

Thyroid cancer

(British Thyroid Association / Royal College of Physicians, 2002) (348)

The remit of the guideline group was to develop evidence based guidelines of best current practice for management of thyroid cancer in adults. The guidelines were developed from the Northern Cancer Network Guidelines through a process of literature review, discussion by the multidisciplinary guideline group and external peer review. Evidence was graded Ia to IV, and recommendations graded A to C.

The guideline recommendations on diagnosis and referral are:

Symptoms or signs that warrant investigation (B)

Thyroid cancer usually presents with a lump in the neck which may be clinically solitary or multinodular (IIb, B). There are often no other symptoms or signs. The presence of associated symptoms may indicate that the tumour is more aggressive or has spread to a distant site (IIb, B).

Symptoms needing urgent referral (B)

The presence of any of the following may be indications for urgent referral (IIb, B) and such patients should preferably be seen within two weeks (C):

i thyroid lump – newly presenting or increasing in size
ii thyroid lump in a patient with a family history of thyroid cancer
iii thyroid lump in a patient with a history of previous neck irradiation (IIb, B)
iv thyroid lump in very young (usually <ten years) or very old (usually >65 years) especially men
v unexplained hoarseness or voice changes associated with a goitre
vi cervical lymphadenopathy (usually deep cervical or supraclavicular region)
vii stridor (this is a late presenting sign and patients should be seen immediately)

Physical examination (B)

The patient should have a full examination focussing on inspection and palpation of the neck, including the region of the thyroid, the deep cervical nodes and all other node groups in the neck, particularly the supraclavicular nodes. The pulse and blood pressure should be recorded.

Who to refer to? (B)

Patients should be referred to a surgeon or endocrinologist who has a specialist interest in thyroid cancer and is a member pf the MDT (IIb, B). A clinical oncologist or nuclear medicine physician may also be appropriate if a member of the MDT.

Oral cancer

(Oral Cancer Awareness Group 2000) (349)

This review was prepared by the Scottish Oral Cancer Awareness Group to provide guidance to primary health care teams. In providing advice on prevention, the guidance highlighted the risk factors of tobacco, alcohol, nutrition (a diet high in fruit and vegetables was recommended), sunlight exposure, human papilloma viruses, oncogenes, and pre-existing mucosal abnormalities including leukoplakia, erythroplakia and speckled leukoplakia. Primary health care professionals were encouraged to help patients reduce their level of risk with an emphasis on smoking cessation and sensible drinking.

The early symptoms of oral cancer were described as a (i) non-healing ulcer or sore, (ii) any lump or thickening, (iii) any white or red patch, (iv) persistent soreness. However, whilst large cancers are often painful, especially as they are likely to be ulcerated, and may have infiltrated nerves, small lesions are often painless. The presence or absence of pain or soreness is therefore not a reliable early sign. Late symptoms were described as (i) difficulty chewing or swallowing, (ii) difficulty moving the tongue or jaw, (iii) numbness of the tongue or other area of the mouth, (iv) swelling of any part of the mouth which may cause dentures to fit poorly or become uncomfortable, (v) a lump in the neck. Common presenting signs were described as (i) red patch, (ii) white and red patch, (iii) ulceration or erosion, (iv) induration, (v) fixation of the tongue to local structures, (vi) lymphadenopathy.

Primary studies

(Dolan, 1998)(102)

A US study collecting presenting symptom data from 492 patients seen at the Boston Veterans

Affairs Medical Centre form July 1998 until June 1995. The majority of the patients were males (459) and all had smoked and 74% drank alcohol. The most common symptoms associated with head and neck cancer were local pain, neck mass, voice change, dysphagia, weight loss, referred pain, bleeding, stridor and cranial nerve dysfunction. The percentages of symptom occurrence at diagnosis are contained in the table below. However the study concluded that with the exception of voice change and glottic cancer no symptom or symptom complex was found to have strong enough association to be a reliable indicator of early head and neck cancer.

Table 16 Symptoms associated with Head and Neck Cancer (Dolan, 1998)(102)

Signs and Symptoms	Present at time of diagnosis (%)
Local pain	53
Neck Mass	46
Voice change / Hoarseness	44
Dysphagia	38
Weight Loss	29
Referred pain	26
Bleeding	8
Asymptomatic	8
Stridor	6
Cranial nerve dysfunction	1

Oral Cancer

(Lo et al, 1998)(350)

A total of 263 patients (156 females and 107 males), affected by oral lichen planus were followed between 1986-1996 in Italy in order to determine how many developed cancer.

This study also investigated the clinical aspects of cases of oral squamous cell carcinoma affecting patients with oral lichen planus. Fourteen cases (5.3%) developed oral squamous cell carcinoma: ten (3.8%) in an area of pre- existing oral lichen planus, three (1.1%) in other sites, and in one case the diagnoses of oral lichen planus and squamous cell carcinoma were synchronous (0.4%). Three patients were positive for anti-HCV antibody.

Of the 263 patients with oral lichen planus, 156 (59.3%) were in females. Age ranged from 22 to 80 years, with a mean of 55.5 years; 57.2 years for women and 54.7 years for men. The follow up period ranged from two to ten years, with a mean of 5.7 years. 74 (28.13%) patients were smokers. Nine of the fourteen patients who developed squamous cell carcinoma were male (64.3%) and five were female (35.7%); at the time of squamous cell carcinoma diagnosis the patients' ages ranged from 25 years to 66 years, with a mean age at presentation of 53 years (52.7 years for males and 53.4 years for females). Three aetiological theories were possible: 1) oral lichen planus transforms into squamous cell carcinoma, thus being truly premalignant; 2) the altered surface epithelium could be more susceptible to carcinogens, viruses or chemical irritants; 3) a carcinoma could appear coincidentally in the area affected by oral lichen planus.

(Holmes, 2003)(351)

In this US case series, clinical information about 51 patients with newly diagnosed oral or oropharyngeal squamous cell carcinoma were collected through patient interview and chart audit. Thirty-six patients had squamous cancer of the oral cavity and 15 had cancer of the oropharynx. The mean age of the study population was 62.2 years (range 29 to 88 years). Seventy-six percent of patients had a smoking history, and 67% admitted to occasional or heavy use of alcohol. Three patients had a family history of squamous cancer of the mouth or throat. The average clinical size of the lesions was 2.7cm.

Detection of a lesion during an office visit for an unrelated reason or routine office visit (non-symptom-driven detection) occurred in 18 cases. Detection during these non-symptomatic driven

examinations took place in dental offices (N=15), a denturist's office (N=1), and in oral and maxillofacial surgeons' offices (N=2). Lesions detected during a non-symptom driven examination were of a statistically significant lower average clinical and pathologic stage (1.7 and 1.6 respectively) than lesions detected during a symptom directed examination (2.6 and 2.5 respectively).

Lesion (symptom-driven detection) occurred in 33 cases during appointments made by patients. Symptom driven examinations took place in dental offices (N=18), primary care offices (N=7), oral and maxillofacial surgeons' offices (N=4), and otolaryngologists' offices (N=4). Detection of a lesion during a non- symptom driven examination was associated with a significantly smaller lesion clinically (2.2; SD, 1.1 cm) than one detected during a symptom-directed examination (3.0; SD, 1.2cm).

Tonsillar Malignancy

(Beaty et al, 1998)(231)

A retrospective review was undertaken of the medical records of 453 patients who had undergone tonsillectomy at a US hospital in the preceding ten years. There was a strong statistical association between the presence of risk factors and malignancy (P<.0001). Features postulated as predictive of a diagnosis of tonsillar malignancy included a prior history of head and neck cancer P<.0001; tonsillar asymmetry P<.0001; palpable firmness or visible lesion of the tonsil P<.0001, neck mass P<.0001; unexplained weight loss P<.0001; and constitutional symptoms including fatigue, night sweats, fevers and anorexia P=.003. These risk factors were correlated with the pathologic diagnosis in the reviewed cases.

Of the 453 patients included, 25 had a tonsillar malignancy confirmed histopathologically. Patient age ranged from 18 to 72 years, with a mean age of 29.8 years. The mean age was 28.4 years for patients with benign lesions, and 54.4 years among those with malignant lesions. This difference was statistically significant (P.0001). There were 210 (49%) men and 218 (51%) women with benign disease. There were 17 (68%) male and 8 (32%) female patients with malignant lesions, (not a statistically significant difference). Of the 428 patients with benign disease, 87 (20%) identified themselves as tobacco smokers. Among the 25 patients with malignant pathology, 10 (40%) identified themselves as smokers. Tobacco smoking was significantly associated with the diagnosis of malignancy (P<0.05).

No patient without the postulated features was found to have malignancy. Of the 25 patients with malignant tonsillar pathology, 23 had two or more features, and two patients had one feature only. Tonsillar asymmetry, found in 20 of the 25 cases was the sign most frequently associated with malignancy. Of the 453 patients, 70 had at least one of the features identified during their preoperative assessment. Of this group, 25 had malignant tonsillar lesions. Of the remaining 383 patients with no features identified, none had histologically demonstrable malignancy.

The same statistical protocol was used to analyse the patient group excluding those with a prior history of cancer because this group may have included some patients with recurrent or persistent disease rather than a primary malignancy. The chi-square and Fisher's Exact tests resulted in p values of 1) history of cancer P<.0001; 2) tonsillar asymmetry P<0.001; 3) palpable firmness or visible lesion of the tonsil P<0.0001; 4) neck mass P<0.0001; 5) unexplained weight loss P= 0.0004 and 6) constitutional symptoms P=0.03. No patients with three or more features had benign tonsillar pathology. Modelling analyses that included all patients in the study indicated that advanced age, tonsillar asymmetry, history of cancer, and presence of a neck mass yielded a predictive model for malignancy with an R of 0.772. Patients' smoking or alcohol history or sex was not significantly correlated with malignancy.

Table 17 Comparison of demographic data and tobacco and alcohol use information for patients with and without tonsillar malignancy (Beaty et al, 1998(231))

	Patients without malignancy	**Patients with malignancy**	**P Values**
Mean age (*yr*)	28.4	54.4	<.001
Men	210 (49%)	17 (68%)	NS
Women	218 (51%)	8 (32%)	NS
Smokers	87 (20.3)	10 (40%)	<.05
Alcohol abuse	29 (6.8%)	11 (44%)	<.001

29 patients (6.8%) among the 428 with benign lesions were identified as alcohol abusers. Among the 25 with malignancy, 11 (44%) had a history of alcohol abuse; this difference was significant (P 0.001).

Table 18 Comparison of frequencies of clinical features between patient groups with and without pathologic diagnosis of tonsillar malignancy. (Beaty et al, 1998(231))

	Patients with malignancy (N=*25)*	**Patients without malignancy (N=*428)***	**P Values**
History of cancer	15 (60%)	9 (2.1%)	<.0001
Tonsillar asymmetry	21 (84%)	36 (8.4%)	<.0001
Tonsil firmness/lesion	13 (52%)	0 (0.0%)	<.0001
Neck mass	10 (40%)	6 (1.4%)	<.0001
Weight loss	5 (20%)	0 (0.0%)	<.0001
Constitutional symptoms	2 (8%)	0 (0.0%)	.003

Nasal Carcinoma

(DiLeo et al, 1996)(352)

Patients with primary nasal septal squamous cell carcinoma of three university affiliated hospitals were identified from tumour registries and medical records. Sixteen patients were found to have histologically confirmed squamous cell carcinoma originating from the nasal septum. The 12 male and four female patients had a mean age of 62 years (range: 45 to 88 years). The time from first symptom to presentation averaged 12 months (range: 0-48 months), and the most common initial symptom was a nasal mass. The time from the initial physician visit to the diagnosis of squamous cell carcinoma of the nasal septum averaged six months (range: 0-48 months). On physical examination, the most common findings were nasal ulcerations, masses, septal perforations and skin changes. A history of heavy smoking was reported in 15 of the 16 patients.

Laryngeal Cancer

(Hoare et al, 1993)(353)

In this case series, information was collected about the first 300 patients referred to a hoarse voice clinic in Birmingham from 11 participating general practices with a total list size of 83,200 patients. A total of 271 patients eventually attended the clinic. All patients with a hoarse voice for four weeks were referred by general practitioners who were asked to make a presumptive diagnosis of laryngeal cancer, vocal cord palsy, laryngitis or other conditions.

When seen in the clinic, 102 (34%) had normal voices and larynxes. Thirty- nine patients (14%) were admitted for direct laryngoscopy and biopsy under general anaesthetic. Ten (3.3%) were found to have laryngeal cancer of which eight were early lesions. All of those with cancer were current or past smokers. Although 40% of the study population were men, 80% of those with cancer were men.

A hoarse voice for four or more weeks was regarded in this study as a symptom requiring specialist assessment. It was feasible to offer this service without appointments to patients with persistent hoarseness. There were six cases of cancer among the 25 patients in whom general practitioners diagnosed malignancy. They did not diagnose malignancy in seven other cases of cancer or dysplasia. This gave a sensitivity and specificity for general practitioner diagnoses of 46% and 24% respectively. The mean duration of symptoms before initial general practitioner consultation was 14 weeks and the time between this consultation and attendance at the hoarse voice clinic was three weeks. This study indicated that the diagnosis of the cause of prolonged hoarseness without visualising the larynx was unreliable. Symptoms were insufficient to make an accurate diagnosis.

Risk Factors

(Llewellyn, 2001)(151)

This study reviews the literature surrounding risk factors associated with oral cancer in young people (classified as those under 45 years). Six search databases were used limited to publications in England between 1957and 2000.

Sex distribution: There is conflicting evidence, for example carcinoma of the tongue has been previously thought of as a disease predominantly affecting males, however there is now evidence that trends are altering and male dominance is not the case in younger patients. Information concerning head and neck showed no sex difference in those under 40 years of age with older patients.

Alcohol and tobacco: Tobacco has long been accepted to be a carcinogen causing initiation and promotion of cancer in the oral cavity and the data supports this. Despite the tendency for alcohol consumption to be related to tobacco smoking some study's indicated that in males, alcohol may be a more significant factor. In those under 40 years papers indicate that exposure may be of too short a duration for malignant transformation to occur in younger patients. However Betel quid chewing (with or without the inclusion of tobacco) was identified as a major risk factor for oral cancer in the older Asian populations.

Genetic and Familial factors: Some research indicated that oral cancers may arise through a series of mutations in tumour suppressor genes and that these mutations are strongly correlated with environmental factors such as smoking and alcohol consumption. Results over familial episodes of cancer as a possible risk factor were found to be inconclusive.

(Office for National Statistics, 2001)(17)

Larynx

There were just under 600 deaths in males from laryngeal cancer in England and Wales in 1999. As with incidence, mortality from laryngeal cancer is rare in the under 40s but rises steeply thereafter. The most affluent groups have the lowest rates; mortality in the most deprived groups is approximately four times that in the most affluent groups. The steeper gradient with deprivation in mortality than in incidence suggests that survival is worse in the more deprived groups.

There is a north-south divide in the incidence of laryngeal cancer. Incidence was substantially higher in the Northern and Yorkshire and North West regions with a rate around 30% above the average for England and Wales. The incidence in Anglia and Oxford, South Thames, Trent, South West and

West Midlands is below average. The regional variation in mortality is generally similar to that for incidence. Survival from cancer of the larynx in England and Wales was rated as moderately good with one-year relative survival of 83% and after five years of 64% for patients diagnosed in 1991-93. Five year relative survival decreases with increasing age at diagnosis, from 75% in the youngest age group (15-39) to just over 50% in the oldest (80-99).

Lip, mouth and pharynx

Cancers of the lip, mouth and pharynx combined have been documented as the eleventh most common malignancy in males and the sixteenth most common in females in England and Wales, with approximately 3,800 new cases diagnosed each year. The major risk factor is tobacco smoking, particularly with regard to cancers of the tongue, mouth, and pharynx. Pipe smoking is also linked to lip cancer and chewing tobacco to gum and cheek tumours. Alcohol ingestion increases risk, whilst long term exposure to sunlight has been linked with lip cancer.

Pharyngeal cancers comprised 34% of all lip, mouth and pharyngeal tumours, with mouth the second most common site (26%), followed by cancers of the tongue (22%). A further 10% occur in the salivary glands, mainly the parotid. The remainder occur in the lip (9%). In 1994, nearly 80% of male, and over 70% of female, lip, mouth and pharyngeal tumours were papillary and squamous cell neoplasms: epithethelial neoplasms accounted for 12% of cases for both males and females, and 12% were adenocarcinomas.

There were almost 2,400 new cases of lip, mouth and pharyngeal cancer diagnosed in males in England and Wales in 1997 compared with 1,900 in 1971, an increase of 24%. Over the same period the number of cases in females rose by 21% to over 1,400. Cancers of the lip, mouth and pharynx are rare in the under 40s. In both sexes the incidence rates increase with age. The incidence of this group of cancers in males was about twice that in females in all age groups. Incidence in elderly men has fallen from 100 per 100,000 to 38 (a drop of over 60%). There have, however, been increases in rates in the 55-64 age group of over 40% in men and 25% in women. The incidence of lip, mouth and pharyngeal cancer in males shows regional variation with above average rates in the north of England and in Wales. The tongue, salivary glands, oral cavity, oropharynx and nasopharynx together constituted nearly 90% of all lip, mouth and pharyngeal cancers diagnosed in 1986-90. Five year survival has been higher in women than men: tongue, 50% and 36% respectively; salivary glands 62% and 47%; oral cavity 52% and 43%; oropharynx 37% and 33%; and nasopharynx 38% and 29%.

Familial papillary thyroid carcinoma

(Musholt et al, 2000)(354)

A meta-review of the literature on familial papillary thyroid carcinoma (FPTC) was undertaken in Germany to identify the characteristics of families with frequent occurrence of papillary thyroid carcinoma (PCT) or multinodular goitre (MNG) or both. Hereditable predisposition to papillary thyroid carcinoma and other multinodular goitre (MNG) without evidence of an association with other malignancies as a distinct entity has been recognised only recently.

A database of patients with thyroid cancer was searched for potential FPTC families at the Hannover University Medical School. Clinical examinations were performed in six of 12 Hannover kindreds identified and blood samples of all family members were collected for genetic analyses. Based on the meta- review and the team's own experience, predictive criteria to identify families at risk were developed.

Primary criteria for susceptibility to FPTC were identified as 1) papillary thyroid carcinoma in two or more first-degree relatives and 2) MNG in at least three first or second-degree relatives of a papillary thyroid carcinoma patient. Secondary criteria included diagnosis in a patient younger than 33 years, multifocal or bilateral papillary thyroid carcinoma, organ exceeding tumour growth (T4), metastasis (N1, M1), and familial accumulation of adolescent- onset thyroid disease. A hereditary

predisposition to papillary thyroid carcinoma was considered if both primary criteria or one primary criterion plus three secondary criteria were present.

From 1958 to 1999 a total of about 160 kindreds with two or more relatives suffering from papillary thyroid carcinoma (with or without MNG in family members) were identified in the literature search. Patient age at the time of diagnosis of malignant thyroid disease ranged from 8 to 66 years but was often below 33 years. Approximately one-third of patients presented with organ-exceeding tumours. Bilateralism, tumour multifocality, or both were seen in about 40% to 50% of cases. There was early metastatic spread to loco-regional lymph nodes in a considerable number of patients and distant metastases in up to 5% of patients. In addition, even small multifocal tumours presented with lymph node metastases. Characteristic features of FPTC were outlined as early onset, a more aggressive biologic behaviour than that of sporadic papillary thyroid carcinomas, tumour in multiple thyroid sites, and metastasis even in micro- papillary thyroid carcinomas. A high incidence of MNG developing at a young age, and adolescent-onset thyroid disease such as hypo/hyperthyroidism, immunothyroiditis, or adenoma were identified as common features of blood relatives of FPTC patients.

(Lewin et al, 1998)(355)

The aim of this case controlled study was to investigate the association between tobacco smoking and alcohol consumption, and squamous cell carcinoma of the head and neck. A total of 605 males aged 40-79 living in two geographic regions were studied in addition to 756 controls selected by stratified random sampling from population registries. Among those who were tobacco smokers at the time of the study, the relative risk of head and neck cancer was calculated at 6.5% (95% confidence interval, 4.4-9.5%). After cessation of smoking, the risk gradually declined, and no excess risk was found after 20 years. The results suggested that tobacco smoking and alcohol intake had a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. Moderate alcohol intake (10-19 grams per day) had little or no effect among non-smokers.

For different intensities of smoking, the RRs were 6.1 (95% CI =4.0-9.5) for men smoking <15 grams per day, 6.1 (95% CI =4.0-9.3) for men smoking 15-24 grams per day, and 6.6 (95% CI = 3.4-12.7) for men smoking 25 grams per day, suggesting little or no impact of mean smoking intensity. Nevertheless, smoking cessation and the duration of smoking each had a decisive impact on risk.

The cancer subsites in the cases were: the oral cavity in 128 , the pharynx in 138 (75 oropharynx and 63 hypopharynx), the larynx (mainly glottic) in 157, and the oesophagus in 123 cases. Analysis by cancer subsite showed similar results, although the relative effect of smoking was more pronounced for cancers of the pharynx and larynx than for cancers at the other subsites. For current smokers, the RR (with 95% CI) were as follows: for cancer of the pharynx, 8.5 (4.0-18.2); larynx 7.5 (3.9-14.2); oesophagus 5.2 (2.6-10.3); and oral cavity 4.9 (2.6-9.2). For men who had smoked 45 years or longer: pharynx, RR =10.1 (4.6-22.1); larynx, relative risk =7.6 (3.9-14.7); oesophagus, RR =5.4 (2.7-11.0); and oral cavity, RR =6.3 (3.2-12.4).

There was a gradual increase in the risk of cancer of the head and neck with increasing alcohol intake. However, moderate alcohol intake (10-19 grams per day) had little or no impact on the risk of cancer in ex-smokers and in men who had never smoked.

Table 19. Smoking and Relative Risk of Head and Neck Cancer[b] in Swedish Men Ages 40-79 Yrs (Lewin et al, 1998(355))

			Relative risk (95% confidence interval) adjusted for	
Smoking	**No. of cases**	**No. of referents**	**Design[c]**	**Design[c] Alcohol[d]**

Never smoked	44	193	1.0	1.0
Ever smoked	501	448	5.0 (3.5-7.0)	4.0 (2.8-5.7)
Current smokers	385	214	8.4 (5.8-12.2)	6.5 (4.4-9.5)
Ex-smokers	116	234	2.1 (1.4-3.1)	1.9 (1.3-2.8)
Stopped smoking				
1-10 yrs ago	61	75	3.5 (2.2-5.7)	3.2 (2.0-5.2)
11-20 yrs ago	32	76	1.8 (1.1-3.1)	1.7 (1.0-2.9)
=21 yrs ago	23	83	1.1 (0.6-2.0)	0.9 (0.5-1.7)
Age at start				
<15 yrs	110	77	6.5 (4.2-10.1)	5.0 (3.2-7.9)
15-19 yrs	257	220	5.2 (3.6-7.6)	4.0 (2.7-5.9)
20-24 yrs	101	102	4.4 (2.8-6.7)	3.8 (2.4-5.9)
=25 yrs	33	49	2.8 (1.6-4.9)	2.6 (1.5-4.6)
Duration of smoking				
<30 yrs	50	156	1.3 (0.8-2.0)	1.2 (0.7-1.9)
30-44 yrs	168	148	4.9 (2.3-7.3)	3.9 (2.6-5.9)
=45 yrs	283	144	9.3 (6.3-13.8)	7.2 (4.8-10.8)
Total consumption[c]				
<125 kg tobacco	53	145	1.6 (1.0-2.5)	1.5 (1.0-2.4)
125-250 kg tobacco	181	146	5.5 (3.7-8.2)	4.3 (2.9-6.5)
> 250 kg tobacco	267	157	7.5 (5.1-11.0)	5.9 (4.0-8.8)
Intensity of smoking[e,f]				
<15 g tobacco/day	202	211	4.1 (2.8-6.0)	3.4 (2.3-5.1)
15-24 g tobacco/				
Day	230	189	5.5 (3.8-8.1)	4.4 (2.9-6.5)
=25 g tobacco/day	69	48	6.5 (4.0-10.7)	4.8 (2.9-8.1)
Deep inhalers[g]				
Yes	341	176	8.9 (6.1-13.0)	6.7 (4.5-10.0)
No	41	33	5.3 (3.0-9.3)	3.9 (2.1-7.0)

[a]Cigarettes, cigarillos, cigars, pipe.

[b]Squamous cell carcinoma of the oral cavity, oro- and hypopharynx, larynx, and esophagus.

[c]Age (40-54, 55-64, 65-79 yrs) and region (Stockholm and the South Sweden healthcare area).

[d]Four categories (<10, 10-19, 20-49, =50 g alcohol/day).

[e]One cigarette or cigarillo = 1 g, 1 cigar = 5 g.

[f]Total consumption divided by duration of smoking (g per day).

[g]Among current smokers. Data missing for 3 cases and 5 referents.

Moderate alcohol consumption was found to increase the risk only among current smokers. The joint effect of high alcohol intake (≥20 grams per day), with an RR of 4.2 and current smoking RR 6.3, was nearly multiplicative: RR =22.1. Analysis by subsite showed the strongest relative effect of alcohol for cancer of the oesophagus (RR =8.6, 95% CI =3.8-19.2) and pharynx (RR =8.5, 95% CI=4.0-18.1) at an alcohol intake of ≥50 grams per day. For the oral cavity, the corresponding effects was: RR = 2.0 (95% CI= 0.9 - 4.7).

Table 20. Duration of Smoking for Current Smokers and Ex-Smokers and Relative Risk of Head and Neck Cancer in Swedish Men. Ages 40-79 Years (Lewin et al, 1998(355))

	Relative risk (95% confidence interval No. of exposed cases/exposed referents	
Duration of smoking	**Current smokers**	**Ex-smokers**
=45 yrs	7.3 (4.8-11.0)	4.4 (2.4-8.0)
	247/113	36/31
30-44 yrs	6.13 (3.8-9.8)	2.4 (1.5-4.0)
	120/74	48/74
<30 yrs	2.4 (1.1-5.3)	1.0 (0.6-1.7)
	18/27	32/129
Unexposed (never smokers: 44 cases/193 referents.		
Relative risks are adjusted for age (40-54, 55-64, 65-79 yrs), region (Stockholm and the South Sweden		
Healthcare area), and alcohol intake (<10,10-19,20-49, =50g alcohol/day).		

Those who reduced their smoking tended to under-report their past habit. Hence, smokers could have understated the number of cigarettes they smoked per day in the past. This would result in some underestimation of the effect of the mean intensity of smoking in the current study. Under-reporting of alcohol intake was another possibility. Patients with a serious disease could be less likely to under-report their alcohol intake than healthy subjects (controls). If exposed referents were classified as unexposed, the effect of alcohol intake would be overestimated. If highly exposed referents were classified as moderately exposed, the effect of a high alcohol intake would also be overestimated, but the effect of moderate alcohol intake would be underestimated.

(Talamini et al, 1994)(356)

An early detection programme for cancer of the head and neck was conducted from January 1991 to January 1993 in north-eastern Italy, an area with high mortality rates for there cancers. A total of 627 high-risk individuals (including 491 males, median age 57 years and 136 females, median age 47 years), were referred to a research nurse by 21 general practitioners who agreed to participate in the selection of high risk individuals. Each general practitioner hosted one of two research nurses to whom all patients above 35 years of age, who reported habitual smoking and intake of more than half a litre of wine or equivalent per day (approximately 60 grams of ethanol per day) were referred.

Of the 627 patients who were interviewed by research nurses and invited to have an ENT examination, 212 (33.8%) accepted and were examined. Head and neck cancer was found in 5 (2.4%) subjects (i.e. one cancer of the oral cavity, one of the pharynx, two of the larynx and

one of the oesophagus, which was suspected because of saliva residues in the hypopharynx); precancerous lesions were detected in 15 (7.1%) additional subjects. Female had a 2.4-fold higher odds of non-compliance with the offered examination than males. Acceptance tended to be lower in younger age groups (OR of non compliance in individuals below age 45 as compared to those aged 65 or above=2.1). The presence of upper aerodigestive tract symptoms (6.2% of the overall group) exerted a significant influence on compliance with the programme, making attendance at the ENT examination 2.4-fold more frequent than in the absence of symptoms.

With respect to major risk factors for head and neck cancer, current smokers were more reluctant to attend the ENT examination (OR in current smokers vs. non smokers = 3.4, 95% CI 1.8-6.3). Drinkers and former drinkers were particularly likely to accept the invitation. It was concluded that the response of targeted patients to the invitation to undergo an ENT examination was low and the most important risk factor of smoking for head and neck cancer onset, was associated with a significantly lower compliance.

17.2 Investigations

17.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

17.2.2 Evidence Question:

In people attending primary care services with head and neck symptoms, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

17.2.3 Evidence Statement:

There is no evidence that investigations in primary care are helpful in diagnosing cancers of the head and neck (III)

The evidence about the role of investigations in the detection of head and neck cancers was largely restricted to the use of toluidine blue on oral cancer and fine needle biopsy for thyroid nodules. Four secondary studies and two primary studies were identified for inclusion, all reporting level III evidence.

Secondary studies

Thyroid cancers

(Lawrence, 2002)(357)

In this informal review (50 references) the authors state that fewer than 5% of all adults will have a palpable thyroid nodule, but this is still a large number of individuals who require evaluation. Important aspects of history taking with a patient in whom a thyroid nodule has been noted include age, gender, family history of thyroid cancer, dysphagia, and presence of symptoms of hypermetabolism. Key features of evaluation by physical examination are the size and location of the thyroid abnormality, the degree of firmness of the nodule, the presence of other nodules in the thyroid, palpable cervical lymph nodes, vocal cord paralysis, and tachycardia and/or tremor. The major categories of thyroid abnormality in such patients include cysts, adenomas, thyroiditis and cancer. Fine needle aspiration biopsy (FNAB) has proved to be the most efficient diagnostic tool.

(British Thyroid Association / Royal College of Physicians, 2002)(348)

These recent guidelines made the following recommendation about initial investigations in primary care of patients with thyroid nodules.

Appropriate investigations pending hospital appointment (B)

Thyroid function tests should be requested by the general practitioner. Euthyroid patients with a thyroid nodule may have thyroid cancer and should be referred to a member of the multidisciplinary thyroid cancer team. Patients with hyper- or hypothyroidism and a nodular goitre should be referred routinely to an endocrinologist. Initiation of other investigations by the general practitioner, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and cost in making the diagnosis of cancer (IIb, B).

Oral cancer

(Johnson, 1998)(358)

The author evaluated toludine blue staining as a screen for oral cancer by systematically reviewing the evidence from trials (from 1964 to 1997). The trials were divided into those using a single application of the stain (17 trials and a total of 2948 patients) and those using a second application of the stain or a period for resolution of transient inflammatory lesions (five trials and 924 patients). It was concluded that the sensitivity and specificity of toluidine blue as a test for early detection of oral cancer was adequate, but it must not be seen as a replacement for a detailed visual and digital examination. The use of a second test 14 days later was recommended, as was mandatory biopsy of clinically suspicious lesions/areas even if staining is negative. For clinicians in primary care settings specific training is required for correct application of the test and correct interpretation of the results.

(Epstein, 1997)(359)

In this review involving a search of Medline and Cancerlit 1990 to 1995, evidence was sought on diagnostic tools to assist in biopsy site selection and subsequent diagnosis of patients at risk for oral cancer. The identified studies indicated that there was consensus that oral examination of patients at risk for oral squamous cell carcinoma should be conducted on a regular basis. Toluidine blue has been shown to be useful as an adjunct to the clinical examination when used by experienced clinicians. Exfoliative cytology was not currently used as a routine measure for the evaluation of lesions of the oral mucosa, but further development and the application of biologic markers to cytologic specimens may increase its value. Fluorescent imaging of malignant lesions of the oral mucosa has been shown to be sensitive and specific in animal models but thus far has been reported in only one human trial. The sensitivity and specificity of these techniques when used by general practitioners have not been assessed. Further, none of the above procedures has yet been shown to be a cost-effective public health measure in screening for oral cancer.

Primary Studies

(Caplan et al, 2000)(360)

This was a one-year retrospective chart review of patient records. A table was constructed to record the use of fine-needle aspiration (FNA), cytology, radionuclide scanning and thyroid ultrasonography by 49 primary care physicians (non specialists) evaluating 81 thyroid nodules. Although only a modest number of aspirations were performed it was concluded that FNA cytology was a safe and accurate test. The study concluded that fine-needle aspiration cytology, adopted as the initial test for diagnosing thyroid nodules reduced the use of imaging studies and substantially decreased the cost of thyroid nodule management.

(Warnakulasuriya,1998)(361)

The efficacy of 1% toluidine blue (TB) in the identification of oral malignancies and potentially

malignant oral lesions was evaluated among a group of Asian patients (N=102) with undiagnosed oral lesions and conditions (N=145). The study involved patients who had all been referred to, or had attended specialist centres with unconfirmed oral mucosal lesions. The rinse protocol followed manufacturer's instructions except that the study was limited to a single rinse per person. 86 clinically detected lesions, dye retained or not, were biopsied. Microscopy diagnosis and, where relevant, degree of dysplasia were recorded independently by two experienced histopathologists blinded to the dye results. When there was disagreement, concordance was reached following consultation. All the histopathologically confirmed malignancies (N=18) demonstrated stain uptake and there were no false negatives, yielding a test sensitivity of 100% for the detection of invasive carcinoma. Eight of 39 oral epithelial dysplasias were toluidine blue-negative, giving a false negative rate of 20.5% and a sensitivity of 79.5% for oral epithelial dysplasias. In view of the small size of the study, caution in required in generalising from the findings.

17.3 Delay and Diagnostic Difficulties

17.3.1 Key Clinical Questions:

In people attending primary care services with head and neck symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with head and neck symptoms/signs relevant to the head and/or neck may or may not need urgent referral with suspected cancer?

17.3.2 Evidence Questions:

In people attending primary care services with head and neck symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with head and neck symptoms/signs may or may not need urgent referral with suspected cancer?

17.3.3 Evidence Statements:

Delay

There is no significant association between gender, or age, or socio-economic status and delay in diagnosis of oral cancers (III)

Delays in the diagnosis of tongue cancers can occur when the initial professional evaluation does not lead to a follow-up or referral for further examination (III)

Pharyngeal cancers have nine times the odds of being diagnosed at a later stage than laryngeal cancers (III)

Tumour size of oral squamous carcinomas correlates significantly with the professional delay but not with the patient delay (the smaller the tumour size the longer the delay) (III).

Physician delays in diagnosing oral and oropharyngeal sqaumous cell carcinoma are most often associated with base of tongue and tonsil primaries (III)

Patients with regular dental care are more likely to have stage I or II primary epithelial tumours of the oral cavity compared with those who do not have regular dental care (III).

Diagnostic Difficulties

Primary care physicians encounter head and neck cancers only infrequently. They have difficulty in recognising the features of oral cancer (III)

Little relevant evidence was found. The literature searches identified a large number of case reports describing unusual presentations of head and neck cancers, and of informal reviews. However, there was no systematic review and only four relevant primary studies.

Delay

Introduction

In this section the evidence identified surrounding delays in diagnosis of head and neck cancer is summarised, including the psychosocial and socio- demographic factors that influence such delays. We have examined both patient and general health care professional delays, excluding delays in treatment that occur within a secondary or tertiary care setting.

Most of the evidence is based on small observational studies. Some methodological problems in the available research have been outlined by Allison et al (1998 (362)) when conducting their review, and indeed corroborated by us when appraising the studies. In addition to the merely descriptive nature of most studies, sample sizes are usually small, information about important variables has not been collected and/or has not been controlled for in the analyses, data on diagnostic delay have been collected retrospectively, and several studies have either failed to define the diagnostic delay periods or have defined them differently.

Secondary papers

(Allison et al, 1998)(362)

This is the only review identified. It focuses mainly on factors that affect the diagnostic process, and the consequences that diagnostic delay has on the prognosis of oral cancer patients. It is an informal review that acknowledges the paucity of good quality literature that goes beyond the pure quantitative description of diagnostic delays.

In the UK, a study of 96 cases of oral cancer demonstrated that family physicians were significantly less likely to delay referral and more likely to make the correct diagnosis than dentists (Schnetler, 1992(363)). However, delayed referral was defined as beyond two days. There was no statistical difference between the proportion of dentists and physicians delaying three weeks.

In a retrospective study of 543 oral and oropharyngeal cancer patients in Israel, Gorsky (1995(364)) found that physicians were significantly more likely to refer patients with late stage disease.

Primary papers

(Holmes, 2003)(77)

This US study used patient interview and chart audit to gather information on 51 patients with newly diagnosed oral squamous cancers. Detection of a lesion during an office visit or unrelated reason occurred in 18 cases and symptom driven detection occurred in 33 cases, all of these in dental offices. Seven lesions were discovered in general medical offices all associated with symptom driven appointments.

Of the 33 patients who sought care for symptoms related to their lesion, 19 sought care from regional specialists. 14 symptomatic patients sought care from their primary care physician. Patients referred from dental offices had early stage (stage I or II) disease (79%) whereas only 28% of

patients referred from the primary care physician were at early stage.

(Hollows, 2000)(365)

A UK retrospective study aiming to investigate the delays in referral and treatment of patients with oral cancer. 100 consecutive cases of referred oral squamous cell carcinoma where studied from March 1993 to January 1998. 56% of the cases were referred by general medical practitioners and 36% general dental practitioners. Overall 95% of patients were treated within six weeks of first consultation with general practitioners being more likely to refer urgently.

Only 39% of patients presented within four weeks and 29% delayed for more than three months making patient delay the most significant. No correlation was found between patient delay and cigarette smokers or alcohol consumption. No significant difference was observed in age, sex or T-stage. Significant delay occurred when patients were referred indirectly.

(Jovanovic, 1992)(191)

This study evaluated the referral patterns (patient and doctor delay) of 50 consecutive Dutch patients referred to a specialist centre with squamous cell carcinoma of the oral cavity between June 1990 and July 1991.

Patient delay (classified as time period between point of noticing discomfort to first visit to general medial practitioner or to general dental practitioner) ranged from one week to two years with the mean being 103 days and a median of 35 days. Doctor's delay (classified as the period between first consultation and final diagnosis) ranged from one day to six months, the mean delay was 22 days and median was 11 days.

Oral cavity cancer (Delay)

(Kantola et al, 2001)(366)

The study's aim was to investigate the detection of tongue cancer in primary care and to examine the prevalence of oral symptoms among patients attending primary care. The authors identified from population databases all patients (108) in the locality who had been diagnosed as having tongue cancer. They then recorded detailed data on the first medical visit from the patients' medical files (primary health centres, private medical or dental practitioners), and finally collected data on demographic and clinical variables from the cancer centre (75 patients).

At the initial visit, patients with tongue cancer were correctly referred for further examinations in 49 (65%) cases. In 12 (16%) of cases, the patient was not referred but was scheduled for a follow-up visit, and was neither referred nor followed up in 14 (19%). When compared with the referred patients the median professional delay was somewhat longer for the unreferred but increased dramatically if no follow up was arranged (0.6 months, range=0.1-2.4; vs. 1.2, range=0.3-2; vs. 5.2, range=0.7-18.2; P<0.001). Adjusted relative hazards of death were significantly increased for those non-referred followed up patients (1.4), and the non-referred/non-followed up patients (6.3). The high-risk patients included those who sought an early professional assessment, those who made the appointment for a completely different reason and only mentioned the symptom suggestive of cancer incidentally, those that had a small ulcerative lesion, those with an inability to live alone at home, rural domicile, and blue-collar workers. There were no statistically significant differences in the ability to refer cancer patients correctly between physicians and dentists. The referred patients tended to have exophytic tumours located on the marginal edge of the tongue, which are more readily visible (P=0.02). The lesions suspected to be cancer tended to be palpated more often than the unsuspected ones (P=0.04).

(Kerdpon, 2001)(367)

The purpose of the study was to identify the factors related to patient and professional delay in

diagnosis of oral squamous cell carcinoma in southern Thailand. The authors interviewed participants (161) using a structured questionnaire. Interview questions covered demographic variables (age at diagnosis, area of residence, occupation, marital status and religion) amongst other factors. Demographic variables were confirmed with the hospital record before filling in the questionnaire.

Mean patient delay was 90.6 days, professional delay 51.2 days and total delay 141.8 days. About half of the patients who consulted a professional had a biopsy or were referred to a higher level hospital. 82.6% of patients consulted doctors, 15.5% dentists and 1.9% community health workers. Of all the variables examined (sex, age, marital status, tumour size, lymph node metastasis, TNM stage, religion, area of residence, occupation, initial sign or symptom, site of lesion, type of health care professional, treatment-seeking before professional consultation, traditional herbal medication received before professional consultation and smoking habit, alcohol drinking and betel quid chewing) only traditional herbal medication was a significant predictor for patient delay. Those who received traditional herbal medication before consulting a health care professional had a longer patient delay (HR 0.46, 95% CI 0.28-0.76). There was no significant association between any of the variables investigated and professional delay. Total delay was significantly influenced by religion and traditional herb medication. Buddhists had less total delay than Muslims (HR 0.68, 95% CI 0.49-0.95). Patients who used traditional herb medication had a longer total delay.

(Wildt et al, 1995)(368)

The purpose of the study was to assess and describe the importance of the different elements of delay in diagnosing patients with a squamous cell carcinoma and to investigate the association between delay and tumour and patient factors, and also to examine whether the delay can be used as an independent prognostic factor. The authors examined patient delay, professional delay, and total delay in 167 patients at a university hospital in Denmark.

The patient's choice of primary medical contact was a general practitioner in 45% of cases, ENT specialist (14%), dentist (35%) and others (7%). The median total delay was four months, of which 71 days were patient delay. Tumour size correlated significantly with professional delay but not with patient delay, the proportion of patients with a professional delay above the median value (45 days) increasing with decreasing tumour size. Tumour site, STAGE grouping and histological score did not correlate significantly with either patient delay or professional delay. The patient delay did not correlate significantly with any of the patient-related factors. In contrast, professional delay was significantly correlated with sex, women having a longer professional delay than men. It also correlated with age, as the oldest age groups had the longest professional delay. The professional delay was not significantly related to the type of professional advice sought, whether general practitioner, ENT specialist or dentist.

(Schnetler, 1992)(363)

A UK study was conducted to compare the diagnosis and referral patterns of medical and dental practitioners. The referral letters of all patients in three oral surgery departments in two regions, with a diagnosis of an intraoral tumour, were examined from 1986-1991. A delay was recorded if the practitioner had not referred the case within two days of the original examination.

The median age at presentation was 66 years with males at 63 years and females 70.5 years. Fifty patients (52%) were referred from their general practitioner, 39 (41%) from their dentist and seven (7%) from other hospital departments. The median duration of the tumour recorded from patients' histories was 2.5 months for general practitioners and dentists. The median size of the tumour on referral was 2cm for both general practitioners and dentists. Over 70% of the tumours occurred in the floor of the mouth and tongue, termed the 'sump' region. With tumours overlying soft tissues (tongue, floor of the mouth, cheek and lip) 78% were referred by medical practitioners, and 72% of tumours overlying hard tissues (alveolus, retromolar region and palate) were referred by dentists (Chi-squared test $P<0.001$). Lymph node enlargement (either metastatic disease or reactive hyperplasia) was identified in 28 patients on presentation at the hospital clinic (29%). The median

size of the tumour in these cases was 3cm, with 86% of these tumours occurring in the sump region. Patients were more likely to consult their medical practitioner when the lesion overlay soft tissue, and to the dentist when the tumour overlay the hard tissues of the mouth. The majority of lesions occurred in the sump region area of the oral cavity, with lymphadenopathy existing most often when the tumour has developed in these sites.

Table 21 Practitioner diagnosis referring pattern (Schnetler, 1992(363))

	Correct diagnosis	Incorrect or no diagnosis	Total
GDP referral	8	31	39
GMP referral	26	24	50
Hospital doctor	5	2	7
Total	39	57	96
GDP referral with lymphadenopathy	1	8	9
GMP referral with lymphadenopathy	13	6	19

Table 22 Practitioners' working diagnoses (Schnetler, 1992(363))

Diagnosis	GMP referral (%)	GDP referral (%)
Malignancy	26 (52)	8 (20.5)
Infection	11 (22)	12 (31)
White patch	4 (8)	4 (10)
Chronic ulcer	2 (4)	2 (5)
Sore patch	2 (4)	2 (5)
Swelling	2 (4)	4 (10)
No diagnosis	2 (4)	1 (3)
Friction	1 (2)	6 (15)

A correct diagnosis was made in 52% of medical practitioner referrals and 20.5% of dental referrals (Chi-squared test P<0.01). The patients with palpable regional lymph nodes appeared to have more extensive disease. In these cases a correct diagnosis was made in 68% of medical practitioner referrals and 11% of dental referrals, (Fisher's exact test (P<0.01). A correct diagnosis was made in those cases referred the same day in 69% of medical and 20% of dental referrals. The diagnosis was made immediately in the majority (85%) of correctly diagnosed medical practitioner referrals. In 20 of the 43 cases of delayed referral, the delay was three weeks or more. However, the median delay in dental referrals was ten days (range three days to one year) whereas medical referrals the median delay was four weeks (range one week to eight months). Patients with lymphadenopathy were delayed in 67% of dental referrals (two patients more than three weeks and 37% of GMP referrals (four patients more than three weeks). There was no statistical significance between the two groups.

Table 23 Practitioner delay referring pattern

	Delay	No delay
GDP referral	24	15
GMP referral	18	32
Hospital doctor	1	6
Total	43	53
GDP correct diagnosis	5	3
GMP correct diagnosis	4	22
GDP referral with lymphadenopathy	6	3
GMP referral with lymphadenopathy	7	12

The results indicated that a relatively young, fit population was presenting to clinics with advanced disease, with a median size tumour of 2cm, of 2.5 months duration, and with one in three cases presenting with lymph node enlargement.

(Elwood and Gallagher, 1985)(369)

The authors aimed to examine the factors associated with stage at time of diagnosis and with interval between recognition of the first symptom and histologic diagnosis of primary epithelial tumours of the oral cavity. The study was a consecutive series of patients (160) seen at a cancer centre with newly diagnosed cancer of the oral cavity. Data were obtained from the admission history and the patients' records, and from patients' interviews using a structured questionnaire. Patient variables assessed were alcohol consumption and smoking, lifetime occupational history (socio-economic classification), and dental care.

Of the 160 patients, 55% had stage I or II disease. The factor most strongly associated stage was regular dental care (70% of patients who had regular dental care had stage I or II tumours, compared with 40% of those who did not have regular dental care, P=0.0002). Socio-economic status and alcohol consumption were also related to differences in stage distribution (60% of patients with high socio-economic status and 65% of patients who drank less than nine ounces of alcohol per week had stage I or II tumours). The association of stage of disease and socio-economic status became non- significant once controlling for the effects of the other two variables. The interval between recognition of the first symptom and diagnosis was not significantly related to these factors, but it was shorter for men. There was no association between this interval and age, marital status, smoking history, diet and religion. There was a tendency for tumours on more easily visible surfaces to be diagnosed earlier. The interval between recognition of the first symptom and histologic diagnosis did not differ significantly with the site of the tumour.

(Cooke, 1977)(370)

The study was an attempt to analyse the factors underlying delay between the patient's first symptom and the institution of treatment for oral cancer. The case histories of patients attending a teaching hospital to ascertain information on factors underlying delay in diagnosis (patient and professional delay).

The most common reason given by the patient for failing to seek early advice was that the lesion did not hurt. The major presenting symptom was ulceration (60%) and only 10% of patients experienced pain. 50% of patients were referred from general medical practitioners and 30% from general dental

practitioners. There was only a degree of urgency in the referral letter or card for these patients from 56% of the general practitioners and 53% from the general dental practitioners. The delay in patients being referred to hospital for confirmation of diagnosis was mainly caused by a low degree of suspicion.

(Shira, 1976)(371)

This study included 34 patients who had been referred to a Department of Oral Surgery in Aarhus, Denmark. Information was obtained from the patients and hospital records about: sex, age, referral from physician or dentist, symptoms, referral diagnosis, time lapse from first symptoms until consultation with physician or dentist, time lapse from the first consultation with physician or dentist to referral and final diagnosis, previous treatment, localisation, bone involvement, final treatment, control period, survival period.

The tumours occurred more often in men than in women, and most often in the group aged 50 to 70 years. Twenty-four patients consulted a physician or dentist within three months after the appearance of the first three symptoms. The average period from the time that the patient first observed the symptoms until a consultation with a physician or dentist was 4.9 months. Twenty of 32 patients were referred within three months, the average period for all patients was 5.6 months.

Oral cavity / pharyngeal cancer (Delay)

(Pitiphat et al, 2002)(372)

Patients (105) attending three teaching hospital-based clinics were interviewed using a structured questionnaire. Risk factor data included demographic and socio-economic characteristics, information on tobacco use, alcohol consumption, family history of cancer, intra-oral status, and weight change. Tumour size and TNM stage at time of diagnosis were also assessed. The interval from the self-reported date when oral cancer signs and/or symptoms were first noted to the date of definite diagnosis was recorded.

The time from initial diagnosis to definitive diagnosis ranged between 0 and 780 days, with a median of 30 days. Fifty-five patients had a delay of 21 days or more (52.4%). Length of delay was significantly longer among single patients, non-smokers, or those with stage IV tumours. There was no significant association between age and diagnostic delay. The authors found no association between gender and delay in diagnosis either. Surrogate measures for socio-economic status, such as educational level and unemployment did not affect the time to diagnosis. There was no significant association between delay in diagnosis and alcohol use.

(Allison et al, 1998b)(373)

The aim of the study was to investigate the relationship between patient and professional diagnostic delays, and prognosis in a group of upper aerodigestive tract cancer patients. Patients were interviewed to collect information on socio-economic and demographic variables, the development of the cancer, symptomatology, health care professionals consulted, and the period of time taken for each stage in the diagnostic process. 77% of the sample presented initially to a family physician and 16.5% consulted a dentist.

Patients under the age 65 years had a significantly increased risk of being diagnosed with late stage disease when compared with those 65 years and older (OR=1.91, 95% CI= 1.07-3.41). Gender and education were not associated with disease stage. The risk of late stage disease appears to be increased among those who lived alone, although the significance of this was marginal (OR=1.97, 95% CI= 0.93-4.17). Comorbidity and dental status at the time of diagnosis were not associated with disease stage. Those subjects who had a mucosal lesion or voice change as their presenting symptom had a significantly reduced risk of being diagnosed with late stage disease when compared with those subjects presenting with a swelling. Subjects with a pharyngeal cancer had odds of being diagnosed with late stage disease eight times those of subjects with oral cancer. No

association was found between increased patient delay and risk of late stage disease. However, there was a pattern of increased odds for late stage disease with increased professional delay, with these odds being three times greater among those subjects delayed more than three months compared to those with less than one month's professional delay (P for trend 0.03). Those subjects who first consulted a dentist, rather than a family physician, had a reduced risk of late stage disease of borderline significance.

Stepwise multiple logistic regression demonstrated that: (i) pharyngeal cancers have nine times the odds of oral or laryngeal cancers for late stage disease; (ii) professional delay >one month has approximately twice the odds of being associated with late stage disease than professional delay <one month; (iii) older patients (>65 years) have approximately half the odds for late stage cancer of those <65 years). The type of primary health care professional first consulted no longer remained a significant predictor of disease stage in the multiple regression analysis.

(Kowalski et al, 1994)(374)

The study investigated the importance of various pre-treatment factors such as demographic and socio-economic factors and lateness of case referrals for patients (336) with newly diagnosed carcinomas of the oral cavity and oropharynx. Prior to any medical treatment patients took part in an interview with questions about socio-economic and demographic variables, history of tobacco smoking and alcohol consumption.

In the case of 59 patients (17.6%), there was no delay in referral to a head and neck service. The patient was only responsible for delay in reaching a head and neck service in 196 cases (58.3%). A doctor delayed the referral for a median of 12.3 months in 19 cases (5.7%), a dentist for 6.5 months in 11 cases (3.3%), and a pharmacist or drug store clerk for 3.5 months in 13 cases (3.9%). In 38 cases (11.3%) there was a delay of 8.5 months because patients were seen by more than one health professional. Duration of symptoms and patient and professional delays were not associated with the risk of advanced disease in unifactorial analysis. The risk of having advanced disease was moderately lower in females (RR 0.45, 95% CI=0.24-0.86), marginally lower in older patients (RR =0.54, 95% CI=0.27-1.08), and not dependent upon family income and educational levels. Alcoholism was not associated with the stage of disease at diagnosis. A significant reduction in risk for advanced stage was seen when a painful ulcer was the first symptom (RR =0.24, 95% CI=0.13-0.45). A substantial increase in risk was observed in cases with odynophagia and/or dysphagia (RR=4.52, 95% CI=1.99-10.26). Tumours on less visible surfaces or oral cavity or oropharynx tended to be advanced at time of diagnosis.

(Guggenheimer et al, 1989)(375)

The study was undertaken to identify possible explanations for patient and/or professional delays and to determine whether or not these delays were related to tumour stage at diagnosis for oral and oropharyngeal squamous cell carcinomas. Delay was related to age, gender, education, alcohol consumption, and tumour T stage at the time of diagnosis. A personal interview questionnaire was administered by three of the investigators.

Delay by doctors occurred in 30% of cases. Neither short nor long delays had a statistically significant relationship to tumour T stage at time of diagnosis. The length of patient delay was also not related to age, gender, educational level, or history of alcohol consumption. Physician delays were most often associated with base of tongue and tonsil primaries. Tongue and floor of mouth tumours accounted for the major share of dentist's misdiagnoses.

Solid head and neck malignancy (Delay)

(Jones et al, 2002)(376)

The authors undertook an audit of the management of 75 patients with suspected solid head and neck malignancy, referred by general practitioners to an ENT department in the UK. Their aim was

to compare the local services with the national targets, and to identify any problems during the diagnosis and treatment of head and neck cancer patients. Data were recorded from case-notes and hospital and general practitioner records.

Thirty-seven patients presented with hoarseness, 15 with a neck lump, 14 with pain, three with haemoptysis and two with a visible ulcerative lesion. The longest delay was due to late presentation of the patient (mean waiting time =4.9 months, range = 1-20), and late referral by the general practitioner (mean waiting time = 5.1 weeks, range = 2-12).

Diagnostic Difficulties

Primary studies

(Macpherson, 2003)(377)

In this UK study, questionnaires were sent to a random sample of 357 general practitioners and 331 dental practitioners to investigate knowledge, examination habits and preventative practices regarding oral cancer. 58% of dental practitioners reported performing regular examinations for signs of oral cancer, however general medical practitioners examined only in response to soreness.

Both the majority of general practitioners (85%) and dentists (63%) felt that they did not feel confident in examining for oral cancer. 66% of general practitioners felt that they should have a major role in the detection of oral cancer but stated that it should remain primarily the remit of the dental team.

57% of the medical respondents stated that they would consider urgent referral for a intra-oral lesion present for four to five weeks and 37% for referral after two to three weeks. 74% of general practitioners would refer to hospital and 22% to a dental hospital. Of the dentists, 54% stated that they would refer suspicious lesions after tow to three weeks. Only 56% stated they would normally refer to a dental hospital and 46% to a general hospital.

(Teppo, 2003)(140)

This study evaluates a population based sample of 66 patients with laryngeal carcinoma in Finland between 1990 and 1995 to determine the effects of patient and professional diagnostic delay. It concluded that whereas no connection could was shown between patient delay and prognosis, long professional delay was an independent and statistically significant determinant of worsened prognosis.

The median patient delay was two months. Patients presented sooner after noticing a neck lump than from other symptoms (P=0.005). In 46% of the cases patient delay was three months or longer, and delay of three months or more was common in patients with lower socio economic background (P=0.009) but not related to other characteristics.

Median professional delay was three months although 17% of patients recorded experienced a delay of 12 months or more. No link was established between professional delay and patient characteristics or between patient and professional delay.

(Horowitz, 2002)(378)

A qualitative study using one face to face focus group of ten dental hygienists and one telephone focus group of seven dental hygienists in the US in 1998. It aimed to ascertain information on dental hygienist's awareness and opinions of oral cancer, oral cancer examinations and related factors. The study reported the provisions of oral cancer examinations and barriers for not providing them.

It was concluded that the provision of routine oral cancer examinations depended heavily on the

confidence of the specific dental hygienist on their skills in conducting the examination, time constraints and internal policy in the practice which they are employed. Notably the majority of the hygienists included in this study were 'astounded' and 'shocked' at the prevalence of oral cancer. Hygienists stated that cancer screening was often not the focus of their examination and was not expected. Additionally it was commented that sometimes these examinations may not be performed as people can be uncomfortable being examined in this environment.

(Greenwood, 2001)(379)

A prospective study was undertaken in England in which a questionnaire was sent to 420 primary care clinicians (half dentists and half doctors) to assess the knowledge of both groups in examining patients with oral cancer. The response rate was 68.1% for dentists and 71.9% for general practitioners. The article reported that dentists were more likely to have diagnosed cases of oral cancer than general practitioners (OR=2.68, 95% CI 1.6, 4.4). Important differences arose between the groups in terms of risk factor knowledge and clinical examination techniques. One explanation was that general practitioners had received less training in oral pathology than dentists and therefore might be expected to have less knowledge of oral cancer and related issues.

Dentists were more likely to list alcohol as a risk factor than general practitioners (OR+6.9, 95% CI3.9, 12.1). The proportion of dentists and doctors identifying smoking as a risk factor was 93.7% and 90.7% respectively. This difference was not significant (OR =1.5, 95% CI 0.6, 3.6). Dentists were significantly less likely than general practitioners to state they would examine all sites in the mouth (OR=0.5, 95% CI 0.3, 0.8). Dentists showed a preference for examining areas relating to the tooth bearing or potential denture bearing tissues, rather than for some of the more high-risk sites, for example, the floor of the mouth. They were also more likely than general practitioners to identify various presentations of oral cancer and pre- malignant disease (OR+13.6 and 25.7 respectively).

The article did not provide details of how many cases of cancer were correctly identified by dentists and general practitioners.

(Clovis et al, 2002)(380)

In 1998, Dentists in British Columbia and Nova Scotia were surveyed about their knowledge and opinions on oral and pharyngeal cancer. Of the 670 dentists supplying usable responses (response rate 55.2%) only 56.7% agreed that their knowledge of the subject was current. Most dentists correctly identified tobacco use (99.4%) and alcohol use (90.4%) as risk factors, but fewer correctly identified factors such as the use of spicy foods (57.0%) and poor oral hygiene (46.3%) as not being risk factors, a finding that was attributed to a high level of misinformation. Only 42.5% identified both erythroplakia and leukoplakia, in that order, as the conditions most likely to be associated with oral cancer. It was stressed that early detection and screening during routine examination was the single most critical intervention influencing survival. Fewer than half knew that familial clustering of cancer and poor- fitting dentures were not real risk factors. Only a small proportion knew that a family history of cancer was not in itself a risk factor for oral cancer.

The procedure for complete examination of the tongue, the fact that early oral cancer is asymptomatic, and the appearance of early oral cancer lesions were correctly identified by large numbers of respondents. Just over half knew that most oral cancer was diagnosed at an advanced stage.

(Canto et al, 2002)(381)

A qualitative descriptive study on physicians' knowledge, opinions and practices about oral cancer examination was undertaken in Maryland. The methods used included one focus group with ten physicians, and nine one-to- one interviews. Physicians were not surprised that they detected more lesions than dentists, although most did not provide oral examination on a routine basis. Patients were more likely to see physicians than dentists because US health insurance coverage did not

include dental care. Also, physicians' opinions indicated that patients were afraid of going to a dentist and only associated them with pain in their teeth or gums. Patients also consulted the doctor about the tongue or buccal mucosa. Patients consulted physicians for other medical problems that enabled them to raise additional issues such as a sore in their mouth or throat.

There was a misconception that oral cancer was painless and asymptomatic, and that early lesions were small. Physicians needed more information about how to conduct a comprehensive oral cancer examination. Their knowledge about this examination was based on their variable medical training. It was related to whether or not physicians had completed an ENT or oncology rotation, or on their residency experience and the location where training was received.

(Kamal, 1999)(382)

A retrospective study was undertaken to highlight some of the presenting features of nasopharyngeal carcinoma as seen in a large hospital over a period of 20 years in Jordan. Tumours were detected at an advanced stage with 34% having metastasised most frequently to bone. Data collected during the period revealed that nasopharyngeal carcinoma accounted for 1% of all malignant tumours with an age range from six to 89 years, and a mean of 39.5 years. A high incidence of childhood nasopharyngeal carcinoma was also noticed (two percent of all childhood malignant tumours).

The study stressed the importance of full ENT examination in cases of persistent middle ear disease, recurrent or persistent nasal symptoms or headache, or neck swelling; and routine bone scans in all patients with nasopharyngeal carcinoma. The tumours were frequently symptomless or initially evoked symptoms that were common to other minor clinical conditions, and consequently did not attract serious patient attention. Some of these silent tumours were overlooked on clinical examination in the early stages. Seventy patients (77%) presented with a single complaint and 21 (23%) presented with multiple complaints. The most common single presenting symptom was neck swelling (45.5%).

In 37 patients (41%) carcinoma affected one site of the nasopharynx, most frequently a lateral wall. Thirty-five patients (38%) had multifocal malignant involvement of the nasopharynx. In 19 patients (21%) the nasopharynx appeared normal and no site of involvement could be seen at the time of first diagnosis.

Difficulties in early diagnosis by general practitioners included the small size of tumours, near normal appearance of nasopharyngeal mucosa or the inherent presence of massive lymphoid tissue obscuring the underlying lesions.

The findings of this study should be treated with caution since it was undertaken in Jordan where the incidence of this cancer is relatively high and the patient population was different to England and Wales. Consequently, the significance of the findings of this study to general practice in England and Wales is uncertain.

17.4 Support and Information needs

17.4.1 Key Clinical Question:

What are the support and information needs of patients who are being referred for suspected cancer? Are the needs different in different groups of patients?

17.4.2 Evidence search question:

What are the support and information needs of patients who are being referred for suspected head and neck cancer? Are the needs different in different age, sex, ethnic and cultural

groups of patients?

17.4.3 Evidence Statement:

There is no evidence about the needs of patients at referral. Extrapolation from evidence of studies of patients after diagnosis indicates that social support and access to information are important (III).

Little evidence could be identified dealing with the information and support needs of patients at referral. Studies of patients after diagnosis are included.

Secondary studies

(De Boer et al 1999)(383)

This article updates an earlier literature review that included 117 reports of studies conducted between 1966 and 1984 and that had given only limited insight into the rehabilitation process because of methodological shortcomings and the lack of a theoretical basis in most of the primary studies. This article reviewed recent literature (1985-1996) on the physical and psychosocial impact of head and neck cancer. Disturbances in psychosocial functioning and psychological distress were reported by a considerable number of patients.

Family, friends, professional caregivers, and fellow patients have all been identified as potential sources of support. Open discussion of illness in the family, social support from others, and adequate information from specialists were found in one study to be predictors of positive rehabilitation outcomes in patients with head and neck cancer. Other studies have confirmed the significant contribution of social support to positive rehabilitation outcomes, particularly when the support comes from family and close friends.

(Semple, 2002)(384)

This paper reviewed the literature on patients' needs for appropriate information, and involved searches of electronic databases including Medline and Cinahl from 1990 to 2001. Head and neck cancers are among the least common cancers in the UK but these patients have very specific and significant needs. Written information is a cost-effective intervention that complements verbal advice given by healthcare professionals. Evidence suggests that patient information leaflets are of poor quality and are in language that is difficult for the public to understand. Considerable time, effort and user involvement are required to produce acceptable and appropriate information leaflets for patients.

Primary studies

(Sherman et al, 2000)(385)

This study involved 120 patients with advanced disease who were grouped according to the following phases of illness: (1) pre-treatment, (2) on treatment, (3) <six months after treatment (4)>six months after treatment. Coping was assessed with the COPE questionnaire, and outcome measures assessed general distress (Profile of Mood States) and illness-specific distress (Impact of Events Scale). Use of specific coping responses differed among the groups. Denial ($P<.05$), behavioural disengagement $P<.05$), suppression of competing activities ($P<.01$), and emotional ventilation ($P<.10$) were most characteristic of patients who were receiving or had recently completed treatment. There were no differences in flexibility of coping or overall effort expended, but patients who were on treatment or who had recently completed treatment used the greatest number of strategies. Generally, denial, behavioural disengagement, and emotional ventilation were associated with greater distress. Results suggest that phase of illness may be important in shaping patients' responses to life-threatening illness.

(Boundouki et al, 2003)(386)

The study aim was to determine the influence of a patient information leaflet on mouth cancer to improve knowledge, reduce distress and increase intention to accept a mouth screen over a two month period. The design was a randomised controlled trial in two dental practices. Standardised multi-item scales of the three outcome measures were employed. The patient information leaflet was given to a randomised intervention group of patients in the waiting room. A single sheet questionnaire was completed by both groups of patients at baseline in waiting room (immediately following leaflet administration in intervention arm of study). Repeat questionnaires were completed at eight weeks by all patients through postal system. Mann- Whitney U-tests comparing outcome variables between patients with and without access to the leaflet at baseline and eight weeks were performed. Multiple logistic regression was used to predict re-reading of the leaflet at home. Useable replies were received from 317 patients (60% response rate). All measures showed some benefit of immediate exposure to the leaflet at follow-up. Older patients, less initial knowledge, and self-reported smoking positively predicted the re-reading of the leaflet. The introduction of a mouth cancer patient information leaflet into dental practice may help to inform patients about oral cancer, moderate distress and encourage acceptance of an oral health screen. However, the study did not address the needs of patient at the time of referral.

18 Brain and CNS cancer

General recommendations

1 A patient who presents with symptoms suggestive of brain or CNS cancer should be referred to an appropriate specialist, depending on local arrangements. D

2 If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with a local specialist should be considered. If rapid access to scanning is available, this investigation should also be considered as an alternative. D

Specific Recommendations

3 In patients with new, unexplained headaches or neurological symptoms, the primary healthcare professional should undertake a neurological examination guided by the symptoms, but including examination for papilloedema. The absence of papilloedema does not exclude the possibility of a brain tumour. D

4 In any patient with symptoms related to the CNS (including progressive neurological deficit, new onset seizures, headaches, mental changes, cranial nerve palsy, unilateral sensorineural deafness) in whom a brain tumour is suspected, an urgent referral should be made. The development of new signs related to the CNS should be considered as potential indications for referral. C

Headaches

5 In patients with headaches of recent onset accompanied by either features suggestive of raised intra-cranial pressure (for example, vomiting, drowsiness, postural related headache, headache with pulse synchronous tinnitus) or other focal or non-focal neurological symptoms (for example, blackout, change in personality or memory), an urgent referral should be made. C

6 In patients with unexplained headaches of recent onset, present for at least 1 month but not accompanied by features suggestive of raised intracranial pressure (see recommendation 1.12.5), discussion with a local specialist or referral (usually non-urgent) should be considered. D

7 In patients with a new, qualitatively different unexplained headache that becomes progressively severe, an urgent referral should be made. C

8 Re-assessment and re-examination is required if the patient does not progress according to expectations. D

Seizures

14 A detailed history should be taken from the patient and an eyewitness to the event if possible, to determine whether or not a seizure is likely to have occurred[15]. C

15 In patients presenting with a seizure, a physical examination (including cardiac, neurological, mental state) and developmental assessment, where appropriate, should be carried out. C

16 In any patient with suspected recent onset seizures, an urgent referral to a neurologist should be made. C

Other neurological features

17 In patients with rapid progression of:

a. subacute focal neurological deficit [B]

b. unexplained cognitive impairment, behavioural disturbance, or slowness or a combination of these [C]

c. personality changes confirmed by a witness (for example, a carer, friend or a family member) and for which there is no reasonable explanation even in the absence of the other symptoms and signs of a brain tumour [D]

An urgent referral to an appropriate specialist should be considered. B/C/D

Risk Factors

18 In patients previously diagnosed with any cancer an urgent referral should be made if the patient develops any of the following symptoms:

a. recent onset seizure

b. progressive neurological deficit

c. persistent headaches

d. new mental or cognitive changes

e. new neurological signs. C

Introduction

Epidemiology

The Office for National Statistics reports that brain tumours account for 1.6% of all cancers in England and Wales with an estimated 4,293 cases diagnosed in 2001. The disease is more common in males and is the 12th most common cancer in men and 15th in women(17).

Mortality trends of both males and females are similar to incidence rates as shown by and Figure 28, both incidence and mortality increasing with age(17). There were 2,908 deaths from brain cancer in 2002, 1,673 in men and 1,235 in women.

Figure 27 Newly diagnosed cases of brain and CNS cancer in 2001 in England and Wales. (77)

[15] National Institute for Clinical Excellence (2004) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. *NICE Clinical Guideline* No. 20. National Institute for Clinical Excellence. Available from: www.nice.org.uk/CG020

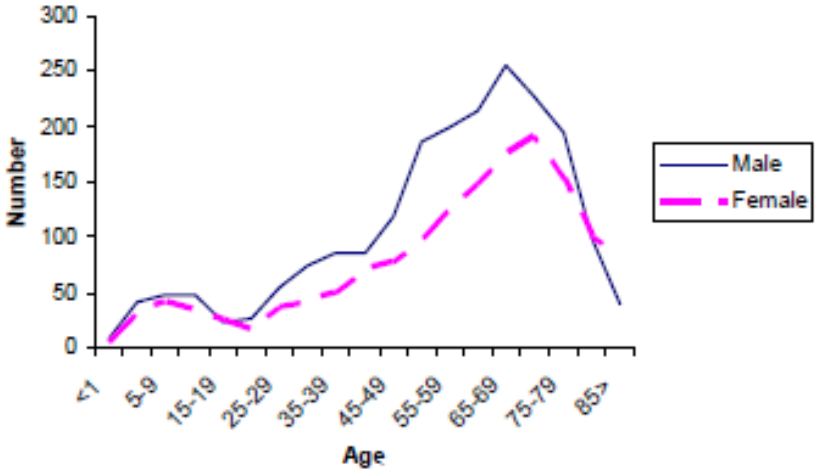
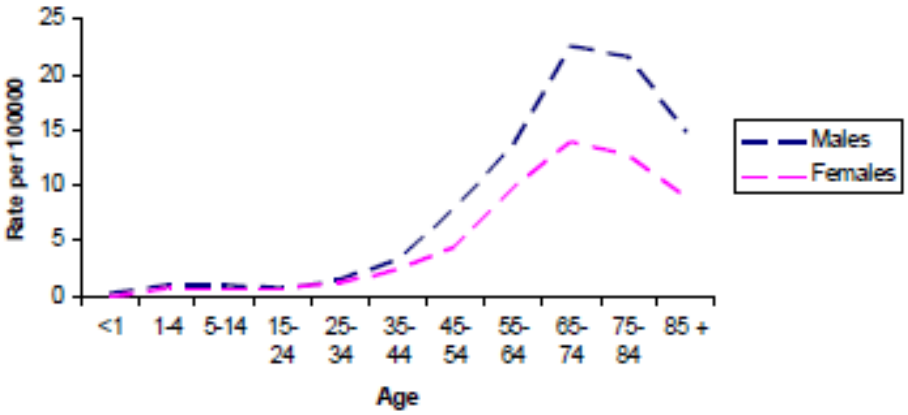


Figure 28 Mortality figures from brain and CNS cancer for 2002 in England and Wales.(78)



Pathology

Primary tumours

Primary tumours of the central nervous system and its coverings are intrinsic or extrinsic to the neuraxis. Intrinsic tumours are neuroepithelial in origin, and most are derived from glial cells, particularly the astrocyte. Many neuroepithelial tumours infiltrate the brain, which makes surgical resection difficult or impossible. Radiotherapy and chemotherapy can usefully supplement surgery, but frequently produce long-term side-effects. Extrinsic tumours derived from the meninges or cranial / spinal nerves are mainly mesenchymal in origin. Meningiomas are the commonest of these tumours, and many are cured by surgery (Ellison and Love, 2004).

Gliomas represent approximately 60% of primary brain tumours and include astrocytomas, oligodendrogliomas, and ependymomas. Accounting for 80% of gliomas, diffuse astrocytic tumours are graded according to these histopathological characteristics: cell pleomorphism, mitotic activity, vascular proliferation, and necrosis, and take the following grades in the latest WHO classification.

Grade II (Low Grade) astrocytomas
Grade III (High Grade) anaplastic astrocytoma
Grade IV (High Grade) glioblastoma

Embryonal tumours of the central nervous system are rare. The commonest, the medulloblastoma,

is situated in the cerebellum, and about 70% occur in childhood.

Meningiomas are common among primary brain tumours, and their incidence increases with age. They may be incidental findings at autopsy. Schwannomas, which are tumours of peripheral nerve sheath, are also relatively common, and occur mainly on the acoustic and spinal nerves. Many meningiomas and schwannomas are cured by surgery.

Primary lymphomas can occur in the central nervous system, and a significant proportion of these occurs in the context of immunosuppression, e.g. AIDS.

Secondary tumours

It has been estimated that brain metastases occur in 25-35% of all cancer patients. These secondary tumours result from the spread of malignant cancers from other sites to the brain. Mortality rates from this disease are high and curative treatment is often impossible; as a result treatment focuses on limiting neurological deterioration. The most common cancers causing brain metastases are lung, breast and malignant melanoma.

18.1 Signs and Symptoms

18.1.1 Key Clinical Questions:

How common is the disease in certain population groups, such as age, sex, ethnicity groups?

Which symptoms, signs and other features raise a suspicion of cancer, and those that make cancer less likely as a diagnosis?

Does family history discriminate patients who should be referred? What is the influence of co-morbidity on suspicion and referral?

18.1.2 Evidence Question:

In people attending primary care services, which symptoms and signs and other features including family history when compared with the "gold standard" are predictive of a diagnosis of brain and central nervous system cancer; and which symptoms and signs are not?

18.1.3 Evidence Statements:

The average general practitioner will have one new case of brain cancer approximately every eight years (III)

Most patients with headaches do not have brain cancers (III)

Duration of ten weeks or less, pain not of tension type, and vomiting increase the likelihood of brain cancer (III)

Dizziness is a poor predictor of brain tumours (III) Brain tumours may present with seizures (III)

Brain tumours may present with behavioural disturbance, slowness and other non-specific symptoms (III)

Focal neurological disturbance may be a presenting feature of brain cancer (III)

Secondary studies

(Hoffman et al, 1999)(387)

A structured literature review was undertaken of studies identified from Medline searches (1966-1996) on the aetiology, prognosis and diagnostic evaluation of dizziness. Studies were included that presented original data on at least ten dizzy or vertiginous patients 18 years of age or older with diagnostic test results comparable with a gold standard or applied to a control group. The most common aetiologies for dizziness were peripheral vestibulopathies (35% to 55% of patients) and psychiatric disorders (10% to 25% of patients). Cerebrovascular disease (5%) and brain tumours (<1%) were infrequent. The history and physical examination were stated as leading to a diagnosis in about 75% of patients.

The most common central nervous system cause of dizziness in primary care patients was cerebrovascular ischemia or infarction (median 5%, range 2% to 10%); tumours were found in <1% of dizzy patients. Tumour rates were higher (2% to 3%) in older patients referred to neurologists. Acoustic neuromas typically presented with gradual hearing loss. Nonetheless, investigators have reported normal hearing in 7% of patients with acoustic neuromas smaller than 1cm in diameter. For acoustic neuromas between 1cm and 3cm, normal hearing was found in 3%; no patients with tumours greater than 3cm had normal hearing.

(Kroenke, 2000)(388)

A Medline search between 1966 and 1996 identified 12 studies of the presentation of dizziness in consecutive patients. Study sites involving 4,536 patients included primary care offices (N=2), emergency room (N=4), and referral clinics (N=6). Dizziness was attributed to peripheral vestibulopathy in 44% of patients, a central vestibulopathy in 11%, psychiatric causes in 16%, other conditions in 26%, and an unknown cause in 13%. Certain serious causes were relatively uncommon including cerebrovascular disease (6%), cardiac arrhythmia (1.5%), and a brain tumour (<1%). Dizziness was ascribed to vestibular or psychiatric problems in more than 70% of cases.

Brain tumour was detected in 32 patients (0.7% of the 4,536 patients assessed). Seven studies reported one or more cases whereas five studies reported no tumours. Other central vestibular explanations were reported in 57 patients (1.2%), including 18 patients with abnormal examination findings (vertical nystagmus, abnormal brain stem evoked potentials) without a specific diagnosis, 17 with cerebellar atrophy, seven with migraine, six with multiple sclerosis, three with epilepsy, and six with other diagnoses.

Differences in the patient populations presumably accounted for some of the wide variability in frequency of specific causes. Since only two studies were primary care based, it was difficult to draw precise conclusions about the frequency of various causes of dizziness in unselected patients in the primary care setting.

Primary studies

Brain

(Becker et al, 1988)(389)

The aim of the study was to examine the clinical characteristics of new headaches and document the diagnostic and management strategies employed by primary care clinicians. A total of 120 primary care physicians in 38 practices in the US and Canada participated in the study and recorded data from November 1982 until December 1983. The final study group consisted of 1,331 patients who made first visits for new. A total of 332,818 office visits were recorded during the period, of which 0.4% were fist visits for new headaches.

At first visit, most patients (76.6%) were managed without diagnostic tests. Drugs were prescribed for 73.6%, and advice was given for 58.6%. Only 2.0% of patients had computerised tomographic

scanning ordered at first visit.

Of persons with a new headache presenting at first visit, 23.8% were diagnosed as having tension and 12.8% as having vascular headaches. Nearly one half (47.8%) were classified as having headaches other than tension or vascular. A total of 15.3% were undiagnosed. Patients with vascular headaches were more likely than those diagnosed as having tension headaches to report occurrence of aura (24.7% vs. 1.3%), nausea or vomiting (46.5% vs. 18.9%) and unilateral focus (50.0% vs. 13.2%). These differences were significant ($p<.05$). Headache severity was related to the ordering of CT scan ($P<.001$) and x-ray examinations ($P<.007$) at first visit. x-ray examinations were ordered most frequently for patients with other or undiagnosed-mixed headaches ($P<.006$); CT scan and blood tests were also used mostly ($P<.0001$) for patients with undiagnosed-mixed headaches.

Patients with disabling headaches at first visit were more likely to be hospitalised ($P<.001$); referral was not related to headache intensity. Patients were 2.05 times as likely to be referred at the second visit than the first ($P<.05$), and the percentage of those hospitalised similarly increased (2.0%).

Primary care clinicians in this study were two thirds as likely to order an x-ray examination as were physicians. Expensive tests were seldom ordered at first or subsequent visits, even when headaches were classified as severe or disabling.

Table 24 Clinical findings in patients with new headache at first visit (N=1,331 patients)* (Becker et al, 1988(389))

Findings	Number	Percent
Headache diagnosis		
Tension only	317	23.8
Vascular only	170	12.8
Other**	636	47.8
Undiagnosed or mixed	204	15.3
Headache intensity		
Mild	672	50.5
Severe	517	38.8
Disabling	93	6.9
Not determined	44	3.3
Febrile illness		
Present	307	23.1
Absent	996	74.8
Not determined	28	2.1

*Data were missing on five patients regarding intensity and on four patients regarding diagnosis

**Other denotes headaches not vascular or tension, eg, those associated with influenza, sinusitis, trauma or intracranial mass lesions.

(Christiaans et al, 2002)(390)

A prospective study was conducted by a Dutch team to assess the diagnostic value of neurologic evaluation in cancer patients with new or changed headache in identifying intracranial metastases. Between February 1997 and February 2000, general practitioners and specialists referred cancer patients with new or changed headache to a department of Neurology. All patients underwent a structured history and neurologic examination. The gold standard diagnostic test in all patients was magnetic resonance imaging (MRI) of the brain within one week after the neurologic examination.

68 consecutively referred patients with headache included (48 females and 20 males). The mean age of the patients was 57 years (range 24-88 years; standard deviation ± 13.3 years). Breast carcinoma was the primary tumour in 32 patients (47.1%) and lung carcinoma was the primary tumour in 12 patients (17.6%). MRI scans demonstrated intracranial metastases in 22 patients (32.4%).

An association was found between intracranial metastases and seven variables: interval between headache onset and neurologic consultation of ≤10 weeks (odds ratio [OR] of 11.2; 95% confidence interval [95% CI], 1.4-91.1), emesis (OR of 4.93; 95% CI, 1.6-15), pain not of tension type (OR of 5.7; 95% CI, 1.8-17.7), Mini-mental state examination score of ≤ 23 (OR of 11.0; 95% CI, 1.1-105.9), apathy (OR of 10.0; 95% CI, 1.0-95.7), coordination disturbance (OR of 3.43; 95% CI, 1.1-4.3), and Babinski sign (OR of 6.47; 95% CI, 1.1-36.6). In multiple regression, three variables were found to be significant independent predictors: headache duration of ≤10 weeks (OR of 11.0; 95% CI, 1.1-108.2), pain not of tension type (OR of 6.7; 95% CI, 1.8-25.1), and emesis (OR of 4.0; 95% CI, 1.1-14.3). When at least one of the three predictors were present,

all patients with intracranial metastases could be identified. If this rule had been applied, 12 MRI scans (26%) could have been omitted in patients without intracranial metastases.

As a single predictor, emesis predicted one of the 22 cases of metastases (5%) and there were no negative MRI findings. As a single predictor, a headache duration of ≤10 weeks predicted four of the 22 positive MRI scans (18%) (with metastases) and 19 of 46 negative MRI scans (41%). The combined presence of the predictors of emesis and headache of duration ≤10 weeks predicted five of the 22 positive MRI scans (23%) and seven of 46 negative MRI scans (15%). The combined presence of pain not of tension type and headache duration of ≤10 weeks predicted six of the 22 cases of metastases (27%) and three of 46 negative MRI scans (7%). The combined presence of emesis and pain not of tension type predicted none of the 22 positive MRI scans and one of 46 negative MRI scans and one of 46 negative MRI scans (2%).

Table 25 Univariate Analysis of Predictors for Intracranial Metastases in Cancer Patients with New or Changed Headache (Christiaans et al, 2002(390))

	Metast-ases absent		**Metast-ases present**			
	(N = 46)		(N = 22)			
Baseline patient characteristics						
Age (yrs)						
24-58 vs. 59-88	22	(48)	15	(68)	2.3 (0.8-6.8)	0.13
Gender						
Female vs. male	32	(70)	16	(73)	1.2 (0.4-3.6)	1.00
Referral						
Spec.vs. gen pract	22	(48)	21	(96)	22.9 (2.8-184.8)	**0.0001**[a]
Primary tumour						
Lungs vs. breast/other	6	(13)	6	(27)	2.5 (0.7-8.9)	0.18
Breast vs. lung/other	24	(52)	8	(36)	0.5 (0.2-1.5)	0.30
Other vs. lung/breast	16	(35)	8	(36)	1.1 (0.4-3.1)	1.00
Interval b/w onset headache-first visit (wks)						
0-10 vs. 11-36	30	(65)	21	(96)	11.2 (1.4-91.1)	0.007
Interval b/w primary tumour -first visit (mos)						
0-62 vs. 63-244	31	(67)	19	(86)	3.1 (0.8-12.0)	0.14
Medical history						
Nausea	21	(46)	15	(68)	2.6 (0.9-7.4)	0.12
Emesis	9	(20)	12	(55)	4.9 (1.6-15.0)	**0.005**

Diplopia	0	(0)	4	(18)		**0.009**
Blurred vision	7	(37)	6	(27)	0.6 (0.2-1.9)	0.59
Speech disturbance	5	(11)	5	(23)	2.4 (0.6-9.4)	0.27
Arm/leg weakness	5	(11)	3	(14)	1.3 (0.3-6.0)	0.71
Gait disturbance	8	(17)	7	(32)	2.2 (0.7-7.0)	0.22
Seizure	1	(2)	1	(5)	2.1 (0.1-35.9)	0.55
Pain worse at night	24	(52)	10	(46)	0.8 (0.3-2.1)	0.79
Pain triggered by exercise	16/44	(36)	8/21	(38)	1.1 (0.4-3.2)	1.00
Pain worse with Valsalva	15	(33)	9	(41)	1.4 (0.5-4.1)	0.59
maneuver						
Pain score[b]						
6-10 vs. 1-5	33/44	(75)	16	(73)	0.9 (0.3-2.8)	1.00
Pain type						
Other vs. tension-type	8	(17)	12/21	(55)	5.7 (1.8-17.7)	**0.004**
Pain medication						
Yes vs. no	38	(83)	17/22	(72)	0.7 (0.2-2.5)	0.74
KPS						
0-60 vs. 70-100	6/43	(14)	7/22	(32)	2.9 (0.8-10.0)	0.11
Neurological examination						
MMSE						
1-23 vs. 24-30	1/45	(2)	4/20	(20)	11.0 (1.1-105.9)	**0.03**
Apathy	1	(2)	4	(18)	10.0 (1.0-95.7)	**0.04**
Papilledema	2/39	(5)	6/18	(33)	9.3 (1.6-52.1)	0.09
Cranial nerve deficit	6	(13)	7	(32)	3.1 (0.9-10.8)	0.10
Speech disturbance	1	(2)	0	(0)		1.00
Motor disturbance	2	(4)	3	(14)	3.5 (0.5-22.5)	0.32
Sensory disturbance	3	(7)	2	(9)	1.4 (0.2-9.3)	0.66
Co-ordination disturbance	9	(20)	10	(46)	3.4 (1.1-4.3)	0.04
Babinski sign	2	(4)	5	(23)	6.5 (1.1-36.6)	0.03

OR: odds ratio; 95% CL: 95% confidence interval. Spec: specialist: gen pract: general

practitioner: b/w: between; KPS: karnofsky performance status score: MMSE: mini mental state Examination.

[a]P values in bold type were statistically significant.

[b]Pain was scored on a scale of 1-10, with a higher score indicating greater pain.

Patients with intracranial metastases were referred mainly by specialists (21 of 22; 96%). The group of patients who were referred by specialists had more symptoms and signs compared with patients referred by general practitioners. The results of the study demonstrated that the discriminative ability of the medical history, including headache features, was low. The neurologic examination did not appear to contribute to the prediction model. It was concluded that few patients could be excluded from undergoing MRI because of the low specificity of clinical features in this group of patients. Therefore, MRI was considered to be warranted in the investigation of patients with cancer who develop new or changed headaches.

Table 26 Multivariate Analysis of Predictors for Intracranial Metastases (Christiaans et al, 2002(390))

Headache = 10 wks	11.0 (1.1-108.2)	0.04
Pain not of tension-type	6.7 (1.8-25.1)	0.004
Emesis	4.0 (1.1-14.3)	0.03
ROC area	0.83 (0.72–0.93)	
OR: odds ratio: 95% CI: 95% confidence interval: ROC: receiver operating characteristics curve.		

(Ambulatory Sentinel Practice Network, 1987)(391)

The study included 3847 patients making 4940 consecutive visits for headache during a 14 month period to 38 primary care practices of the Ambulatory Sentinel Practice Network in the USA and Canada. The clinical characteristics of patients and therapeutic strategies employed by doctors were investigated. Data were recorded between November 1982 and December 1983 about each consultation at which headache was discussed, investigated or treated. While tension headache or vascular headache were the most frequent diagnoses (30.4% and 23.8% respectively), almost one third (31.6%) of visits were for headaches associated with a variety of other causes such as sinusitis, influenza, trauma and mass lesions. Almost half of the visits (47.2%) were for headaches which were new or changed in character. Many visits (13.7%) were for headaches associated with febrile illnesses. Vascular headache was more likely to be diagnosed in patients who had unilateral symptoms, or if nausea or aura accompanied their headaches than in patients with none of these symptoms.

Of 690 patients who made a second visit only 56.4% presented with exactly the same combination of symptoms on both occasions. More than one-quarter (27.0%) of the 37 patients with all three migraine like symptoms at the first visit who made a second visit, and 30.4% of the 92 patients who initially presented with two migraine like symptoms, had none of these symptoms when they returned. Headache intensity changed for 42.9% of the 690 patients making a second visit. Changes in diagnosis accompanied these symptom changes. Thus, almost one-third of patients given a tension or vascular headache diagnosis at the first visit had a different diagnosis at the second visit.

Table 27 Number of diagnoses of headache by 'vascular' symptoms present (percentages given in parentheses) (Ambulatory Sentinel Practice Network, 1987(391))

Diagnosis					
Vascular symptoms	Total number of diagnoses	Tension	Vascular	Other	No diagnosis/ mixed
None	2700	1113 (41.2)	321 (11.9)	929 (34.4)	337 (12.5)
Unilateral headache only	685	131 (19.1)	161 (23.5)	280 (40.9)	113 (16.5)
Nausea or vomiting only	738	198 (26.8)	165 (22.4)	246 (33.3)	129 (17.5)
Warning or aura only	67	8 (11.9)	37 (55.2)	11 (16.4)	11 (16.4)
Any two symptoms	524	47 (9.0)	316 (60.3)	85 (16.2)	76 (14.5)
Any three symptoms	197	4 (2.0)	177 (89.8)	8 (4.1)	8 (4.1)

*Diagnoses were not recorded at 29 visits.

Investigation of headache was limited to history and physical examination. Only a small minority of headache patients underwent an x-ray examination (4.5%), electroencephalogram (1.1%) or computerised tomographic scan (3.0%). The rate of computerised tomographic scanning was greater at second and third visits than first visits (3.8% and 4.5% vs. 2.2%). Referral to consultants and hospitalisation were also infrequent. Nearly three quarters of patients (71.0%) had no investigations at any visit and were never referred to consultants or hospitalised. Only 35.9% of patients were advised to make a return visit; half of these did so.

Risk Factors

No relevant papers could be identified.

18.2 Investigations

18.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care before referral?

18.2.2 Evidence Question:

In people attending primary care services with brain and central nervous system symptoms, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

18.2.3 Evidence Statement:

A CT or MRI scan is the most useful investigation in suspected brain cancer (III)

Other investigations in primary care do not assist in the diagnosis of brain or CNS cancer (III)

Secondary studies

(Consensus Conference 1982)(392)

At the National Institutes of Health (NIH), the Consensus Development Conference brings together investigators in the biomedical sciences, clinical investigators, practising physicians, and consumer and special-interest groups to make a scientific assessment of technologies, including drugs, devices, and procedures, and to seek agreement on their safety and effectiveness. They concluded that CT should not be employed as a routine screening procedure when a low diagnostic yield is anticipated. In general, patients with headache should be considered for CT scanning only if the symptom is severe, constant, unusual, or associated with abnormal neurological signs. In infants and children, CT is useful as a primary diagnostic tool in the evaluation of intracranial haemorrhage and mass lesions. CT is not necessary in evaluating conditions of the majority of children with headaches because the occurrence of a surgically treatable lesion is extremely low. The clinical situation must, in each case, be considered individually.

Primary studies

(Becker et al Part 1 1993)(393)

This study was undertaken to investigate the reasons for clinicians in primary care ordering CT scans and the results obtained. Data were collected over 19 months. Clinicians in 58 practices (in the US and Canada) ordered 349 CT scans. Most scans were ordered because the clinician believed that a tumour (49%) or a subarachnoid haemorrhage (9%) might be present. 59 were ordered because of patient expectation or medicolegal concerns. Of the 293 reports reviewed, 14 indicated a tumour, a subarachnoid haemorrhage, or a subdural haematoma. Two of the 14 (14%) were false positives. 44 (15%) of the reports noted incidental findings of questionable significance. It was concluded that because there are no clear guidelines for the use of CT for the investigation of headache, physicians must exercise good clinical judgement in their attempts to identify treatable disease in a cost-effective manner.

(Becker et al Part 2 1993)(394)

The initial diagnosis of intracranial tumour, subarachnoid haemorrhage, and subdural haematoma can be difficult. This study was undertaken to determine the incidence and presenting signs and symptoms of these disorders in primary care settings, and to determine whether a more aggressive investigative strategy for patients with headache is justifiable.

Weekly return cards and a chart audit were used to collect data over a 19 month period on every patient who had a new diagnosis of intracranial tumour, subarachnoid haemorrhage, or subdural haematoma. 25 new tumours, 17 subarachnoid haemorrhages, and eight subdural haematomas were reported in 58 practices (a rate of 12/100,000 patients per year). Only half of these patients had headaches, and no abnormalities were found on neurological examination of many. Diagnosis was delayed in only four patients with headache caused by a brain tumour and in three patients with subarachnoid haemorrhages. Diagnosis was delayed in two of the latter because of false negative CT scans.

Although clinical findings and CT scans are not reliable indicators, clinicians are able to detect the majority of these rare conditions without undue delay by selecting a small subset of patients for further investigation. More extensive use of CT scans appears to be a poor strategy to improve detection of these serious disorders, as increased use would lead to increased health care costs

and unintended adverse effects, and provide little benefit.

(Larson et al 1980)(395)

161 highly selected patients with headache were studied to assess the impact of CT on diagnostic evaluation. A careful history and physical and neurological examinations were adequate screens to detect intracranial mass lesions or systematic disease associated with headache. In patients with normal findings from neurological examination, no clinically important abnormalities were detected by CT, skull x-ray, angiography, or nuclide brain scan. The cost of finding a case of brain tumour was estimated to be at least $1,265 for patients with abnormalities on neurological examination and $11,901 for patients with normal findings on neurological examination. Neurodiagnostic evaluation of headache patients with normal findings from neurological examination is expensive and was clinically unrewarding in this series.

18.3 Delay and Diagnostic Difficulties

18.3.1 Key Clinical Question:

In people attending primary care services with brain or central nervous system cancer symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with head and neck symptoms/signs relevant to the brain or central nervous system may or may not need urgent referral with suspected cancer?

18.3.2 Evidence Question:

In patients attending primary care services with brain or central nervous system cancer symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation of brain cancer?

What diagnostic difficulties do primary care practitioners themselves report in determining whether a person who presents with brain or central nervous system symptoms/signs may or may not need urgent referral with suspected cancer?

18.3.3 Evidence Statement:

Delay

Insufficient evidence could be identified in order to draw evidence statements on delayed presentation in primary care with brain cancer symptoms. Nonetheless the papers found are presented below.

Diagnostic Difficulties

The initial presenting features of brain or CNS cancer can mimic the presentation of other less significant (but very common) disorders, for example, fatigue, or headaches (III)

Delay may occur when doctors fail to reconsider the initial diagnosis when symptoms fail to improve as expected (III)

Delay

Spinal cord

(Levack et al, 2002)(396)

The authors examined the diagnosis, management and outcome of patients diagnosed with malignant cord compression at three cancer centres. The aim of the study was to assess the natural history of malignant cord compression from the onset of patient symptoms to the time of diagnosis. Specifically the study aimed to document delays in the diagnosis of malignant cord compression, to analyse their duration and where they occurred. Demographic data included age, sex, and residential postcode (using 1991 Carstairs deprivation categories which were matched on to records).

The thoracic spine was the commonest site of malignant cord compression (68% of episodes). 7% of cases occurred in the cervical region. At diagnosis, 82% of patients were unable to walk or only to be able to do so with help. This finding was not influenced by patient age (P=0.33) or deprivation category (P=0.45). 94% of patients reported pain, and had been present for approximately three months. The site of pain did not correspond to the site of compression. 85% of patients had noticed weakness and 68% of patients had noticed sensory problems for some time before diagnosis (median interval 20 and 12 days respectively). Patients experienced pain for approximately three months before a definitive diagnosis was established and treatment given. 83% of patients told their general practitioner about the pain within three weeks (median = 18 days). The general practitioner referred approximately three weeks after the patient had first told them of their symptoms (median = 18 days; IQ range 2-66 days). Referral was no faster for those patients known to have cancer at the time of telling their general practitioner (P=0.32).

(Husband, 1998)(397)

This study examined the delay in presentation, diagnosis, and treatment of malignant spinal cord compression. It also sought to define the effect of this delay on motor and bladder function at the time of treatment. Patients were interviewed at the time of hospital admission.

The median delay from onset of symptoms of spinal cord compression to treatment was 14 (0-840) days. Of the total delay, three days were accounted for by patients, three days by general practitioners, four days by the district general hospital, and 0 days by the treatment unit (0-114 days). Initial presentation to the regional cancer centre with symptoms of malignant spinal cord compression led to a significant reduction in delay to treatment and improved functional status at the time of treatment.

Diagnostic Difficulties

Very limited relevant evidence was identified about the diagnostic difficulties experienced by primary care practitioners in the early detection of brain and central nervous system tumours. There were no secondary studies and only one observational (level III) primary study.

(Salander et al, 1999)(398)

A Swedish team undertook a study of symptom development and obstacles to early diagnosis. A consecutive sample of 28 patients (18 men and ten women) with the diagnosis of malignant glioma and their spouses were interviewed about symptom development, help seeking and experiences of medical care. The project was undertaken in 1991-1993 and studied the psychological aspects of brain tumour in patients aged between 18-70.

Headache

Persistent and intense headache and seizure were the most common symptoms experienced at the time of diagnosis. Headache was persistent in about half of the ten cases, and was closely accompanied by vertigo and/or vomiting. Seven patients first turned to primary care for help, and three to an emergency unit. Two were immediately referred for a CT scan. The others were

diagnosed as 'sinusitis', work related, vestibulitis, pregnancy, and headache due to tension or just sent home for expectant management. The patient's spouse insisted on a CT examination in three of the cases. Whilst patients indicated the acute onset of headache as the starting point of the disease, the majority of spouses described preceding symptoms of fatigue, slowness, irritation or behavioural dysfunction.

Seizure/falling

Nine patients sought professional advice immediately after experiencing a seizure or falling. Five first turned to primary care and four to a hospital. All but two patients were referred for CT examination. These two patients received the diagnosis 'inflammation of the balance nerve' and 'sinusitis.' In line with the headache group, the spouses added descriptions of preceding symptoms including memory disorder, fatigue, falling asleep in the middle of the day, irritability or other socially detectable manifestations of dysfunction in addition to headache.

Motor or sensory dysfunction

Five patients first consulted their general practitioner and one patient consulted the hospital. Three were immediately referred for CT scan. The others were diagnosed as suffering from the adverse effects of hypertensives, or having experienced minimal stroke, and one was sent home for expectant management. Preceding diffuse symptoms were less prominent in this group compared to the headache and seizure group.

Obstacles on the pathway to medical care Dramatic or unusual symptoms were associated with shorter times to diagnosis. Less unusual symptoms such as headache were attributed to trivial causes and postponed help seeking. Personality change was identified as an obstacle. One patient who lived alone did not enter the medical care pathway due to a personality change. Patient avoidance strategies in response to the threat of disease contributed to patient delay in seeking medical attention.

Most spouses witnessed months to years of diffuse global dysfunction whereas patients described their symptoms in terms of bodily experiences and acute onset. The observations of the spouse were important in providing contextual information that could enable changes to be assessed more clearly and shorten the time to diagnosis. Social surroundings were thus important. The importance of acknowledging the spouse as an informant in facilitating differential diagnosis was stressed. Communication with the spouse to clarify preceding symptoms and peculiarities in everyday life was a substitute for the patient's lack of insight and motivation. However, in some cases the spouse's passivity and successive adaptation to the patient's problems could also act as impediments to seeking professional advice.

Physician factors in the diagnostic process that affected the time lag for referral were related to the fact that headache, for instance, had numerous reasonable causes that seemed more likely than a brain tumour. The 'reasonable diagnosis' usually harmonised with the patient's explanations of the effects of chronic disease or work related interpretations. Sometimes physicians' inflexibility created difficulties when they were reluctant to abandon their initial diagnosis. For example, a patient was being treated for sinusitis despite an intensification of headache and vomiting, and being unable to use hedge clippers or knot his tie. He twice returned to his doctor before a hospital referral was made but became unable to walk before he received a hospital appointment. It was emphasised that fatigue for four months, intensifying headache for four weeks and suddenly being unable to explain how to use a lawnmower were indications that should have triggered suspicion of disease beyond sinusitis.

The majority of patients reported in this study first turned to primary care. Eight (40%) were immediately referred to the emergency unit at the local hospital. Since headache was an extremely common symptom in primary care in Sweden, and a general practitioner is confronted with a brain tumour once every third year, the difficulty in differential diagnosis can hardly come as a surprise. The most common alternative diagnoses were sinusitis and vestibulitis. The wide

variation in time from physician consultation to diagnosis revealed that a multitude of factors were exerting an influence on the diagnostic process.

(Becker et al, Part 1, 1993)(393)

The presenting signs and symptoms of intracranial disorders in primary care settings in the US and Canada were reported in this study to determine whether a more aggressive investigative strategy for patients with headache was justifiable. In their previous study, Becker et al found that primary care physicians used CT selectively, ordering scans only for approximately 3% of patients with headache. They were unable to determine whether this strategy led to significant or harmful delays in diagnosis. The present study was initiated to study the signs and symptoms with which these patients presented to primary care physicians, and estimate the extent to which a more aggressive investigative strategy for patients with headaches would have led to earlier diagnosis.

Fifty-eight practices participated in the study. Data collection began in March 1986 and continued until October 1987. Weekly return cards and a chart audit were used to collect data over 19 months on every patient who had a new diagnosis of intracranial tumour, subarachnoid haemorrhage, or subdural haematoma. Information was obtained concerning the severity and symptom characteristics of the headache, presence or absence of papilloedema, abnormalities on neurological examination, and presence or absence of other symptoms that could indicate the presence of intracranial problems (such as seizures, loss of consciousness, changes in strength, sensation, or neurological function, changes in headache pattern or severity that awakened the patient from sleep. These practices conducted a total of 712,750 patient visits.

A total of 25 new intracranial tumours, 17 new cases of subarachnoid haemorrhages, and 8 newly diagnosed subdural haematomas were reported during the recording period. Only 26 of the 50 patients with a subarachnoid haemorrhage, subdural haematoma, or tumour in this study reported a headache. Only one half of these patients had headaches, and no abnormalities were found on neurological examination of many. Many of the patients with headache had no abnormalities noted on neurological or fundoscopic examination. This was the case for nine (75%) of the patients with headache and intracranial neoplasms, five (45%) of those with a subarachnoid haemorrhage, and two of the three patients with an subdural haematoma. An additional three patients with tumours and three with subarachnoid haemorrhages had symptoms such as new seizures, or changes in function suggesting a neurological problem prior to their diagnosis. Three patients (one with a primary malignancy and two with benign tumours) had a change in headache pattern as their only ominous symptom.

Over-reliance on the symptom of headache as an indicator of serious intracranial disease could lead to under-diagnosis. Over one half of the patients in the study with a tumour or subdural haematoma had no headache. Patients with subarachnoid haemorrhage may have had a headache but no other clinical findings at the time of the initial examination. Diagnosis was defined as delayed if the interval between the first presentation with a headache and the performance of the first CT scan was greater than two weeks in the case of brain tumours or two days in the case of subarachnoid haemorrhages or subdural haematomas. Recognition within these intervals appeared to be associated with better outcomes. Four patients with brain tumours visited their primary physician with a headache one month or more before a diagnostic CT scan was performed. Headache was even less common in patients with a subdural haematoma, but was present in all of the patients with a subarachnoid haemorrhage who were able to provide a history. Diagnosis was delayed in only four patients with headache caused by a brain tumour and in three with subarachnoid haemorrhages. Diagnosis was delayed in two of the latter because of false-negative CT scans.

The general practitioners identified a group of patients with headache who were at high risk for tumour or subarachnoid haemorrhage but did not clearly specify the clinical indicators they used. The neurological examination alone appeared not to be a sufficient indicator of risk. Insistence on the presence of neurological signs or symptoms before ordering a CT scan would have missed a significant proportion of the benign tumours and subarachnoid haemorrhages detected in this study, and may have played a role in the diagnostic delays that occurred.

This study based in primary care practices, did not identify a large number of patients for whom a clinically significant delay in diagnosis occurred. Instead, it revealed a highly selective clinical approach that correctly identified over 70% of the patients with headaches due to subarachnoid haemorrhage, tumour, or subdural haematoma.

The authors maintained that more extensive use of CT scans appeared to be a weak strategy to improve detection of these serious disorders, as increased use would lead to increased health care costs and unintended adverse effects, and provide little benefit.

18.4 Support and Information needs

18.4.1 Key Clinical Question:

What are the support and information needs of patients who are being referred for suspected cancer? Are the needs different in different groups of patients?

18.4.2 Evidence Question:

What are the support and information needs of patients who are being referred for suspected cancer? Are the needs different in different age, sex, ethnic and cultural groups of patients?

We found almost no evidence on this question to inform specific recommendations relating to brain cancers. General recommendations about the support and information needs of patients being referred for suspected cancer are included in chapter seven.

Primary studies

(Salander et al 1996)(399)

The purpose of this study was to generate new insights into how the patient constructs a new sense of reality when confronted with the malignant brain tumour diagnosis. Within grounded theory methodology, 30 patients with malignant gliomas were interviewed twice, in direct connection with diagnosis, surgery and radiotherapy. In addition, their partners were interviewed, and quantitative instruments (the Standardized Mini-Mental State Examination and the Reaction to the Diagnosis of Cancer Questionnaire) were used as additional references for assessing patients' cognitive and emotional state. Eleven patients were excluded from the final analysis because of cognitive impairment or personality change.

Most of the patients were aware of the fact that the brain tumour exposed them to grave danger, but they were also able to use various cognitive manoeuvres to create protection and hope. This process originated from different sources: the body; helpful relations; cognitive schemata; and the handling of information.

Consideration is given by the authors to how the patient brings together reality and hope, thus creating his/her own illusion. These findings are also related to psychoanalytic theory, proposing a theoretical reference with clinical implications when discussing "What to tell cancer patients".

19 Bone cancer and sarcoma

1 A patient who presents with symptoms suggesting bone cancer or sarcoma should be referred to a team specialising in the management of bone cancer and sarcoma, or to a recognised bone cancer centre,depending on local arrangements. D

2 If a primary healthcare professional has concerns about the interpretation of a patient's

symptoms and/or signs, a discussion with the local specialist should be considered. D

3 Patients with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest (and especially if not in the joint), or an unexplained limp should be investigated by the primary healthcare professional urgently. The nature of the investigations will vary according to the patient's age and clinical features.
- In older people metastases, myeloma or lymphoma, as well as sarcoma, should be considered. [C(DS)]

Specific Recommendations

Bone tumours

4 A patient with a suspected spontaneous fracture should be referred for an immediate X-ray. [B(DS)]

5 If an X-ray indicates that bone cancer is a possibility, an urgent referral should be made. [C(DS)]

6 If the X-ray is normal but symptoms persist, the patient should be followed up and/or a repeat X-ray or bone function tests or a referral requested. [C(DS)]

Soft tissue sarcomas

7 In patients presenting with a palpable lump, an urgent referral for suspicion of soft tissue sarcoma should be made if the lump is:
- greater than about 5 cm in diameter
- deep to fascia, fixed or immobile
- painful
- increasing in size
- a recurrence after previous excision.

If there is any doubt about the need for referral, discussion with a local specialist should be undertaken. C

8 If a patient has HIV disease, Kaposi's sarcoma should be considered and a referral made if this is suspected. C

Introduction

The commonest primary bone tumours are osteosarcoma and chondrosarcoma, Ewing's sarcoma being less common. Osteosarcoma occurs most commonly in adolescents and young adults, and accounts for 20% of primary bone cancers and 5% of childhood tumours. A second peak in incidence is seen in the elderly who are more likely to have Paget's disease. It is more common in males than female. The exact numbers of these cancers may be higher than indicated in the figures because some cases are not reported. In 2002, there were 242 deaths in England and Wales from primary bone cancers, 153 men and 89 women, with 228 new cases being diagnosed in 2001.

Ewing's sarcoma is a primary malignant small round cell tumour of bone. Most patients are aged between 10 and 15 years old. It usually occurs in the axial skeleton. Chondrosarcomas are malignant tumours of cartilage, typically arising from middle age. It is more common in men. Soft tissue sarcomas are rare tumours of mesenchymal tissue, accounting for less than 1% of all cancers. They may occur at any age including in children, although they are more common over the age of 55 years. The malignant sarcomas include angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant schwannoma, rhabdomyosarcoma amongst others. It should be pointed out that Gastro-Intestinal Stromal Tumours (GISTs) are mesenchymal malignancies and therefore sarcomas, but GIST is not considered in this guideline. Patients with GIST may present with a variety of gastrointestinal symptoms or signs, including abdominal or epigastric discomfort or pain, often unrelated to eating, vomiting, a palpable abdominal mass, or evidence of GI bleeding. General

features include anaemia, fatigue and fever.

Figure 29 Newly diagnosed cases of bone and sarcoma cancer in 2001 in England and Wales. (77)

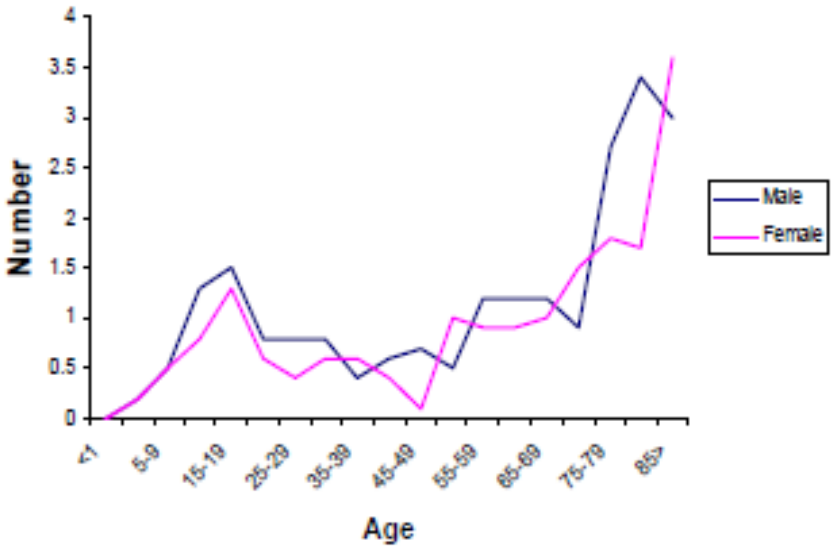
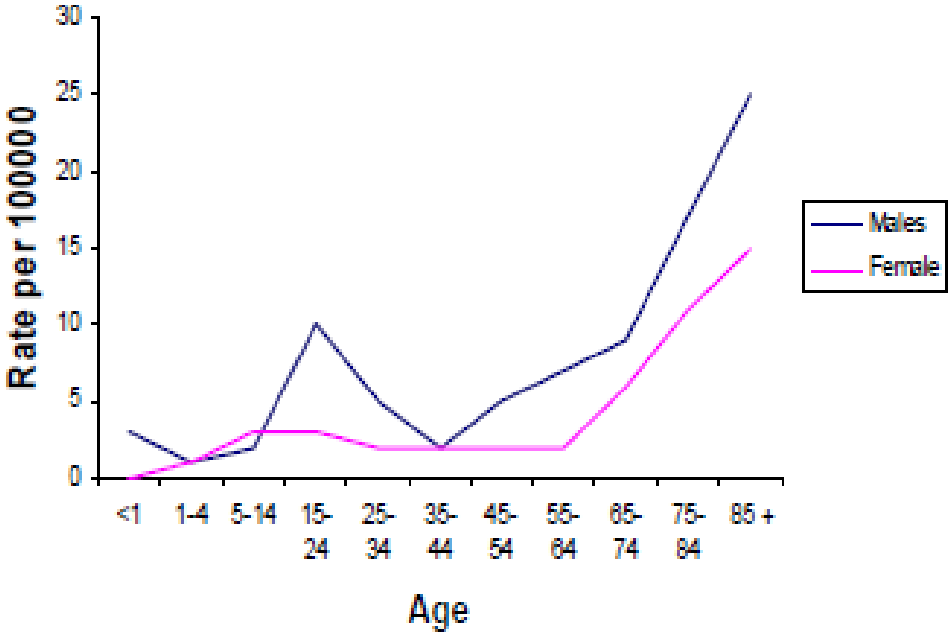


Figure 30 Mortality figures from bone and sarcoma cancer for 2002 in England and Wales. (78)



Review of cancer referral audits

The review identified eleven relevant audits (CRD, 2004). The proportion of two week referrals found to be in accordance with the symptoms listed in the guidelines ranged from 0% to 100% (six audits). The proportion of patients referred in the two week system found to have cancer ranged from 0% to 20% (seven audits). The proportion of two week referrals judged to be clinically appropriate ranged from 67% to 100% (four audits). All of these audits were based on samples of eleven patients or less.

19.1 Symptoms and Signs

19.1.1 Key Clinical Question:

Which symptoms, signs and other features raise a suspicion of sarcoma, and those that make cancer less likely as a diagnosis? Does family history discriminate patients who should be referred?

19.1.2 Evidence Question:

In people attending primary care services, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of sarcoma; and which symptoms and signs are not?

19.1.3 Evidence Statements:

Primary bone tumours

Primary bone tumours can occur in children and adults of any age, but are most common between the ages of 10 and 25 years of age. (III)

Primary bone tumours are rare. A typical general practitioner would expect to encounter a case once in 100 years. (III)

The most common presenting symptom in primary bone tumours is regional pain. Associated symptoms include a palpable mass, and tenderness. (III)

A recent history of minor trauma does not exclude the possibility of primary bone tumour. (III)

Soft tissue sarcomas

Soft tissue sarcomas occur at any age, but are more common over 30 years of age. (III)

Soft tissue sarcomas are uncommon. A typical general practitioner would expect to encounter a case once in 30 years. (III)

The most common presenting feature in soft tissue sarcomas is a palpable mass with or without pain or discomfort. (III)

The commonest site for soft tissue sarcomas is the lower limb, followed by the upper limb, then the trunk, although they can occur almost anywhere. (III)

Secondary studies

Primary bone tumours

No secondary reviews were identified for the presenting symptoms and signs of primary bone tumours in primary care.

Soft tissue sarcomas

(Rosenthal and Kraybill, 1999)(400)

This article is an authoritative review of soft tissue sarcomas in the context of primary care. These tumours were reported as being rare (less than 1% of all malignancies in the USA, family physicians probably encountering only two cases during a typical working lifetime). In a series of malignant soft tissue tumours treated in one centre in the years 1980-1989, 24% were malignant fibrous histiocytomas, 14% liposarcomas, 12% undifferentiated sarcomas, 8% leiomyosarcomas, 6% malignant schwannomas, 6% dermatofibrosarcomas,
5% synovial sarcomas, 5% fibrosarcomas, and 20% other.

The review reported that soft tissue sarcomas usually present as an asymptomatic mass. Patients often waited an average of four months before seeking medical attention, and a definitive diagnosis may be delayed for another six months in 20% of patients. No one feature reliably indicated if a mass is a sarcoma. Two thirds are deep seated and larger than most subcutaneous tumours. The physical examination may reveal a firm, non-tender mass that may seem well defined as a result of compression by surrounding tissues.

Primary studies

Primary bone tumours

(Widhe and Widhe, 2000)(401)

A group of patients aged up to 30 years old was identified from the Swedish cancer registry and records were obtained for 102 with osteosarcoma and 47 with Ewing's sarcoma. Eighty-six (58%) patients' first consultation had been with a general practitioner, and 42 (28%) with a doctor at an emergency ward. Eleven (7%) had presented to a school doctor, and eight (5%) a military doctor. Seventy-one (70%) patients with osteosarcoma and 34 (72%) with Ewing's sarcoma consulted because of regional pain. Twenty-six (25%) of those with osteosarcoma consulted with pain and a palpable mass, and seven (15%) of those with Ewing's sarcomas consulted with pain and a mass. Only four (4%) of those with osteosarcoma and five (11%) of those with Ewing's sarcoma did not report pain at the first medical visit. These patients all had a palpable mass only. Only twenty-one (21%) of those with osteosarcoma and nine (19%) of those with Ewing's sarcoma had pain at night. However, 87 (85%) of those with osteosarcoma and 30 (64%) of those with Ewing's sarcoma reported pain related to strain. Intermittent pain at rest was reported by 57 (56%) of those with osteosarcoma and 27 (57%) of those with Ewing's sarcoma.

Forty-eight (47%) of patients with osteosarcoma and 12 (26%) of those with Ewing's sarcoma related the onset of symptoms to trauma occurring at about the time the symptoms began. The majority of the traumatic incidents were of a similar type and magnitude to those regularly experienced by participants in common sports.

All of the 149 patients had some findings on examination at the first visit (see Table 28).

Table 28 Findings on examination at first visit.(401)

	Osteosarcoma	Ewing's sarcoma
Local tenderness	94 (92%)	33 (70%)
Palpable mass	40 (39%)	16 (34%)
Painful movement of joint	40 (39%)	16 (34%)
Restricted movement of joint	23 (23%)	8 (17%)
Fever (reported or measured)	3 (3%)	14 (30%)
Atrophy of muscle	5 (5%)	0 (0%)

Limp (noted or reported);	28 (31%)	19 (40%)
tumours in upper limb excluded		

Bauer et al, 1999(402)

This article summarised data from the Scandinavian Sarcoma Group Register for cases notified to the register 1986-1993. Data were reported from Norway, Sweden and Finland. In the eight years, 3152 patients were reported, including 1031 with bone sarcomas.

Among bone sarcomas, the commonest sites were the femur (34%), tibia (13%) and humerus (9%). 84% of patients with bone sarcoma had been referred to a sarcoma centre before open biopsy or surgical treatment.

Soft tissue sarcomas

Lawrence et al, 1987(403)

The article reported a US national survey of the presentation of soft tissue sarcoma in adults (aged 18 or over). Data were obtained from 504 hospitals in 1977-78 involving 2355 patients, and in a second stage of the study from 645 institutions in 1983-4 involving 3457 patients. 8.9% of the sarcomas were in the head and neck, 17.9% trunk, 13.1% the upper limbs, 46.4% the lower limbs, 12.5% retroperitoneal, and 1.3% in the mediastinum. The female to male ratio was 1.0:1.1 (the ratio in the entire US population was 1.0:0.95). 86% of patients were described as white, 10% black and 1% asian (the same as the race distribution of the US population). Among this adult population, 20.7% were under 40 years, 27.6% 40-60 years, and 51.8% over 60.

The major presenting symptom was the presence of a mass (64%); one third had pain or discomfort as the initial symptom. A family history of sarcoma occurred in 0.8% of patients, and a family of other cancer was not unusually high in comparison with the general population.

(Rydholm, 1997)(404)

This article reported a population-based case series of people with sarcoma in southern Sweden. Lipomas are the commonest soft tissue tumour, and the findings in 428 patients with lipoma were compared to those with sarcoma. Lipomas were almost non-existent in children, and in adults were uncommon in the hand, thigh, lower leg and foot. The median size of solitary subcutaneous lipomas was 3cm, 80% being smaller than 5cm. The annual incidence of lipoma was estimated at 1/1000. In comparing these findings with findings relating to the sarcoma case series, patient age and duration of symptoms did not differentiate patients with lipoma from those with sarcoma. The median sizes of subcutaneous and deep-seated sarcomas were 4 cm and 8 cm respectively. The solitary lipoma:sarcoma ratio was 150:1 for tumours <5 cm, 20:1 for tumours >5 cm, and 6:1 for tumours >10 cm. For deep-seated tumours, the lipoma:sarcoma ratio was 4:1. One third of the soft tissue sarcomas were in the thigh.

On the basis of these data, recommendations were formulated as follows: Refer before surgery all patients with soft tissue lesions that fulfil any of these criteria:

- larger than 5 cm
- deep-seated
- otherwise suspected of malignancy (for example, rapid growth, firm consistency).

Bauer et al, 1999(402)

This article summarised data from the Scandinavian Sarcoma Group Register for cases notified to the register 1986-1993. Data were reported from Norway, Sweden and Finland. In the eight

years, 3152 patients were reported, of whom 2121 had soft tissue sarcomas.

Among soft tissue sarcomas the most common sites were the thigh (33%), trunk wall (15%) and lower leg (12%). 58% of patients with soft tissue sarcoma had been referred to a sarcoma centre before open biopsy or surgical treatment.

Bauer et al, 2001(405)

This article reported a series of 1851 cases of adults (aged 16 or over) with soft tissue sarcoma of the limbs or trunk wall notified to the Scandinavian Sarcoma Group Register 1986-1997. The median age at diagnosis was 65 years (see Table 29).

Table 29 Age classified incidence of diagnosis of sarcoma.(405)

Age group	Males	Females	Total	%
16-19	20	22	42	2
20-29	76	50	126	7
30-39	82	75	157	9
40-49	134	113	247	13
50-59	116	101	217	12
60-69	193	151	344	19
70-79	270	217	487	26
80-89	86	122	208	11
90-99	13	10	23	1
Total	990	861	1851	100

41% of tumours were in the thigh, 14% the trunk wall, and 11% the lower leg. 32% were subcutaneous, 32% intramuscular, and 32% deep, extramuscular. The median recorded size was 7cm (6 cm among those under aged 40 years increasing to 8cm in those aged over 80 years).

(Stefanovski et al, 2002)(406)

A cancer centre database in Italy was used to identify 395 patients who had been treated for primary soft tissue sarcoma 1985-1997. The median age at diagnosis was 53 years (range 10-94 years). There were 172 females (43.5%) and 223 males (56.5%). The most common sites were lower limb (44.8%), upper limb (12.4%), and superficial trunk (12.2%). Fifty-nine % of the patients had lesions >5cm.

Risk Factors

Patients who have previously had retinoblastoma or been treated by radiation therapy are reported as at increased risk of sarcoma. However, we did not identify relevant papers for inclusion in the guideline.

19.2 Investigations

19.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care before referral?

19.2.2 Evidence Question:

In people attending primary care services with symptoms or signs potentially related to sarcomas, which investigations when compared with the "gold standard" are predictive of a diagnosis of cancer, and which are not?

19.2.3 Evidence Statements:

An x-ray is the first investigation for suspected primary bone tumours. (III)

There was no evidence about the primary care investigation of soft tissue sarcomas.

Secondary studies

Primary bone tumours

(American College of Radiology, 1999)(407)

This good quality evidence review presented appropriateness criteria for imaging techniques for evaluating bone tumours. A routine x-ray was given the highest rating of appropriateness for investigation of patients with suspected bone lesions. When a classically benign-appearing lesion is detected on routine x-ray, additional studies may not be necessary unless surgical intervention is contemplated. When routine x-ray features are indeterminate or the lesion is more aggressive and considered to be potentially malignant, additional imaging studies are frequently required. MRI has been demonstrated to be superior to CT for staging bone tumours before treatment.

Primary studies

Primary bone tumours

(Widhe and Widhe, 2000)(401)

In this study of patients aged 30 or under notified to the Swedish cancer register, 68 (67%) of patients with osteosarcoma and 28 (60%) of those with Ewing sarcoma had a radiograph organised at the first medical visit. However, the correct diagnosis was not established for all patients who had a radiograph. The radiograph was misinterpreted by the radiologist as normal or inconclusive for six (9%) of those with osteosarcoma and 12 (43%) of those with Ewing's sarcoma. When a radiograph was ordered at the first visit, the doctor's delay to diagnosis averaged eight weeks, compared to 19 weeks when a radiograph was not ordered ($P<0.0001$).

19.3 Delay and Diagnostic Difficulties

19.3.1 Key Clinical Questions:

What diagnostic difficulties do primary care practitioners report in determining whether a woman/man who presents with symptoms/signs suggestive of sarcoma may or may not need urgent referral with suspected cancer?

In people attending primary care services with sarcoma symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

19.3.2 Evidence Questions:

What diagnostic difficulties do primary care practitioners report in determining whether a person who presents with symptoms/signs that might be related to sarcoma may or may not need urgent referral with suspected cancer?

In people attending primary care services with sarcoma symptoms, which psychosocial and socio-demographic factors are associated with delayed presentation? Which factors influence delay by patient and which delay by provider?

19.3.3 Evidence Statements:

No evidence on the diagnostic difficulties of sarcoma by primary healthcare professionals was identified.

Delay in the detection of soft tissue sarcoma can occur in up to a quarter of patients, and is associated with misdiagnosis at the initial consultations (III).

Introduction

No articles reporting studies of the difficulties encountered by primary care professionals in identifying patients to be referred for suspected sarcomas were identified. However, specialist advisors to the guideline group confirmed that the identification of sarcomas and bone cancers was a often difficult for primary care professionals.

Only three primary studies of relevance to the question of delay were identified: one addressed diagnostic delays in soft tissue sarcomas, the other explored diagnostic delays in bone sarcomas and one addressed both. Evidence about any association between prognosis and delayed diagnosis was either lacking or contradictory.

Primary studies

Primary bone and soft tissue sarcomas

(Ashwood et al, 2003)(408)

A prospective audit was undertaken to investigate sources of delay in diagnosis and the rates of misdiagnosis of bone and soft tissue sarcomas. Details of 100 consecutive patients referred to a specialist centre in the UK were collected between 1997 and 1998.

56 men and 44 women were referred by four different routes: orthopaedic services, other specialities, general practitioners and from within the hospital.

Patient delay:

Patients noted symptoms noted for about 14 months before consulting a doctor (range 0 to 26 months). Those who were subsequently diagnosed with malignant disease had symptoms for a shorter time (average 7.6 months, range 0.5 to 11 months).

Doctor delay:

Although doctor delay was not restricted to primary healthcare professionals only, referral took an average of 13.5 months (range 0 to 32 months) with the process tending to be quicker for conditions perceived as malignant.

No reasons for the delay by either patient or doctor were explored.

Primary bone sarcomas

(Sneppen and Hansen, 1983)(409)

The aim of this study was to elucidate the relationship between presenting symptoms or signs and doctor and patient delay. 84 consecutive cases of osteosarcoma and 40 consecutive cases of Ewing's sarcoma admitted to a specialist tumour centre in Denmark between 1962 and 1979 were included in the study. The centre received nearly all cases of malignant bone tumours from a well-defined region with a population of about two million.

The diagnosis was confirmed in all cases by histology. There were 49 females and 35 females among the 84 patients with osteosarcoma (range 8-86 years, mean 28 years) and 29 males and 11 females among the 40 with Ewing's sarcoma (range 2-62 years, mean 17 years). The total delay covered the period from the patient's recognition of the first symptom or sign until his or her arrival at the centre.

In the osteosarcoma group, the total delay averaged 6.4 months, ranging from two weeks to three years. Total delay was not influenced by gender, or anatomical site. Total delay was shorter for patients under 20 years old (4.7 months vs. 9.1 months, P<0.001). For the Ewing's group the total delay averaged 9.6 months, ranging from four weeks to four years. Total delay was not influenced by gender or age. Tumours involving the upper limbs were diagnosed earlier than tumours involving the legs (2.6 months vs. 14.3 months, P=0.02-0.01).

In both groups patients with constant pain had a relatively short delay, although the difference was only significant for patients in the Ewing group (three months delay vs. 12.6 months, P=0.05-0.02). The presence of a swelling was also associated with a shorter total delay both for osteosarcomas and Ewing's sarcomas (P=0.05-0.02, and P=0.10-0.05 respectively). A comparison between the total delay for both diseases and the prognosis revealed that patients with a relatively long or relatively short delay had the same prognosis.

Soft tissue sarcomas

(Brouns et al, 2003)(410)

The aim of this study was to determine patient and doctor related delay in diagnosis and treatment of soft tissue sarcomas, as well as the reasons for this delay. The authors undertook a retrospective review of 100 consecutive hospital patients in Belgium referred for treatment of soft tissue sarcomas between May 1999 and May 2001. Patients with sarcomas of the bone were excluded. Only primary tumours were considered. The authors did not investigate the delay in diagnosis or treatment of recurrent or metastatic disease. The median age of the study population at the time of diagnosis of soft tissue sarcoma was 50.5 years with a range from three to 88 years, 37% being older than 60 years.

Diagnosis was confirmed by review of the histological slides by an experienced pathologist. Patient delay was defined as longer than one month from the first symptom to the first doctor visit. Doctor delay was defined as longer than one month from first consultation until final diagnosis.

Patient delay:

93 patients discovered the mass themselves: 53 patients showed no delay, the median delay of the other 47 patients was four months (ranging from one to 240 months). Of the 93 patients, 16 had pain as a symptom: 31% (N = 5) of the patients who had pain as a symptom delayed, whereas 55% (N = 42) of the patients who had no pain delayed. No correlation with age or location was found.

Doctor delay:
Doctor delay occurred in 27% of patients, with a median of six months (range, 2 to 79 months).

The most frequent reason for delay was misdiagnosis from the start, based only on clinical examination in 59%, on clinical examination and radiology (34%), or on biopsy (7%).

Total delay:

Of the high-grade tumours, 85% were diagnosed within six months, 50% without months (45%).

20 Children's and Young People's Cancer

General Recommendations

1 Children and young people who present with symptoms and signs of cancer should be referred to a paediatrician or a specialist children's cancer service, if appropriate. D

2 Childhood cancer is rare and may present initially with symptoms and signs associated with common conditions. Therefore, in the case of a child or young person presenting several times (for example, three or more times) with the same problem, but with no clear diagnosis, urgent referral should be made. D

3 The parent is usually the best observer of the child's or young person's symptoms. The primary healthcare professional should take note of parental insight and knowledge when considering urgent referral. D

4 Persistent parental anxiety should be a sufficient reason for referral of a child or young person, even when the primary healthcare professional considers that the symptoms are most likely to have a benign cause. D

5 Persistent back pain in a child or young person can be a symptom of cancer and is indication for an examination, investigation with a full blood count and blood film, and consideration of referral. C

6 There are associations between Down syndrome and leukaemia, neurofibromatosis and CNS tumours, and between other rare syndromes and some cancers. The primary healthcare professional should be alert to the potential significance of unexplained symptoms in children or young people with such syndromes. D

7 The primary healthcare professional should convey information to the parents and child/young person about the reason for referral and which service the child/young person is being referred to so that they know what to do and what will happen next. D

8 The primary healthcare professional should establish good communication with the parents and child/young person in order to develop the supportive relationship that will be required during the further management if the child/young person is found to have cancer. D

Specific Recommendations

Leukaemia (children of all ages)

9 Leukaemia usually presents with a relatively short history of weeks rather than months. The presence of one or more of the following symptoms and signs requires investigation with full blood count and blood film:
- pallor
- fatigue
- unexplained irritability
- unexplained fever

- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- persistent or unexplained bone pain
- unexplained bruising.

If the blood film or full blood count indicates leukaemia then an urgent referral should be made. [C(DS)]

10 The presence of either of the following signs in a child or young person requires immediate referral:
- unexplained petechiae
- hepatosplenomegaly. C

Lymphomas

Hodgkin's lymphoma presents typically with non tender cervical and/or supraclavicular lymphadenopathy. Lymphadenopathy can also present at other sites. The natural history is long (months). Only a minority of patients have systemic symptoms (itching, night sweats, fever).

Non Hodgkin's lymphoma typically shows a more rapid progression of symptoms, and may present with lymphadenopathy, breathlessness, SVC obstruction, abdominal distension.

11 Lymphadenopathy is more frequently benign in younger children but urgent referral is advised if one or more of the following characteristics are present, particularly if there is no evidence of local infection:
- lymph nodes are non-tender, firm or hard
- lymph nodes are greater than 2 cm in size
- lymph nodes are progressively enlarging
- other features of general ill-health, fever or weight loss
- the axillary nodes are involved (in the absence of local infection or dermatitis)
- the supraclavicular nodes are involved. C

12 The presence of hepatosplenomegaly requires immediate referral. C

13 Shortness of breath is a symptom that can indicate chest involvement but may be confused with other conditions such as asthma. Shortness of breath in association with the above signs (recommendation 1.14.11), particularly if not responding to bronchodilators, is an indication for urgent referral. C

14 A child or young person with a mediastinal or hilar mass on chest X-ray should be referred immediately. C

Brain & CNS Tumours

<u>Children 2 years and older and young people</u>

15 Persistent headache in a child or young person requires a neurological examination by the primary healthcare professional. An urgent referral should be made if the primary healthcare professional is unable to undertake an adequate examination. D

16 Headache and vomiting that cause early morning waking or occur on waking are classical signs of raised intracranial pressure, and an immediate referral should be made. C

17 The presence of any of the following neurological symptoms and signs should prompt urgent or immediate referral:
- new onset seizures
- cranial nerve abnormalities

- visual disturbances
- gait abnormalities
- motor or sensory signs
- unexplained deteriorating school performance or developmental milestones
- unexplained behavioural and/or mood changes. D

18 A child or young person with a reduced level of consciousness requires emergency admission. C

Children < 2 years

19 In children aged younger than 2 years, any of the following symptoms may suggest a CNS tumour, and referral (as indicated below) is required.
- Immediate referral:
  - new onset seizures
  - bulging fontanelle
  - extensor attacks
  - persistent vomiting.
- Urgent referral:
  - abnormal increase in head size
  - arrest or regression of motor development
  - altered behaviour
  - abnormal eye movements
  - lack of visual following
  - poor feeding/failure to thrive.
- Urgency contingent on other factors:
  - squint. C

Neuroblastoma (all ages)
The majority of children with neuroblastoma have symptoms of metastatic disease which may be general in nature (malaise, pallor, bone pain, irritability, fever or respiratory symptoms), and may resemble those of acute leukaemia.

20 The presence of the following symptoms and signs requires investigation with FBC:
- persistent or unexplained bone pain (and X–ray)
- pallor
- fatigue
- unexplained irritability
- unexplained fever
- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- unexplained bruising .[C(DS)]

21 Other symptoms which should raise concern about neuroblastoma and prompt urgent referral include:
- proptosis
- unexplained back pain
- leg weakness
- unexplained urinary retention. C

22 In children or young people with symptoms that could be explained by neuroblastoma, an abdominal examination (and/or urgent abdominal ultrasound) should be undertaken, and a chest X-ray and full blood count considered. If any mass is identified, an urgent referral should be made. [C(DS)]

23 Infants aged younger than 1 year may have localised abdominal or thoracic masses, and in infants younger than 6 months of age, there may also be rapidly progressive intra-abdominal

disease. Some babies may present with skin nodules. If any such mass is identified, an immediate referral should be made. C

Wilms' tumour (all ages)

24 Wilms' tumour most commonly presents with a painless abdominal mass. Persistent or progressive abdominal distension should prompt abdominal examination, and if a mass is found an immediate referral be made. If the child Or young person is uncooperative and abdominal examination is not possible, referral for an urgent abdominal ultrasound should be considered. C

25 Haematuria in a child or young person, although a rarer presentation of a Wilms' tumour, merits urgent referral.C

Soft tissue sarcoma (all ages)

26 A soft tissue sarcoma should be suspected and an urgent referral should be made for a child or young person with an unexplained mass at almost any site that has one or more of the following features. The mass is:

- deep to the fascia
- non-tender
- progressively enlarging
- associated with a regional lymph node that is enlarging
- >2 cm in diameter in size. C

27 A soft tissue mass in an unusual location may give rise to misleading local and persistent unexplained symptoms and signs, and the possibility of sarcoma should be considered. These symptoms and signs include:

- head and neck sarcomas:
  - proptosis
  - persistent unexplained unilateral nasal obstruction with or without discharge and/or bleeding
  - aural polyps/discharge
- genitourinary tract:
  - urinary retention
  - scrotal swelling
  - bloodstained vaginal discharge. C

Bone sarcomas (osteosarcoma and Ewing's sarcoma) (all ages)

28 Limbs are the most common site for bone tumours, especially around the knee in the case of osteosarcoma. Persistent localised bone pain and/or swelling requires an X-ray. If a bone tumour is suspected, an urgent referral should be made. C

29 History of an injury should not be assumed to exclude the possibility of a bone sarcoma. C

30 Rest pain, back pain and unexplained limp may all point to a bone tumour and require discussion with a paediatrician, referral or X-ray. C

Retinoblastoma (mostly children aged under 2 years)

31 In a child with a white pupillary reflex (leukocoria) noted by the parents, identified in photographs or found on examination, an urgent referral should be made. The primary healthcare professional should pay careful attention to the report by a parent of noticing an odd appearance in their child's eye. C

32 A child with a new squint or change in visual acuity should be referred. If cancer is

suspected, referral should be urgent, but otherwise referral should be non-urgent. C

33 A family history of retinoblastoma should alert the primary healthcare professional to the possibility of retinoblastoma in a child who presents with visual problems. Offspring of a parent who has had retinoblastoma, or siblings of an affected child, should undergo screening soon after birth. C

Investigations

34 When cancer is suspected in children and young people, imaging is often required. This may be best performed by a paediatrician, following urgent or immediate referral by the primary healthcare professional. D

35 The presence of any of the following symptoms and signs requires investigation with full blood count:

- pallor
- fatigue
- irritability
- unexplained fever
- persistent or recurrent upper respiratory tract infections
- generalised lymphadenopathy
- persistent or unexplained bone pain (and X-ray)
- unexplained bruising. [C(DS)]

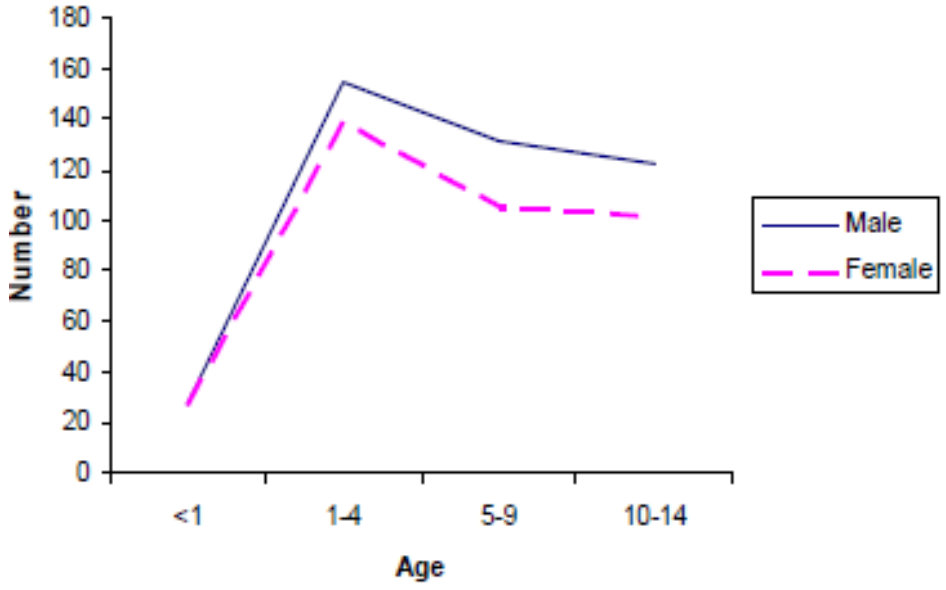
Introduction

The Office for National Statistics estimates that childhood cancers (under 15 years) account for just over 0.5% of all cancers in England and Wales.(17) The mortality rates from childhood cancers has decreased during the past 40 years so that today over 70% of children diagnosed with cancer can be expected to be cured.(411) However, cancer still ranks as the second highest cause of death in children under 15.(411) Adult cancers are predominantly of epithelial origin, but most childhood solid tumours are of mesenchymal or embryonal in origin. The childhood cancers include leukaemia, lymphoma, brain tumours, bone tumours, sarcomas, neuroblastoma, and retinoblastoma. The most common childhood malignancy is acute lymphatic leukaemia (ALL), which accounts for nearly one quarter of all cases. The incidence of the different childhood cancers varies by age, leukaemia and brain cancer tending to be more common in younger children whilst bone and connective tissue cancers have higher incidence in very young or older children with a drop in incidence in the mid age range.

In 2001 there were a total of 807 newly registered cases of childhood and young persons cancers (haematological, urological and brain) of which 372 were in males and 435 in females.

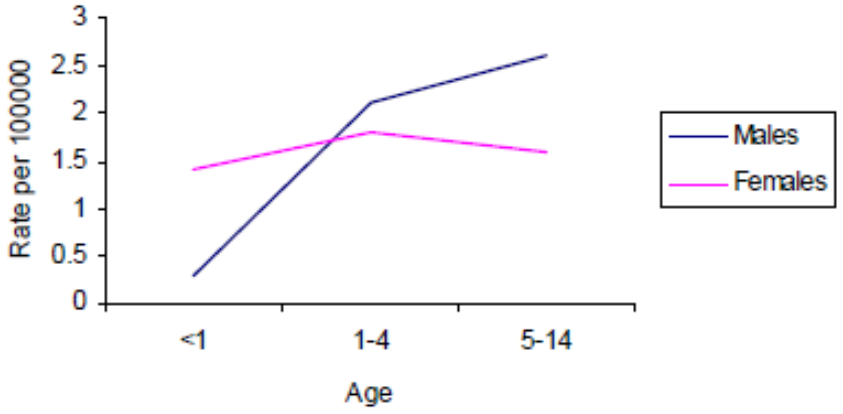
In England and Wales in 2002, 173 males and 122 females aged under 15 years died of cancer (Figure 32). In the 15-19 year age group, there were 86 deaths among males and 65 among females.

Figure 31 2001 Registrations of childhood cancers (haematological, urological and brain) in England and Wales. (77)



Mortality

Figure 32 2002 Mortality rates for childhood cancers (urological, haematological and brain) in England and Wales. (78)



Pathology

Childhood Leukaemia

Leukaemia accounts for one third of childhood cancers.(17) The most common type is acute lymphatic leukaemia(412), the commonest cancer of children, but acute myelogenous leukaemia, juvenile myelomonocytic leukaemia and chronic myelogenous leukaemia also occur(412). The peak incidence of acute lymphatic leukaemia is under five years of age.(411)

Neuroblastoma:

Neuroblastoma is a malignant embryonal tumour derived from neural crest cells and occurring in the sympathetic ganglia, adrenal medulla, and other sites. This is the most common extracranial solid tumour in childhood(413) accounting for 8-10% of all childhood cancers.(411) It most commonly occurs in very young children, with 80% of cases in those aged under four years.

Neuroblastomas are classified according to unfavourable histological groups, based on three factors;

degree of differentiation of neuroblasts, presence or absence of Schwann cells and proliferative index of the tumour.(411) They are heterogeneous and can range from malignant neuroblastomas to benign ganglioneuromas. The favoured staging system is the International Neuroblastoma Staging System presented in Table 30.

Table 30 International Neuroblastoma Staging system (INSS)(411)

Stage	Description
1	Localised tumour confined to area of origin, complete gross excision, positive or negative microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative.
2A	Unilateral tumour with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically.
2B	Unilateral tumour with complete or incomplete gross excision; identifiable ipsilateral lymph nodes positive, and contralateral lymph nodes negative microscopically.
3	Tumour infiltrating across the midline; or unilateral tumour with positive contralateral lymph nodes; or midline tumour with bilateral lymph node involvement.
4	Tumour dissemination to distant lymph nodes, bone, bone marrow, liver or other organs (except 4S).
4S	Localised primary tumour (stage1 or 2) with dissemination limited to skin, liver or bone marrow.

Nephroblastoma (Wilms' tumour)

Nephroblastomas account for 90% of renal tumours in childhood, and (411) over 80% of cases present before the child reaches five. Most Wilms' tumours are unilateral and unicentric.(414) They are embryonal, and associated with several congenital syndromes, although these syndromes account for < 1% of all cases of Wilms' tumours. The favoured staging system is the national Wilms' tumour study group shown in Table 31.

Table 31 National Wilms' Tumour Study Group staging system for Wilms' tumour(411)

Stage	Description
Stage I	Completely excised tumour with intact tumour capsule, no involvement of the vessels of the renal sinus, no evidence of tumour at or beyond the margins of the resection.
Stage II	Completely excised tumour which extended beyond the kidney. Blood vessels outside the renal parachyma may contain tumour. Status post-biopsy or tumour spillage limited to the flank and involving the peritoneal surface, no evidence of tumour at the margins of the resection.
Stage III	Residual non-haematogenous tumour confined to the abdomen with any of the following: (1)positive lymph node involvement within the abdomen or pelvis; (2) penetration of the tumour to the peritoneal surface; (3) peritoneal tumour implants; (4) positive tumour margins; (5) incompletely respectable tumour; (6) tumour spillage outside the flank.
Stage IV	Haematogenous metastases (lung, liver, bone, brain, etc) or lymph node metastases outside the abdomen or pelvis.
Stage V	Bilateral renal involvement at diagnosis.

Rhabdomyosarcoma, Osteosarcoma and Ewing's sarcoma

Sarcomas arise from bone, cartilage, connective tissue or muscle, and usually arise at an older age than embryonal tumours. Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents with an incidence of around 0.4-0.7 per 100,000 children aged 15 or younger. Although originating from the striated muscle it can occur in tissue or organs where striated muscle is not found; the staging system is based on surgico-pathological clinical grouping (*Table 32*). Most cases are sporadic, but the cancer has been associated with some familial syndromes

including neurofibromatosis.

Table 32 Clinical group staging for Rhabdomyosarcoma. (411)

Group		Disease extent
I	A	Localised tumour, confined to site of origin, completely resected.
	B	Localised tumour, infiltrating beyond site of origin, completely resected.
II	A	Localised tumour, gross total resection, microscopic residual disease
	B	Locally extensive tumour (spread to regional lymph nodes), completely resected.
	C	Locally extensive tumour (spread to regional lymph nodes), gross total resection, but microscopic residual disease.
III	A	Localised or locally extensive tumour, gross residual disease after biopsy.
	B	Localised or locally extensive tumour, gross residual disease after 'major' resection (>50% debulking)
IV		Distant metastases

*Permission to reproduce being sought.

Osteosarcoma is the most common malignant bone tumour in children, accounting for approximately 5% of childhood cancers. (413) It usually originates in the metaphysis of long bones, particularly the distal femur, proximal tibia, proximal femur, and humerus. Between 60 and 80% are said to arise around the knee in younger patients.

The second most common malignant bone tumour is the Ewing's sarcoma group, which includes Ewing's sarcoma and peripheral primitive neuroectodermal tumours.(413) Most patients with Ewing's sarcoma are between ten and 15 years old. It typically arises in the axial skeleton, the commonest sites being the pelvic bones, femur, humerus and ribs.

Retinoblastoma

Retinoblastomas arise in the embryonic neural retina with a frequency of one in 15,000-18,000 live births in developed countries. It is often present at birth and 80% of cases occur prior to the child reaching four years.(411) Inherited retinoblastoma is an autosomal dominant trait, although 60% of cases are non-hereditable and unilateral. The remaining 40% are hereditable, of which 15% are unilateral and 25% bilateral. It is staged using the Reese-Ellsworth system.(411)

Table 33 Reese-Ellsworth staging classification of retinoblastoma(411)

Group I: very favourable

A Solitary tumour smaller than 4 disk diameters (at or behind equator)
B Multiple tumours smaller than 4 disk diameters (at or behind the equator)

Group II: favourable
A Solitary tumour 4-10 disk diameters (at or behind equator)
B Multiple 4-10 disk diameters (at or behind equator)

Group III: doubtful

A Any lesion anterior to the equator
B Solitary tumours larger than 10 disk diameters behind the equator

Group IV: unfavourable

A Multiple tumours, some larger than 10 disk diameters B
Any lesion extending anteriorly to the ora serrata

Group V: very unfavourable
A Tumours involving more than half the retina
B Vitreous seeding

Review of clinical audits

The review(13) identified nine relevant clinical audits. The proportion of two week wait referrals that were found to be in accordance with the symptoms in the guidelines ranged from 91% to 100%. The proportion of two week referrals considered to be clinically appropriate ranged from 60% to 100%. No patient referred under the two week system was subsequently diagnosed with cancer (three audits).

20.4 Signs and Symptoms

20.4.1 Key Clinical Question:

In children and adolescents attending primary care services, which symptoms and signs and other features including family history, when compared with the 'gold standard', are predictive of a diagnosis of cancer, and which symptoms and signs are not? Are any non-clinical features associated with a diagnosis of cancer?

20.4.2 Evidence Question:

In people attending primary care services with childhood problems, which symptoms and signs and other features including family history when compared with the 'gold standard' are predictive of a diagnosis of cancer, and which are not?

20.4.3 Evidence Statements:

Leukaemia

Symptoms associated with leukaemia in children and adolescents include fatigue/tiredness, upper respiratory tract infection, fever, abdominal pain, lymphadenopathy, headache, and anorexia. (III)

Leukaemia usually presents with a relatively short history of weeks rather than months. (III)

Lymphomas

Hodgkin's lymphoma presents typically with non tender cervical/supraclavicular lymphadenopathy. Lymphadenopathy can also present at other sites. The natural history is long (months). Only a minority of patients have systemic symptoms (itching, night sweats, fever). (III)

Non Hodgkin's lymphoma typically shows a more rapid progression of symptoms, and may present with lymphadenopathy, breathlessness, SVC obstruction, abdominal distension. (III)

Brain and CNS tumours

Symptoms associated with brain tumours in children and adolescents include headache, vomiting, visual problems, convulsions, behavioural problems, and neurological symptoms. (III)

Bulging fontanelles and/or enlargement of the head may also be present in infants < 1 yr. (III)

Papilloedema is more likely to be present in children over 18 months of age. (III)

Neuroblastoma

Neuroblastomas occur at different sites, and the presenting features depend on the site. The most common presenting feature is a swelling. (III)

The majority of children with neuroblastoma have symptoms of metastatic disease which may be general in nature (malaise, pallor, bone pain, irritability, fever or respiratory symptoms), and may resemble those of acute leukaemia. (III)

Bone and soft tissue sarcomas

The most common presenting feature in osteosarcoma and Ewing's sarcoma is local tenderness, often in association with a mass or pain on movement of a joint. (III)

The most common presenting feature of fibrosarcomas is an enlarging soft-tissue mass. (III)

Retinoblastoma

Leukocoria and strabismus are the most common presenting signs in retinoblastoma. (III)

Secondary studies

No relevant systematic reviews were identified.

Primary studies

Leukaemia

(Jonsson et al, 1990)(415)

This retrospective study undertaken over 13 years in the US sought to establish the relationship between bone pain and haematologic findings in patients with acute lymphoblastic leukaemia. The aim of the study was to assess the association between bone pain preceding the diagnosis and the initial haematologic values. The records of all patients diagnosed with acute lymphatic leukaemia in one specialist centre between January 1976 and December 1988 were reviewed. 296 eligible patients were grouped according to the presence or absence of bone pain: 179 (60%) had no bone pain (group 1); 65 (22%) had some bone pain (group 2); 52 (18%) had prominent bone pain that overshadowed other haematologic manifestations of the leukaemia (group 3).

The haematologic indices were relatively normal in patients presenting with musculoskeletal signs and symptoms as a prominent presenting manifestation of acute lymphatic leukaemia. Patients with prominent bone pain could experience diagnostic delay because their haematological values appeared normal. The haemoglobin and platelets were higher and blast cell and leucocyte counts lower among children with severe bone pain. Statistically significant differences were found between the groups for haemoglobin concentration ($p<0.001$), leukocyte count ($p=0.014$), absolute neutrophil count ($p=0.001$), percentage of circulating blast cells ($p=0.009$) and platelet count ($p<0.001$). In groups 1 and 2, the interval between onset of symptoms and diagnosis was 21 days, but was 38 days in group 3.

(Thulesius, 2000)(416)

The diagnosis of malignant tumours in children between the ages of 0-16 was described from a primary care perspective in a Swedish county. Hospital data on the signs and symptoms of 68 children with paediatric malignancies were gathered between 1984-1995. 72 children were reported to the regional tumour registry during the study period. Four children were excluded because their tumours could not be classified as malignant.

Mean age at diagnosis was 7.8 years. Leukaemia was the diagnosis in 25 children (39%) and brain tumours in another 22 (34%). The remaining malignancies were renal tumours (4), neuroblastoma (3), gut carcinoid (2), non- Hodgkin's lymphoma (2), thyroid cancer (2), malignant teratoma (1), Hodgkin's disease (1), retinoblastoma (1) and osteosarcoma (1).

The most common initial symptoms for leukaemia were fatigue, upper respiratory tract infections.

Table 34 Frequency of initial symptoms for children with leukaemia(416)

Symptoms	Frequency
Fatigue	14/25
Upper respiratory tract infection	11/25
Fever	10/25
Abdominal pain	4/25
Joint pain	4/25
Lymphadenopathy	4/25
Headache	3/25
Anorexia	3/25

Paediatric brain and CNS tumours

(Dobrovoljac et al, 2002)(417)

Patient characteristics most strongly associated with brain tumours in children were studied in order to identify factors related to the pre-diagnostic symptomatic interval in Switzerland. The study included a total of 252 patients admitted consecutively to a Swiss children's hospital between January 1980 and December 1999. There were 150 (60%) males and 102 (40%) females.

At the time of diagnosis, only 30 (12%) patients were monosymptomatic. All other patients had two (N=28), three (N=31), four (N=33), five (N=29), six (N=33) and seven (N=27) or more (N=41) signs/symptoms. Increased intra-cranial pressure (indicated by one or more of headache, nausea/vomiting, papilloedema, sixth nerve palsy, head enlargement, gaze depression, bulging fontanelle, separation of cranial sutures) was noticed in 124 (49%) patients at sign/symptom onset and in 186 (74%) patients at diagnosis. Of these, 74% had hydrocephalus. Common diagnostic difficulties included the correct interpretation of headache, nausea/vomiting, seizures, behavioural changes and squint/diplopia.

Table 35 Frequency of initial signs and symptoms depending on age(417)

Signs and symptoms	All (N=252)	Age <2 yrs (N=50)	Age ≥ yrs (N=202)
Headache	35%	2%	43%
Nausea/vomiting	26%	18%	28%
Seizures	14%	20%	12%
Behavioural changes	10%	12%	9%
Ataxia	8%	8%	8%
Squint/diplopia	8%	6%	8%
Lethargy	5%	4%	5%
Hemiparesis/quadriparesis	5%	8%	4%
Head tilt	5%	12%	3%
Anorexia	3%	6%	2%
Growth failure	3%	-	3%
Sleep disturbance	2%	2%	2%
Polyuria/polydipsia	2%	-	3%
Visual loss	2%	2%	2%
Weight loss	2%	4%	1%
Facial nerve palsy	2%	4%	1%
Enlargement of the head	2%	8%	-
Cranial neuropathies other than III, IV, VI, VII	1%	-	1%
Gaze depression/separation of cranial sutures/bulging fontanelle	1%	4%	-
Dizziness	1%	-	1%
Nystagmus	1%	4%	-
Papilloedema	1%	-	1%
Amenorrhoea	0.5%	-	0.5%
Proptosis	0.5%	-	0.5%

Age had a statistically significant correlation with pre-diagnostic symptom interval for parental delay which was shorter for younger compared with older children r=0.16, P<0.0001. Doctor's delay did not correlate significantly with age.

(Jooma, 1984)(418)

In this case series, the histories of 100 infants presenting to the Neurosurgical Unit of the Hospital for Sick Children in London 1953-1981 with intracranial tumours symptomatic during the first year of life were studied retrospectively. A clinical or histological diagnosis of intracranial neoplasm was made in 1296 children. Eighty-six of these had presented while under the age of 1 year and a further 14, although aged 13 or 14 months at presentation, had been symptomatic during the first year of life and were therefore included in the study.

Sixty of the 100 neoplasms were supratenetorial. A tissue diagnosis was available in 80 cases, 68 following operation and 12 following autopsy. The most common symptoms reported by the parents were vomiting and alteration of psychomotor development. In seven patients a febrile illness preceded more specific symptoms of raised intracracranial pressure, whereas in six a head injury had recently occurred. A head tilt was noted in seven infants with infratentorial tumours and in two each of the infants with hemispheric and axial lesions. Macrocrania and signs of raised intracranial pressure were recognised in a majority of the children. Ten patients with suprasellar tumours had rotary nystagmus or bizarre eye movements. Behavioural disturbances with irritability, somnolence and indifference to surroundings were commonly reported and were important if combined with loss of a previously acquired motor skill or arrest of development. The following signs were observed in infants: papilloedema (N=36), optic atrophy (N=10), nystagmus or abnormal eye movements (N=22), sixth nerve palsy (N=17), seventh nerve palsy (N=13), altered limb tone (N=35), hemiparesis (N=16), truncal ataxia (N=10), abnormal neck posture (N=20), neck stiffness (N=9).

(Thulesius, 2000)(416)

The diagnosis of malignant tumours in children between the ages of 0-16 was described from a primary care perspective in a Swedish county. Hospital data on the signs and symptoms of 68 children with paediatric malignancies were gathered between 1984-1995. 72 children were reported to the regional tumour registry during the study period. Four children were excluded because their tumours could not be classified as malignant.

Mean age at diagnosis was 7.8 years. Leukaemia was the diagnosis in 25 children (39%) and brain tumours in another 22 (34%). The remaining malignancies were renal tumours (4), neuroblastoma (3), gut carcinoid (2), non- Hodgkin's lymphoma (2), thyroid cancer (2), malignant teratoma (1), Hodgkin's disease (1), retinoblastoma (1) and osteosarcoma (1).

Children with brain tumours presented initially with headache, vomiting and disturbances of gait and vision.

Table 36 Frequency of initial symptoms for children with leukaemia or a brain tumour(416)

Symptoms	Frequency
Headache	11/22
Vomiting	6/22
Visual problems	6/22
Convulsions	3/22

(Keene et al, 1999)(419)

A 19 year retrospective case review was undertaken of primary brain tumours in persons younger than 18 years of age at the time of diagnosis who presented at a specialist Canadian centre between 1975 and 1993. The data were used to examine changes in presenting signs and symptoms on the basis of anatomic location and histologic tumour type. There were 200 new cases of primary intracranial neoplasms in children. Loss to other centres at the time of diagnosis was believed to be nonexistent. All tumours were pathologically proven cases except those relating to the brain stem for which only radiological diagnosis was undertaken. The mean age of the entire group was eight years.

Hemispheric tumours occurred in 52 patients. The presenting signs were seizures 60%, headache 37%, vomiting 23%, changes in behaviour or personality 11%, facial asymmetry 9% and visual difficulties 6%. The initial findings on examination included one or more of the following: no abnormalities (51%), hemiplegia 34%, signs of increased intracranial pressure 23%, cranial nerve dysfunction 3% and macrocrania 3%.

Supratentorial axial or midline tumours occurred in 50 patients. The presenting signs for tumours arising from axial structures included one or more of the following: non-specific headache 60%, polyuria 35%, non-specific malaise 10%, short stature 10% and visual difficulties 5%. The findings on initial examination at the time of diagnosis included signs of increased intracranial pressure 30%, visual field disturbances 25%, and optic atrophy 15%.

Cerebellar tumours were present in 74 patients. The presenting symptoms included vomiting, headache 62%, and in-coordination 55%. The frequency of clinical signs included ataxia 69%, increased intracranial pressure 57%, nystagmus 31%, head tilt 14%, cranial nerve palsies 28% and macrocrania 10%. *Brainstem tumours* affected 19 children. Patients experienced gait difficulties 83%, squint 50%, headaches 25%, vomiting 25% and swallowing difficulties 8%. The initial examination included findings of cranial nerve VI dysfunction 67%, ataxia 50%, cranial nerve VII dysfunction 42%, nystagmus 33%, hemiplegia 33% and head tilt 33%.

(Mehta et al, 2002)(420)

Retrospective and prospective data were collected on 104 Canadian cases of paediatric brain tumours to establish incidence rates as well as identify factors important to a diagnosis. All patients 17 years or younger who were diagnosed as having a brain tumour between 1995 and 2000 at one Canadian specialist centre were included in the study if they were resident within certain local provinces. The brain tumour diagnoses were based on histological findings, serum markers or imaging results.

69 children (66%) exhibited vomiting or nausea as a presenting symptom. Nine of those children did not experience associated headaches. Five of these nine patients experienced vomiting for more than one month. 66 of the children (63%) complained of headaches or exhibited behaviour that indicated its presence (such as clutching the head). 37% (seven of 19) children less than four years of age exhibited behaviour that could be positively confirmed as indicating headaches. Among older children, 76% (28 of 37 children) and 67% (31 of 46 children) of those four to eight and nine to 17 years of age respectively had complaints of headaches as one of their presenting symptoms. Great variation existed among children in the characteristics of their headaches. Many children experienced headaches that occurred at any time of day, headaches that responded to paracetamol (acetaminophen) and headaches that were relieved with vomiting. Among the 66 children with histories of headaches, 85% (56 of 66 children) exhibited evidence of either nausea or vomiting at some point during their histories.

Many children did not experience headaches that increased in intensity, duration or frequency. 23 patients (22%) did not exhibit evidence of headaches, nausea or vomiting. Among these 23 cases, 18 presented with either a seizure or a focal neurological deficit. The most common neurological findings were focal weakness and cranial nerve dysfunction. Behavioural changes, failure to reach certain milestones and incidental imaging findings were responsible for identification in the remaining five cases. Of the 104 children, 52 exhibited behavioural changes, which were most often described as changes in temperament.

(Flores, 1986)(421)

This retrospective case series examined and compared delay from symptom onset to diagnosis in US children with primary brain tumours (79), Wilms' tumours (45) and acute leukaemia (123). The methodology employed in selecting the cases was not described in detail. In 65 (82%) the diagnosis was made after performing a biopsy. Fourteen children did not undergo biopsy and the diagnosis of a brain tumour was made on radiological evidence only.

The patients were all less than 20 years of age at diagnosis with a mean age for brain tumours of 7.6 years, 3.6 for Wilms' tumour and seven years for acute leukaemia. Common presenting symptoms and signs in children with brain tumours were ataxia and abnormalities in gait observed in the zero to five year old patients. Headaches were described more frequently in the six to 20 year old age group. Seizures were observed in the six to 20 year old group, while none were recorded among children zero to five years of age. Nausea and vomiting frequently occurred in all groups. The severity of the presenting symptoms and signs were graded as follows. Grade 1: single symptom such as headache, vomiting, weight loss or mood or behavioural changes with normal neurological findings. Grade 2: included grade 1 symptoms plus papilloedema, or seizures. Grade 3: included grade 2 symptoms and signs in conjunction with focal neurological deficits such as cranial nerve palsies, visual field deficits and gait, motor, cerebellar or sensory deficits. Grade 4: included grade 3 symptoms and signs along with depressed level of consciousness or coma.

Of the 79 patients, seven could be classified as grade 1, 14 as grade 2, 38 as grade 3 and two as grade 4. One patient with grade 4 symptoms had an ependymoma and the other had a medulloblastoma. There were 18 patients who could not be classified with this scale because insufficient information had been recorded in the clinical notes.

(Honig, 1982)(422)

The hospital records of 105 children consecutively diagnosed in one specialist centre in the US with brain tumours from 1965-1978 were reviewed to investigate occurrence and features of headaches at presentation. The final diagnosis of brain tumour included 29 gliomas (28%), 22 astrocytomas (21%), 15 medulloblastomas (14%), 14 craniopharyngiomas (13%), and 25 other varied tumours (24%).

Of the 105 children, 72 (69%) had associated headaches. Headaches were occipital in location in 16 children (28%), unilateral in 13 (22%) and diffuse in 29 (50%). 32 children (67%) were either awakened from sleep by the pain or were in pain on arising. Eight of 61 children had unusually severe or prolonged headaches and 19 (31%) had changes in headache frequency or severity. Vomiting was described as intermittent in 26 of 72 (36%), daily in eight of 72 (11%) and pernicious in two of 72 (3%). The vomiting was described as intermittent in 26 of 72 (36%), daily in eight of 72 (11%) and pernicious in two of 72 (3%). The vomiting increased in frequency (four patients) or first began (11 patients) following the onset of the headaches in 15 of 72 children (21%). In nine of these 15, the change coincided with increased frequency or severity of the existing headache pattern. Five patients were vomiting prior to the onset of their headaches.

68 children (94%) with headaches had neurologic and/or ocular signs at the time of diagnosis. In 60 of these, signs developed following the onset of their headaches. Thirty-three of 60 (55%) had

findings within two weeks and 51 (85%) had an abnormality on physical examination within two months of the onset of their headaches. Within four months, 53 of 60 (88%) had neurological and/or ocular signs. The numbers of patients with ocular signs and symptoms were papilloedema (42), diplopia (11), decreased acuity (8), squint (9), nystagmus (5), optic atrophy (4), blurred vision (3), blindness (2), failure of upward gaze (2), anisocoria (1), optic atrophy on side of tumour and papilloedema of the opposite disc (1).

(Tomita et al, 1985)(423)

This US case series aimed to describe the anatomical distribution of brain tumours, their clinical presentation and the results of treating 100 patients in the US during the first 24 months of life. During the period 1952-1984, 608 infants and children with intracranial tumours were treated at a children's hospital in Chicago. One hundred of these (16.4%) had been diagnosed and treated during the first 24 months of life. There were 57 males and 43 females. The histological classification was confirmed with the exception of three children. Group 1 comprised 57 children who were diagnosed and treated during the first 12 months and the remaining 43 at 13 to 24 months of age as indicated in Table 37 and Table 38.

The majority of cerebellar fourth ventricle tumours were malignant, predominantly medulloblastomas. Among cerebral hemispheric-lateral ventricle tumours, choroid plexus papillomas and benign astrocytomas were most common. Of the suprasellar third ventricle tumours, benign astrocytomas comprised 72.4%. Approximately 50% of group 1 with either infratentorial or supratentorial tumours showed macrocephaly beyond the 95th percentile, whereas 25% of group 2 had macrocephaly. Approximately 72% of the anterior fontanelles of the patients harbouring either infratentorial or supratentorial tumours were full, bulging or tense. Hydrocephalus was almost invariably present in association with infratentorial tumours, but its incidence was less in cases with supratentorial tumours (62%). Papilloedema was infrequent despite the high incidence of hydrocephalus and macrocephaly. The incidence of papilloedema was 26.3% in the cases with infratentorial tumours and 18.4% in the cases with supratentorial tumours in group 1, and was 52.6% and 25.0% respectively in group 2.

Table 37 Reasons for neurosurgical consultation(423)

Reason	Group 1 (no. of cases)		Group 2 (no. of cases)		Total
	Infra-tentorial	Supra-tentorial	Infra-tentorial	Supra-tentorial	
Vomiting	11	13	9	8	41
Lethargy/irritability	8	11	10	5	34
Increasing head size	8	18	1	1	28
Gait disturbance	0	1	14	2	17
Failure to thrive	2	7	2	6	17
Seizure	1	6	2	6	15
Developmental arrest	5	3	2	0	10
Delayed milestones	2	4	0	2	8
Peculiar eye movement	0	4	0	3	7
Decreased vision/blindness	0	2	0	5	7
Coma	1	2	0	2	5
Weakness of extremities	0	2	2	1	5
Head tilting	1	0	4	0	5
Head nodding	2	1	0	0	3
Ocular strabismus	0	0	2	1	3
Precocious puberty	0	0	0	2	2
Proptosis	0	1	0	0	1
Nasal discharge	0	1	0	0	1
Facial weakness	0	0	1	0	1
Scalp swelling	0	0	0	1	1
Total	19	38	19	24	100

Table 38 Signs of brain tumours during the first 24 months of life(423)

	Group 1 (no. of cases)		Group 2 (no. of cases)		
Reason	Infra-tentorial	Supra-tentorial	Infra-tentorial	Supra-tentorial	Total
Hydrocephalus	18	28	17	10	73
Full fontanelle	16	26	5	5	52
Macrocephaly	10	19	5	6	40
Papilledema	5	7	10	6	28
Ataxia	4	0	14	1	19
Optic atrophy	2	6	1	9	18
Lethargy	2	7	3	4	16
Hemiparesis	4	5	4	3	16
Ocular nystagmus	1	7	3	3	14
Abducens palsy	4	3	2	2	11
Poor head control	6	3	0	0	9
Facial palsy	3	1	2	1	7
Hypotonia	4	0	2	1	7
Decreased vision	0	2	0	5	7
Head tilting	1	0	4	0	5
Head asymmetry	0	4	0	1	5
Spasticity	1	4	0	0	5
Stiff neck	2	0	2	0	4
Vocal cord palsy	1	0	1	0	2
Hemianopia	0	2	0	0	2
Total	19	38	19	24	100

(Farwell, 1978)(424)

This US case series reported the symptoms associated with intracranial neoplasms in 54 infants (18 months of age or younger) presenting during a 40- year period from 1935-1974. Histologically verified cases of intracranial neoplasms occurring in infants were selected from the Connecticut tumour registry.

Tumours developed in 26 males and 28 females. The symptoms with which these infants presented fat diagnosis were vomiting (47%), increasing head size (32%), lethargy (19%), convulsions (13%), paresis (9%), cranial nerve palsies (9%) and ataxia (6%). The physical findings at diagnosis indicated that 20 patients had an increased head circumference. A bulging fontanelle was reported in 12 cases (27%). Eleven infants (25%) had cranial nerve palsies. Papilloedema (16%) and nuchal rigidity (16%) were each seen in seven instances. Two patients (4%) were comatose and another five (16%) had a diminished level of consciousness. Other findings included ataxia (7%), nystagmus (11%), hemiparesis (9%), hyperreflexia (16%), hypertonia (9%), irritability (6%), hyptonia (11%), extracranial masses (4%) and hyperalertness (6%). Vomiting was the only symptom, besides enlargement of the head that occurred in more than six children. The loss of a previously acquired skill such as rolling over, sitting or crawling was a symptom observed in seven patients, and in two of these, it was the only symptom in addition to abnormal growth of the head. The physical findings were more varied than the symptoms. Nearly half of the children had an increased head circumference, often accompanied by a bulging fotanelle or prominent veins over the scalp. Papilloedema was noted in two children. Cranial nerve palsies occurred in infants with tumours in all locations. However, nystagmus occurred in cerebral hemisphere or brain stem tumours only and was not found in cerebellar tumours.

(Farwell et al, 1984)(425)

The records of the Connecticut Tumour Registry were reviewed for cases of central nervous system tumours presenting over a 40 year period. All the cases of CNS tumours in patients aged 13 to 19 years at the time of diagnosis were selected. Of the total of 144 CNS neoplasms, 133 tumours occurred intracranially and 11 were intraspinal.

Presenting symptoms included those that resulted from increased intracranial pressure as well as those that were local effects of tumours. The most common symptoms were headache (N=65), nausea or vomiting (N=53) and diplopia (30). Visual disturbances such as blurred vision (N=18), dim vision or field deficits were next in frequency followed by ataxia (N=15) and then mental status change (N=8) or longstanding retardation. Less common symptoms included paresis (N=7) and vertigo (N=7). At the time of diagnosis, papilloedema was present in 41 patients.

Neuroblastoma

(Wilson, 1974)(426)

The signs and symptoms, recurrence and survival rates were reported in this UK cohort study of neuroblastoma based on 639 cases followed up for more than five years. The data were collected as part of the Oxford survey of childhood cancers, identified through both registrations and death certificates for children with neoplastic disease in England, Scotland and Wales.

Objective outcome measures were used including long term survival and recurrence rates. Histological confirmation was available for 487 patients although data on all 639 cases were used for reporting the signs and symptoms of neuroblastoma. Five year survival rates enabled the authors to establish associations affecting prognosis, including age at diagnosis, site, histological grade and the sex of the child.

The signs and tumours were varied because they arose in a range of sites. Up to three symptoms

were recorded for each case. Abdominal swelling was most commonly a symptom in the youngest age group, its frequency decreasing with increasing age. The same relationship was evident to a lesser extent for the symptoms of breathlessness and stridor. Conversely, pain was a relatively uncommon symptom in very young children. It was more often reported by older children though this was presumably partly due to the greater ease in eliciting this symptom. Those symptoms related to nerve involvement were also more often reported for older children. There was little difference between the two sexes in the type of symptom reported. The figures reflected the infrequent incidence of abdominal tumours (of the adrenal, abdominal sympathetic ganglia and liver) and thoracic tumours in the youngest age groups while those occurring in the spinal canal and brain were more frequent among older children.

Table 39 Percentage of patients reporting various symptoms by sex and age groups(426)

		% Reporting each symptom							
Age	No.	Abdominal swelling	Febrile illness	Malaise	Pain	Genito-urinary	Respiratory	Swelling other than abdominal	Nerve involved
<1 yr	152	44	9	15	7	30	11	30	8
1	118	43	11	48	12	19	6	38	12
2-4	201	39	8	43	52	27	3	29	20
5-9	111	19	12	23	72	19	5	34	25
10-14	57	14	12	18	75	21	4	37	26

(Mag et al, 1999)(427)

This was a retrospective case series of patients with neuroblastoma diagnosed and treated between June 1982 and February 1997, and was undertaken to investigate presenting features and their prognostic significance. The cases consisted of 78 children ≤12 years of age who had been admitted to one specialist centre in Malaysia. Disease-free survival from diagnosis was the outcome variable of interest. The ages ranged from 0.1 to 11 years old. The diagnosis in all patients was based on tissue biopsy specimen.

The tumour originated from the adrenal glands in 83% and the majority of cases presented at advanced stages III and IV. The main presenting signs and symptoms in decreasing order were pallor, fever, abdominal mass, weight loss and bone/joint pain. Weight loss was reported in 36% and bone or joint pain in 33% of patients. Other presenting symptoms or signs were bleeding, infection or sepsis, seventh nerve palsy and bilateral leg swelling. It was established that the nitial stage at diagnosis was a significant prognostic factor (P=0.03). Low haemoglobin level had an unfavourable prognostic impact (P=0.04).

Soft tissue sarcomas

(Soule et al, 1977)(428)

This US study provided limited information on the presenting features of childhood fibrosarcomas. The clinicopathologic findings were studied in 110 infants and children. A total of 70 cases were identified from the literature and 40 cases were drawn from the author's own files. Cases were included if there was reasonable assurance of a correct histologic diagnosis along with sufficient clinical information to ensure meaningful data. 26 of the 40 lesions were from patients who were seen at the Mayo Clinic between the years 1914 and 1975. The remaining 14 tumours had been referred for evaluation over a nine year period.

The primary symptom of most patients was that of a mass or swelling in the soft tissues. Most of the lesions were enlarging, and with the exception of the congenital tumours were known to have been present from a few weeks to four years. Four patients first complained of discomfort or pain before a tumour was apparent. In some the skin had become tense, shiny and red. One congenital lesion became ulcerated and exhibited partial destruction of the adjacent tibia and fibula by the 13th day of life.

(Golden et al, 2002)(429)

This US study was a case series that included 150 infants and children with malignancy of the abdomen since January 1985. Of children either younger than one year or older than ten years, 26% (11/43) had normal abdominal examinations at diagnosis, compared with only 9% (7/78) of all the remaining children. The authors investigated how these masses were characterised on physical examination. Not all children had every aspect of their masses described fully, but patterns could be identified: 70% (49/70) were distinguished as nontender, 79% (11/14) were recorded as being nonmobile, and at least 87% (61/70) were firm. Not all malignant masses were defined as nontender.

Osteosarcoma and Ewing's sarcoma

(Widhe, 2000)(401)

A retrospective study was undertaken in Sweden to report the initial symptoms and signs of osteosarcoma and Ewing's sarcoma as described in the records of the first medical consultation. The case series of patients with osteosarcoma (61 male and 41 female) or Ewing's sarcoma (28 male and 19 female) were identified from the national population based Swedish Cancer Register of all patients ≥30 years. Records from the first medical visit due to symptoms related to the bone tumour were obtained for 102 patients with osteosarcoma and 47 with Ewing's sarcoma diagnosed between 1983-1995.The ratio of males to females was 1.5:1 for both osteosarcoma and Ewing's sarcoma. The mean age of patients with osteosarcoma was 15.8 years (range 5.5 to 29.5 years) compared with 15.4 years (range 2.5 to 26.0 years) for patients with Ewing's sarcoma. 75 (74%) of the osteosarcomas and 11 (23%) of the Ewing's sarcomas were located around the knee. Most patients consulted because of regional pain alone or in combination with a palpable mass. A palpable mass was reported at the first visit in 40 (39%) of the patients with osteosarcoma and 16 (34%) of those with Ewing's sarcoma. Four patients with osteosarcoma and five with Ewing's sarcoma did not report pain at the first medical visit and had a palpable mass only. 21 (21%) of the osteosarcomas and nine (19%) of the Ewing's sarcomas caused pain at night. 87 (85%) of the patients with osteosarcoma and 30 (64%) of those with Ewing's sarcoma reported pain related to strain. Intermittent pain at rest was reported by 57 (56%) and 27 (57%) patients respectively. 48 (47%) of the patients with osteosarcoma and 12 (26%) of those with Ewing's sarcoma related the onset of symptoms to trauma occurring at about the time the symptoms began that were of a similar type and magnitude as those experienced regularly in common sports. Tendinitus was the most common initial misdiagnosis for 32 (31%) of the osteosarcomas. Patients with Ewing's sarcoma often reported relapsing fever and periods of pain that were followed by few or no symptoms, which misled doctors into believing the condition, was resolving spontaneously.

Retinoblastoma

(Abramson, 1998)(430)

A total of 1265 patients who were on file at New York Hospital and diagnosed as having retinoblastoma between 1960-1990 were included in this case series. Records were reviewed to describe the presenting symptoms and signs. Thirty-two distinct presenting signs of retinoblastoma were identified, the most common of which were leukocoria (56.2%), strabismus (23.6%), poor vision (7.7%) and family history (6.8%).

Table 40 Frequency and percentage of presented signs(430)

Presenting sign	Frequency	%	Presenting sign	Frequency	%
White reflex (leukocoria)	710	56.1	Macrophthalmia/ buphthalmia	9	0.7
Strabismus	298	23.6	Photophobia	7	0.6
Direction not specified	99	7.8	Conjunctivitis	6	0.5
Estropia	133	10.5	Headaches	6	0.5
Exotropia	66	5.2	Proptosis	6	0.5
Unknown presenting sign	125	9.9	Vomiting	6	0.5
Poor vision	98	7.7	Kept eye closed	5	0.4
Family history	86	6.8	Microphthalmia	4	0.3
Irritation	54	4.3	Orbital cellulitis	3	0.2
Routine examination (including for trauma)	36	2.8	Anorexia/ failure to thrive	2	0.2
			Hyphema	2	0.2
'Something looked wrong'	25	2.0	Metastasis/ growths	2	0.2
Anisocoria	24	1.9	Nausea	2	0.2
Heterochromia iridis	23	1.8	Ptosis	2	0.2
Inflammation	23	1.8	Aniridia	1	0.1
Pain	19	1.5	Phthisis	1	0.1
Discharge	16	1.3	Ruptured globe	1	0.1
Nystagmus	13	1.0	Vitreous haemorrhage	1	0.1

Presenting signs and symptoms of retinoblastoma (n=1265)

Leukocoria, the most common presenting sign, was associated with more advanced disease ($p<0.005$). Strabismus correlated strongly ($p<0.005$) with macular involvement. All eyes with strabismus proved to have either tumour in the macula or a retinal detachment at the macula. No statistically significant correlation was found between laterality, sex or race and any

presenting sign or between survival and any intraocular presenting sign.

Risk Factors

Three relatively recent reviews have been cited which provide a summary of risk factors associated with childhood cancer.

Secondary studies

(Linet et al, 2003)(431)

This review summarized risk factors for sarcomas, brain and haematological cancers. The risk factors are classified into **known** (there is good evidence about the role of risk factors), **suggestive** (evidence is fairly strong but not confirmatory), and **limited** (the factor may be a risk but little evidence is available).

Childhood leukaemias

The *known* risk factors are: gender (higher incidence in females in both Acute lymphoblastic (ALL) and acute myeloid leukaemia (AML)); age (peak incidence in those aged 2-4 years for ALL and in infancy for AML); race (incidence ratio white:black, ALL=2.0, AML=1.0); inonising radiation; therapeutic, congenital disorders, ataxia telangiectasia, Fanconi and Bloom syndromes, neurofibromatosis, postnatal ALL and AML Down syndrome; and ALL and AML M7.

Suggestive risk factors for ALL are maternal fetal loss, a mother over 35 years at time of pregnancy and the child being the first born. For AML they are maternal alcohol use during pregnancy, parental occupational exposure to benzene and pesticides.

Limited risk factors for ALL are paternal smoking before conception, postnatal chloramphenicol use, clustering and parental occuapational exposure to hydrocarbons, paints, and motor vehicle exhaust 60Hz magnetic fields
>0.4μT. Whereas a decreased risk of ALL is associated with breast feeding. *Limited* risk factors for AML are maternal marijanua use during pregnancy, parental occupational exposure and residential exposure to presticides.

Childhood Lymphoma

The *known* risk factors are: gender (male:female incidence ratio of 1.3 for Hodgkin disease (HD) and 3.0 for Non-Hodgkin lymphoma (NHL)); age (incidence peaks in adolescence); race (white:black incidence ratio of 1.3 for HD and 1.4 for NHL). HD also includes in its risk factors monozygotic, twins of young adults, affected siblings, infectious mononucleosis and Epstein-Barr virus. Whereas NHL has immunosuppressive therapy, AIDS and congenital immunodeficiency syndromes as additional *known* risk factors.

Childhood brain tumours

This paper records the *known* risk factors as ionising radiation, genetic disorders, age (incidence peaks in infancy), race (white:black ratio of 1.2) and gender (Male:Female per million of 25.9). *Suggestive* risk factors are maternal diet during pregnancy and cured meats. While the *limited* risk factors are family history of brain tumour increases risk(sibling or parent) or family history of epilepsy and/or mental retardation; paternal occupations (including aircraft industry; agriculture; electronics manufacturing; petroleum industry; painting; paper or pulp mill work; printing; metal-related occupations or that involving exposure to paint, ionising radiation, solvents and electromagnetic fields); the use of products containing N-nitroso compounds (including beer, makeup, antihistamines); and residential pesticides.

Childhood malignant bone tumours and soft tissue sarcomas

The *known* risk factors are gender (Male:Female ratio of 1.2 for both bone and soft tissue sarcomas); age (incidence peaks around 13-18 years for bone tumours, and 15-19 years for soft tissue sarcomas); race (incidence ratio of white:black of 1.3 for bone tumours and 0.9 for soft tissue sarcomas); genetic disorders (bone –hereditary retinoblastoma / Li-Fraumeni syndrome / Rothmund –Taemson syndrome) (soft tissue sarcoma –Li-Fraumeni syndrome / Neurofibromatosis); and others (bone –radiation therapy / treatment with alkylating agents / high does of radium) (anatomic location of rhabdomyosarcoma and major birth defects). The *limited* risk factors for bone tumours are: taller stature, trauma, short birth length, parental occupations and exposure to pesiticides. And for soft tissue sarcomas are: low socio- economic status, diagnostic radiographs during pregnancy and parents use of recreational drug.

(Stiller et al, 2002)(432)

This article presented an overview of the risk factors for cancer in adolescents. Certain of these are not well established, while those for which there is strong evidence account for only a small proportion of the total incidence.

The risk of both acute lymphoblastic leukaemia and acute non-lymphocytic leukaemia throughout the age range 5-29 years among people with Down's syndrome is approximately ten times that in the non-Down population. Down's syndrome also appears to be associated with an increased risk of germ cell tumours of the testis and brain and possibly of other sites but the risk of most other solid tumours is lower than in the general population. Neurofibromatosis carries an increased risk for central nervous system tumours and soft tissue sarcomas.

The considerable variation in the incidence of Ewing's sarcoma, with its extreme rarity among black and east Asian populations suggesting a strong genetic component to its aetiology.

The risk of Hodgkin's disease in adolescents and young adults who have an affected sibling is approximately seven times that in the general population. Epstein-Barr virus has a role in the development of some cases, though its relations with histologic subtype, age and ethnic group are complex. Hodgkin's disease is more common among adolescents in populations of higher socio-economic status.

The thyroid gland is especially sensitive to the carcinogenic effects of ionising radiation, with the highest risk for young age at exposure; the excess risk of thyroid cancer persists for at least 40 years after irradiation.

(Hasle et al, 2001)(433)

This article reviewed the pattern of occurrence of malignant disorders in people with Down's syndrome. It was concluded that the overall risk of cancer was not significantly increased in individuals Down's syndrome. However, the distribution of tumour types in Down's syndrome differed from the pattern in non-Down's children. Leukaemia constituted 95% of cases of cancer in children with Down's but only 34% of non-Down's children.

20.2 Investigations

20.2.1 Key Clinical Question:

Should any investigations be undertaken in primary care, before referral?

20.2.2 Evidence Question:

In children and adolescents attending primary care services with symptoms that may be caused by cancer, which investigations when compared with the "gold standard" are

predictive of a diagnosis of cancer, and which are not?

20.2.3 Evidence Statements:

In children or adolescents in whom leukaemia is suspected, a full blood count and film can indicate the diagnosis.(III)

No studies were identified that directly studied the role of investigations in the primary care assessment of children or adolescents presenting with symptoms or signs that may be caused by cancer. Evidence about the primary care investigation of suspected haematological cancers can be found in the chapter dealing with haematological cancers.

20.3 Delay and Diagnostic difficulties

20.3.1 Key Clinical Questions:

In children attending primary care services with symptoms suggestive of cancer, which psychosocial and socio-demographic factors are associated with delayed presentation? Does presentation to some services lead to delay – A&E, physiotherapy? Should parental insistence on referral when symptoms are thought by the professional to be benign be viewed as a feature that should trigger suspicion of cancer?

Are there non-clinical features at the initial consultation(s) that may be helpful in identifying children with cancer?

20.3.2 Evidence Questions:

What factors are associated with delay in the diagnosis of children's cancers? In particular, do they include: mis-referral, presentation to emergency or non-cancer services, patient delay, doctor delay, and differences between ethnic and socio-economic groups, and differences between parents and doctors on the significance of symptoms and signs?

Are there non-clinical features at the initial consultation(s) that may be helpful in identifying children with cancer?

20.3.3 Evidence Statements:

Delay in the detection of cancers in children and adolescents may be associated with differences in the significance attached to symptoms or signs by parents and doctors. (III)

Delay in referral of children with suspected cancer is less common among younger children. (III)

In the case of brain tumours, most delay is accounted for by misinterpretation of the symptoms or signs by the health professional. (III)

Delay in the case of brain and solid tumours is less when the symptoms and/or signs are more dramatic. (III)

Limited evidence is available about the explanations for delays in referral of children with retinoblastomas. Recognition of the significance of leukocoria or strabismus appears to be the principal reason. (III)

Introduction

This section covers the delay that occurs in the diagnosis of the different types of childhood

cancer. No relevant systematic reviews were identified. Studies were not identified that directly considered non-clinical features at initial consultations (attendance with an advocate other than the parent, for example). However, some studies dealing with information and support needs considered aspects of this question (for example, Dixon-Woods et al, 2001(434)).

There were few studies of the reasons for delay in initial diagnosis, and those that had been undertaken often did not discriminate between primary and secondary care related delays. Ethnicity, and its influence on diagnosis, is also insufficiently addressed by the published literature, although evidence indicates that socio-demographic variables do not appear play a significant role in delaying diagnosis in a universal health care system such as the NHS. Diagnostic delays appear to be positively correlated with age (the older the child the later cancer is diagnosed), lack of awareness by parents of the characteristic warning signs and symptoms of childhood cancers (e.g. retinoblastoma), and the difficulties that primary care physicians encounter in diagnosing cancer at an early stage because of the vagueness of presenting symptoms. When easy to administer diagnostic tests are available in primary care, earlier diagnosis is more likely (as it is consistently the case for leukaemia).

All cancers

(Fajardo-Gutierrez et al, 2002)(435)

The study tried to determine whether clinical and social factors influence the time to diagnosis of children with cancer. The authors examined the records of children with cancer diagnosed between 1981 and 1992 at six Mexican hospitals (three of which were part of the National Social Security Network, and three others were hospitals serving a population with no access to other health services). Six trained nurses reviewed 4940 clinical records of children with malignant neoplasms, excluding illegible clinical records (4.8%).

The time to diagnosis for all types of cancer ranged from one to five months. The shortest was for leukaemia (median = one month) and the longest for Hodgkin's disease, retinoblastoma and unspecified malignant neoplasms (median = five months). The association between time to diagnosis and age at diagnosis was different. When grouped by age in years as < 1 (the reference age), 1-4, 5-9, and 10-14; the risk of a delayed time to diagnosis increased with age ($x^2 = 29.12$; $P = 0.0001$), the highest being for the 10-14 group (OR=1.8; 95% CI = 1.4-2.3). Risk for masculine gender and delayed time to diagnosis was low (OR = 1.1; 95% CI = 1.0-1.3). Parental educational level also influenced time to delay, and there was risk of delayed time to diagnosis in the lower compared to the higher educational level group (OR = 1.4; 95% CI = 1.1-1.8 for fathers, and OR = 1.5; 95% CI = 1.2-2.1 for mothers). The population without National Social Security had greater risk of delayed time to diagnosis (OR = 1.3; 95% CI = 1.1-1.4). The risk of delayed time to diagnosis varied among the different cancer types, but in general, age at diagnosis was the variable with greatest influence.

Extrapolation of results to a UK setting requires caution because of differences between health care systems. However, findings on influence of age in diagnostic delay support findings from other studies.

(Thulesius et al, 2000)(416)

The authors examined the primary care and hospital records of children who had been included in a Swedish regional tumour registry between 1984 and 1995. 72 children aged between the ages 0-16 years were identified. Four children were excluded because their tumours could not be classified as malignant. One child with myeloid leukaemia was excluded because the disease was congenital, and another child was diagnosed outside the geographical area. Two children could not be studied because of inadequate records, which left 64 children in the study group. The authors also drew two age-and-sex-matched controls from primary care record archives for each of the 64 children in order to obtain information about the average frequency of a child consulting a general practitioner.

Parent's delay was defined as the interval from first symptoms to first consultation with a physician, and a doctor's delay as the time from first consultation to diagnosis. Treatment delay was the period from diagnosis to start of treatment. Lag time was the time from first symptoms to diagnosis.

Mean age at diagnosis was 7.8 years. Leukaemia was the diagnosis in 25 children (39%), and brain tumours in 22 children (34%). Parent's delay was shorter than four weeks in 22 of 25 children with leukaemia, compared with nine of 20 children with brain tumours (x^2 = 9.59, P = 0.002). For two children with leukaemia, parent's delay was three months or more with a common feature of diffuse and gradually aggravating symptoms and signs such as fatigue, diarrhoea and upper respiratory tract infections. Doctor's delay was <two weeks for 17 of 25 children with leukaemia, compared with seven of 21 children with a brain tumour (x^2 = 5.50, P = 0.019). Lag time was four weeks or less for 19 of 25 children with leukaemia, compared with six of 20 children with a brain tumour (x^2 = 9.52, P= 0.002). Median lag time also was three weeks (r=0-15) for children with leukaemia, and 9 weeks (range 1-199) for children with brain tumours (mean lag time was 3.8 [SD = 3.8] and 19.8 weeks [SD = 43.0], respectively). The mean number of visits to a general practitioner in the year prior to tumour diagnosis was 2.3 for the children with leukaemia and 1.5 for the children with brain tumour (visits leading to diagnosis were included), and 0.2 and 0.6, respectively, the year after diagnosis. In the control group, the mean number of visits to a general practitioner was 1.0 in both years.

(Sloper, 1996)(436)

The study investigated parents' responses to the diagnosis of childhood cancer and the early months of treatment, amongst other variables. Semi- structured interviews were carried out with either the parent taking the main caring role or both parents. The mean time between diagnosis and interview was 6.6 months (range five to ten months). 133 families were identified, from five English hospitals specialising in the treatment of childhood cancer. 98 families (74%) agreed to be interviewed. The eligibility criteria were that the child with cancer was under 18 years old and living at home, had been diagnosed in the last six months, the parents spoke enough English to take part in interviews, and that the family included a sibling between eight and 16 years old.

Over half the families (57%) reported a delay in diagnosis. There were differences in delay between different diagnostic groups: the mean interval was shortest for children with leukaemia (4.8 weeks); longer intervals were reported for lymphomas (17.4 weeks), solid tumours (19.4 weeks) and central nervous system tumours (24.2 weeks). There was a significant relationship between age of the child and reported delay, with older children experiencing more delay (r = 0.243, P = 0.018, N = 94), but no significant associations with other demographic variables of social class or single parenthood.

A common theme was the feeling that parents' own concerns and knowledge of their child were not listened to or accepted by health professionals. Parents also voiced concerns in cases where an initial misdiagnosis was made and this was not fully re-assessed in view of continuing or increasing symptoms.

(Saha et al, 1993)(437)

The authors carried out a retrospective analysis of all children (aged 0-15 years) diagnosed as having cancer at a Scottish hospital between 1982 and 1990. Of the 236 children diagnosed during this period, it was possible to date the onset of symptoms accurately in 184 (78%). Cancers included in the analysis were acute leukaemia (65), brain tumour (28), bone tumour (12), lymphoma (17), neuroblastoma (8), rhabdomyosarcoma (20), and nephroblastoma (18). The remaining 16 patients had chronic myeloid leukaemia.

A child was considered to be symptomatic from the day that unrelieved symptoms that could be directly attributed to a malignancy were first recorded. The lag time was calculated from the date of onset of symptoms until the date of diagnosis to the nearest week.

There was no significant difference in the lag time between males and females. Age was a significant predictor for lag time, with older children having a longer lag time. The mean lag time varied from 2.8 weeks for nephroblastoma to 13.3 weeks in brain tumour. One way analysis of variance showed diagnostic group to be significant for length of lag time, (P <0.001). Both age and diagnostic group remained individually significant in a multivariate analysis. The difference in lag time for children with acute leukaemia was not significantly related to a presenting white cell count of ≥50×1000³/l compared to those presenting with a lower count. The difference in lag time between the stages in all diagnostic cancer groups was not significant either. The authors failed to find a positive correlation between lag time and outcome.

Brain tumours

(Mehta V et al, 2002)(420)

The aims of the study were to investigate the time required for diagnosis and the factors important in the diagnosis of paediatric brain tumours. The study was a combined retrospective and prospective study of 104 consecutive patients with brain tumours. All patients 17 years of age or younger who were diagnosed as having a brain tumour at two Canadian hospitals between 1995 and 2000 were eligible for the study. Children referred from centres outside the region were excluded. Data on patient demographic features, symptoms, time from symptom onset to diagnosis, number of visits to physicians, and specific details regarding tumour type and treatment were collected. The authors examined medical records and undertook structured interviews with the patient/patient's family.

The median time from symptom onset to diagnosis was 3 months. The mean time to diagnosis was 7.3 months (95% confidence interval [CI], 5.0-9.7 months), and only 41% of cases were correctly diagnosed within three visits to various physicians. At least 30% of children required more than seven visits to physicians. Time to diagnosis was not significantly affected by either sex or age. Tumours located in the brainstem required significantly longer times for diagnosis, compared with those located elsewhere (mean = 11.8 months [95% CI, 3.1 -20.4 months] versus 6.6 months [95% CI, 4.2 -9.0 months], P=0.014). Medulloblastomas as a group exhibited significantly shorter diagnostic times, compared with other pathological subtypes (mean = 3.8 months [95% CI, 2.0-5.6 months] versus 8.4 months [95% CI, 5.4-11.3 months], P = 0.006).

(Dobrovoljac et al, 2002)(417)

This was a retrospective study of 252 children with primary brain tumours admitted consecutively to a Swiss University Children's Hospital from January 1980 to December 1999. The authors investigated the associations between the pre-diagnostic symptomatic interval and age, gender, tumour location, histology, year of diagnosis and clinical presentation.

The pre-diagnostic symptomatic interval (PSI) was defined as the interval between the onset of signs/symptoms and the time of diagnosis by MRI, CT or other imaging techniques. In 167 (66%) patients, medical charts allowed a separation of the PSI into an interval between sign/symptom onset and first medical consultation (parental delay) and that between first medical consultation and diagnosis (doctor delay). In children older than two years, the most common initial signs/symptoms were headache, nausea/vomiting, seizures, squint/diplopia, ataxia and behavioural changes. In children younger than two years, the most common initial signs/symptoms were seizures, vomiting, head tilt and behavioural changes.

The median age at diagnosis for all patients was 6.3 years (range 0.0-16.9 years). The median pre-diagnostic symptomatic interval was 60 days (range 0-3010 days) with a parental delay of 14 days (range 0-2310 days) and a doctor delay of 30 days (range 0-3010 days). Only 81 (32%) of the 252 brain tumours were diagnosed within 30 days of onset of signs/symptoms. At the time of diagnosis, only 30 (12%) patients were monosymptomatic. Signs and symptoms of increased intracranial pressure (headache, nausea/vomiting, papilloedema, sixth-nerve palsy, enlargement of

the head, gaze depression, bulging fontanelle, separation of cranial seizures) were noticed in 124 (49%) patients at sign/symptom onset and in 186 (74%) at diagnosis. Of these, 74% had hydrocephalus. Age had a statistically significant correlation with PSI (Pearson's correlation r = 0.32, P <0.0001) with shorter PSI for younger children. The parental delay was significantly shorter for younger than older children (Pearson's correlation r = 0.16, P < 0.05). However, doctor delay did not correlate significantly with age. Patients with signs/symptoms of raised intracranial pressure had a statistically shorter PSI (median 60 vs. 152 days; P=0.007, Mann-Whitney test) and shorter doctor delays (median 20 versus 60 days; P=0.02, Mann-Whitney test) than children without increased intracranial pressure. However, the parental delays in these two groups of patients were similar. Gender did not correlate with PSI, parental delay or doctor delay. During the study period of 20 years, there were no statistically significant changes in the PSI or parental delay. However, doctor delay decreased significantly (Pearson's correlation r = -0.26, P < 0.001).

In 75 (45%) patients, doctor delay was more than 30 days, indicating misinterpretation of intial signs and/or symptoms. Common diagnostic difficulties included the correct interpretation of headache, nausea/vomiting, seizures, behavioural changes and squint/diplopia.

(Edgeworth J et al, 1996)(438)

The authors examined the duration and characteristics of symptoms and signs, and the nature of consultations before diagnosis in a group of children with primary brain. This study was a case series of 74 children, aged 0-16 years, with primary brain tumours admitted consecutively to a London neurosurgical unit 1990 – 1994, and involved review of medical notes and histopathology reports. A semi-structured interview was used to gain information from parents on symptoms and signs, their duration before diagnosis, and the nature of consultations with professionals. The interview included details on changes in the child's psychological functioning in the sixmonths before diagnosis. The final participation rate was 80%.

One month after symptom onset 68% of children had not at that stage been correctly diagnosed, and after six months 20% were still not diagnosed. The interval between symptom onset and diagnosis was shortest for children aged 0-2 years despite there being no significant difference in the histopathology grade, or location of tumours, or parental persistence (number of consultations before diagnosis) across age groups. The mean (SD) duration of signs and symptoms before parents consulted a health professional was 3.0 (13.4) weeks (range 0-104 weeks). In 92% of cases parents took their child to a doctor within one month of symptom onset. The mean (SD) duration of clinical history between initial consultation with a health professionals and clinical diagnosis was 16.0 (24.4) weeks (range 0-130 weeks). One month after initial consultation 58% of children had not yet been diagnosed and 18% were yet to be diagnosed six months after initial consultation.

Before diagnosis, there were a total of 257 (mean 4.6, range 1-12) consultations with professionals in the 56 children for whom this information was available. Of these, 45.5% were with a general practitioner and 9% with an accident and emergency department. 62% of children were seen on four or more occasions before the correct diagnosis was made. Doctors were unable to make a diagnosis in 19% of children and in a further 15% could find nothing wrong. Symptoms and signs were confused with those of migraine in 14 children. Vomiting occurred in 65% and headache in 64% of the children. Detailed analysis of those with headaches showed a mean (SD) duration of 21 (34) weeks (range 0-130 weeks); 34% were always associated with vomiting. In 33% of cases headaches increased in severity; 15% were early morning and associated with vomiting. Initial symptoms were psychological or behavioural in 52% of children in whom information was available. There was no relationship between site of tumour or duration of clinical history and incidence of psychological difficulty for any age group.

Some parents felt that poor communication between professionals including opticians, psychologists and teachers) had contributed to the delay in diagnosis (Many parents reported that professionals looked at the presenting symptoms of each consultation in isolation.

(Flores et al, 1986)(421)

The authors compared the interval from the onset of symptoms to diagnosis in a population of children with primary brain tumours with that of groups of children with Wilms' tumour and acute leukaemia. Variables such as age, symptoms at presentation, and tumour location were analysed in an effort to identify reasons for the delay in diagnosis of brain tumours in children. The authors reviewed the records of 79 children with primary brain tumours diagnosed between 1976 and 1984 at a US university centre. The patients were all less than 20 years of age at diagnosis, with a mean age of 7.6 years. They also examined the records of 45 patients with Wilms' tumour and 123 patients with acute leukaemia. The mean ages of the patients with Wilms' tumour and acute leukaemia were 3.6 and seven years, respectively.

The mean interval from the appearance of symptoms to diagnosis in patients with brain tumours was 26 weeks, with a median of six weeks. Patients less than five years of age who had infratentorial tumours and patients with more severe grades of signs and symptoms were diagnosed earlier. For patients with acute leukaemia the mean time to diagnosis was 4.5 weeks. Of 123 patients with acute leukaemia, 100 (80%) were diagnosed within four weeks. Of the patients with Wilms' tumour, 38 (84%) were diagnosed within four weeks, and 25 (55%) in the first week. The mean duration of symptoms for patients with Wilms' tumour was 2.8 weeks. Of the three types of malignant neoplasms, the primary brain tumour had the longest delays in diagnosis (P<0.0001).

Solid tumours

(Pollock et al, 1991)(439)

The study was a retrospective review of patients with newly diagnosed lymphomas or solid tumours who were treated on US Paediatric Oncology Group protocols.

2684 patients with brain tumour, neuroblastoma, non-Hodgkin's lymphoma, Hodgkin's disease, Ewing's sarcoma, or osteosarcoma were diagnosed between 1982 and 1988, and entered into the therapeutic protocols. 20 patients were excluded from analysis, including four who had no symptoms at diagnosis, seven referred for a non-tumour-related condition but for whom symptom information was incomplete, and nine for whom the date of symptom onset was missing. The remaining 2665 patients composed the study population.

Median lag time ranged from a low of 21 days for children with neuroblastoma to a high of 72 days for those with Ewing's sarcoma. A statistically significant difference was found among tumour types (P <0.001). Age was positively and significantly correlated with lag time (P <0.001) for all tumour types except Hodgkin's disease (P=0.58); that is, as age increased, lag time increased. Gender was significantly associated with lag time only for non-Hodgkin's lymphoma (P=0.02), for which girls had longer lag times. Race was significantly associated with lag time only for osteosarcoma (P=0.002), for which white children had longer lag times.

Multivariate regression analysis was performed separately for each diagnostic group. With the exception of the Hodgkin's disease group, age remained a significant independent predictor of lag time for all diagnostic groups (P<0.05). Consistent with the univariate analysis, gender remained significantly associated with lag time for non-Hodgkin's lymphoma (P=0.02). The multivariate analysis also revealed a significant association between gender and lag time for Ewing's sarcoma (P=0.02). The association differed in these two tumour groups; girls had longer lag times in the non-Hodgkin's lymphoma group but shorter lag times in the Ewing's sarcoma group. Race also continued to have a statistically significant association with lag time only for osteosarcoma (P=0.02).

Signs and symptoms were compared for shorter lag time and longer lag time groups within each diagnostic category. Patients with shorter lag time for brain tumour had a 67% frequency of gait abnormalities and ataxia, compared with 59% for those with a longer lag time (P=0.13), but were similar with respect to other common symptoms of brain tumour. For neuroblastoma, abdominal masses were more common in patients with shorter lag times (31% vs. 19%; P = 0.037). Patients

with shorter lag time for non-Hodgkin's lymphoma had a higher frequency of abdominal masses (13% vs. 5%; P=0.06) and of breathing difficulty and coughing (32% vs. 15%, P=0.007).

The study did not distinguish between physician and patient /parent related delay. The regressions performed for each diagnostic group explained no more than 16% of the variance of lag time, and in the non-Hodgkin's lymphoma group, gender differences may have been explained by a difference in the distribution of histologic subtypes of tumour (not controlled for in this analysis).

Retinoblastoma

(Butros et al, 2002)(440)

The aim of the study was to assess the degree, cause, and consequence of delays from presenting signs to diagnosis of retinoblastoma. The authors examined the clinical charts of 64 patients consecutively presenting to a US Cancer Centre with newly diagnosed retinoblastoma between November 1993 and January 1998. Patients with a family history of retinoblastoma were excluded (N = 7), and analyses were performed on the remaining 57. The patient's history was recorded in a uniform format and obtained in an interview with the parent or primary caregiver.

The following information was obtained: laterality of the disease, age at diagnosis, presenting signs, who first noted the presenting signs, and time from the onset of presenting signs to diagnosis. When any delay was noted, the reasons for the delay and potential consequences were also recorded. A delay in seeking treatment was defined as the interval from presenting signs noted by the patient, parents, or others to the time at which a physician was notified of those signs. A delayed referral from the primary care physician to the ophthalmologist was defined as the interval from the time the physician was notified of the presenting sign to the time a referral was made to an ophthalmologist.

The median times from presenting signs to diagnosis for patients with unilateral and bilateral disease were 1.5 and 2.25 months (range: 0-46 months), respectively. 15% (N = 41) of the patients with unilateral disease had no delay from signs to diagnosis, and 25% (N = 4) of the patients with bilateral disease had no delay form signs to diagnosis. The parents had first noticed the onset of signs in 75% of cases (N = 43). The primary care physician first noted the presenting sign in 5% of cases (N = 3). Leukocoria and strabismus were the most common presenting signs noted in the diagnosis of retinoblastoma. For patients who presented with leukocoria, the median delay to diagnosis was 1.5 months; for patients who presented with strabismus the median delay to diagnosis was 2.5 months. 77% of patients delayed seeking treatment. Primary care physicians delayed referral in 30% of cases (N = 14); in all of these patients, parents stated that they reported the presenting signs to the child's physician, who reassured the parents of normalcy or made a diagnosis different from retinoblastoma, neither of which led to an immediate referral to ophthalmology; 13 (925) of these patients had a median delay of 3.75 months. No adverse consequence of delayed diagnosis could be clearly established, but a trend towards eye loss being associated with longer delays in patients with bilateral retinoblastoma was noted.

(Goddard et al, 1999)(441)

The aims of the study were to establish the extent of diagnostic delay in retinoblastoma, to ascertain whether any factors were associated with delayed diagnosis, and to examine whether or not delay in diagnosis altered treatment outcome. The authors undertook a retrospective study of all patients with retinoblastoma treated at a UK supraregional referral centre between January 1993 and December 1996. Patients known to have a family history, those with dysmorphic features noted before diagnosis of retinoblastoma, and patients resident outside the UK were excluded. 100 patients (of 112 eligible patients) were available for interview during the study period. Parents were asked to recall the sequence of events from the time they first noted "something wrong" with their child's eyes(s) to the diagnosis of retinoblastoma. Particular note was made of ocular symptom(s), their duration before diagnosis, and the nature of contact with primary health care professionals. Patient records were examined to verify the date of diagnosis of retinoblastoma.

Leukocoria was the initial symptom in 52/100 patients, squint was the first symptom noted in 29 patients, the parents of 10 children noted change in the appearance of their child's eye(s) (heterochromia, red, and/or painful eyes), in nine patients the first symptom noted related to decreased visual acuity.

(Haik et al, 1985)(442)

In this case series, 254 cases of retinoblastoma referred to a US Ophthalmic Oncology Center between 1974 and 1983 were reviewed for the following: (1) presenting sign or symptom and date of presentation; (2) date of examination by the primary care physician; and (3) date of examination by an ophthalmologist. Patients with a positive family history of retinoblastoma were considered separately. Four cases were excluded because of insufficient data.

Three diagnostic intervals were considered: time from birth to first symptom, time from first symptom to examination by the primary care physician, and time to subsequent referral to an ophthalmologist. 28 new patients (11%) had a positive family history of retinoblastoma. The median age at diagnosis was six months for patients with a positive family history and 19 months for those with no family history. The longest interval was median time elapsed to first discernable symptom (four months with positive family history [range 1-18 months], and 15 months without [range 1-115 months]). The next longest interval was median time elapsed from the primary care physician to referral to an ophthalmologist (five [range 1-32 weeks] and nine weeks [range 1-128 weeks], respectively). Significant percentages of primary care physicians (47% for children with no positive family history, and 25% for children with positive family history) delayed referral for a significant period of time (19 weeks for both groups). The mean time from first symptom to seeking the opinion of a primary care physician was two weeks (range 1-8 weeks) for children with a positive family history, and five weeks (range 1-100 weeks) for children with a negative family history.

20.4 Support and Information needs

20.4.1 Key Clinical Questions:

What are the support and information needs of patients who are being referred for suspected cancer?

Are the needs variable in different groups of patients? Should access to information be promoted (for example, internet resources?). To what extent should children and adolescents be involved, how, and what are the consent issues?

20.4.2 Evidence Questions:

What information should be generally available on the symptoms, signs and management of cancers of children and adolescents?

In children and adolescents who are suspected of having cancer, to what extent should the primary care professional provide them and their parents/carers with information and involve them in referral decisions?

20.4.3 Evidence Statements:

There is very little evidence about the information and support needs of children, adolescents and families at the time of referral decisions. Evidence from studies of children, adolescents and families after diagnosis indicate that parents often have an executive function in determining the information given to their children, conveying the diagnosis and full information about its significance and management in an understandable way is helpful to children, and that the needs for information and support vary according to the progression of the cancer. (III)

There was little evidence about the role of the primary care professional in provision of information. The provision of limited or incomplete information appears to be less helpful than complete information, but there was also evidence that the provision of the diagnosis by the general practitioner can be acceptable to some parents. (III)

Introduction

This paper considers evidence on the information and support needs that children with cancer and their parents/carers may have around the time of referral. General information about the support and information needs of patients being referred with suspected cancer can be found in Chapter 7. Here, issues particular to children are considered.

We found no prospective evidence about the referral decision, studies invariably being retrospective and involving children and their families after the stage of diagnosis. There is no evidence, therefore, about the significance of the referral decision when the eventual diagnosis is not cancer. We have included information from a review about the support and information needs of children, adolescents and cancer at diagnosis and during clinical management.

Secondary studies

(Scott et al, 2004)(443)

A Cochrane review assessed the effects of interventions to enhance communication with children or young people with cancer on the following: knowledge and understanding of their cancer and its treatment, and psychological, social, behavioural, and physical outcomes. The inclusion criteria specified that study participants had a diagnosis of cancer, so the information needs at referral were not considered. Children or adolescents in remission were excluded.

Nine studies were included, none of which were based in the UK. The authors concluded that although the findings of the studies were difficult to interpret due to methodological issues and the heterogeneity of the studies, some interventions (such as computer-assisted learning, art therapy, school and social reintegration programmes) may lead to improvements in knowledge and understanding of cancer and its treatment, and psychological, social, behavioural, and physical outcomes. The recommendations for practice were:

Healthcare professionals must use their own individual judgement about how better communication with children and adolescents with cancer might be achieved.

The selection of strategies to improve communication or supplement routine communication should take into account factors such as the young person's medical condition, stage of cognitive, emotional and physical development, perceived needs and concerns, readiness and ability to communicate, and with whom they prefer to discuss concerns about their cancer and treatment.

The child or adolescent needs to be considered in the context of their family, and family members may need to be included in interventions aimed at enhancing communication with children and adolescents with cancer.

(Ishibashi, 2001)(444)

In this review, information for patients was divided into three conceptual areas: *what to tell*, *when to tell*, and *how to tell*. Social support was categorised into four supportive resources: family, young people with cancer, healthy friends, and significant adults. The findings of the review are described here.

Information

Information helps children and adolescents with cancer reduce uncertainty and negative feelings and assists them with participation in cancer treatment. It is also conducive to their pursuit of normal lives.

What to tell

Information has been studied according to its type: type and cause of cancer and the treatment process, social life expectations, bad news related to a patient's illness, and social support program and groups.

In one reviewed study of children's thoughts and feelings about their disease, many children with cancer, aged seven to 13 years were reported to have misunderstood the cause of their illness. The children believed that they had caught cancer from another person or an animal. In addition, knowing about their type of cancer and its treatment seemed to decrease the children's fear about painful procedures. The authors suggested that age-appropriate information including the type and cause of cancer and the treatment process should be provided to children with cancer.

Another study reported that children and adolescents with newly diagnosed cancer may have a difficult time in maintaining their friends and making new friends because of the many societal myths and taboos about cancer. Supplying appropriate information on the effects of the disease on their social lives may help children with cancer to maintain relationships with peers.

In another reviewed study, a sample of 56 children aged eight to 16 years answered self-report questionnaires, and their parents were interviewed about the information they had given their children. This study found that children who initially received open information from their mother were significantly less anxious and depressed three months to three years later than children who received less open information. The former children were openly told that they had cancer and that there was a possibility of not getting better and even of dying.

When to tell

Children with cancer need adequate, accurate, and developmentally appropriate information about their illness to understand the meaning of cancer. Information techniques should vary with the child's developmental level and previous experience. Therefore, information should be given to a child with cancer when he or she expresses readiness to receive it.

New information should be given at different developmental stages to re-educate the patient so that fear of the unknown is reduced. For example, a 12-year-old patient, diagnosed with acute lymphocytic leukaemia at age four, indicated that he had just recently learned leukaemia was a cancer Hence, age-appropriate information should be offered, and re-education should be planned at different developmental stages.

Children with cancer who received open information from their parents at the initial stage of diagnosis were significantly less anxious and depressed and had higher self-esteem than children who were provided with open information at a later stage. In addition, if teenagers with cancer were provided with information about their disease at the time of diagnosis, they were better able to trust the staff and cope with painful developments in the future.

One study suggested that telling is not a one-time event, but a process that varies over time. When the child's medical situation changes and new procedures are required, it may be important to provide the child with additional information.

Informational support should be given to the patients throughout treatment and long-term follow-up assessment, at pre-diagnosis, the maintenance phase, completion of cancer therapy, and the relapse and terminal phases, in order to maintain previous family lifestyles and to help the children participate in their own health care at each stage.

How to tell

It is important to provide individualised information to young people with cancer so they understand their illness has been reported. In one study young children with cancer wondered why they had contracted the disease and experienced disruption and distress from their illness. The lack of disclosure seemed to arise from the adult assumption that young children have limited cognitive capacity. Therefore, their parents may be unable to give information in terms the child can understand.

Social Support

Adolescents with cancer who received more support from people they valued developed better coping strategies, and have more normal interactions with their parents and friends. Resources of social support for children with cancer have been investigated in terms of family, other children with cancer, healthy friends, and significant adults.

Family

The family is a major source of support for school-age children and adolescents. However, adolescents with cancer maybe more in conflict with their mothers than the healthy young.

Family cohesion may increase or decrease. In one study, adolescent survivors of cancer showed lower levels of family cohesion than healthy adolescents and their families. The authors suggested that after their treatment, some adolescent survivors of cancer may adopt a hyperindependent attitude. Moreover, the low levels of family cohesion could be related to the motivation of family members to protect each other or their withdrawal of some support. In another study, when adolescents with cancer experienced long term illness, family cohesion increased. In this study, parents reported that the parent-sick child relationship increased because the child with cancer needed attention more than their other children.

Primary studies

(Hoekstra-Weebers et al 2001)(445)

In this prospective Dutch study undertaken to evaluate levels of support, and the concurrent and prospective effects of support on the psychological functioning of 128 parents of paediatric cancer patients, it was found that parents received most support at diagnosis. Self-perceived quantity of support decreased with time, but parents indicated they remained equally satisfied. Support significantly predicted concurrent and prospective distress of fathers, but not of mothers. Dissatisfaction with support and negative interactions were consistent risk factors for fathers. Mothers who adjusted well psychologically received more support and were less dissatisfied than mothers who remained clinically distressed. Nevertheless, no persisting effect of support was found.

(Patistea et al, 2000)(446)

In this Greek study which used open-ended interviews to examine parental psychological reactions, difficulties and resources during the period following the diagnosis of childhood leukaemia, many of the defensive mechanisms described in the literature such as shock, denial, anxiety and guilt, were observed. The most difficult factors for the parents to deal with during the initial period were the psychological upset and the financial burden. Problems associated with relating to others and to the health care system were also identified. Hope, social support and the marital relationship were the most helpful resources in managing the multifaceted problems caused by the diagnosis.

(Cavusoglu, 2000)(447)

The author of this descriptive Turkish study investigated the problems related to the diagnosis and

treatment of 30 adolescents diagnosed with leukaemia. The findings showed that the information needs of the adolescents related more to the treatment and prognosis of the disease than to the aetiology. 50% of the adolescents reported that they experienced social problems, although these problems decreased as the time period after the diagnosis increased and subjects were in the remission stage.

(Slavin et al, 1982)(448)

This study involved interviews of 116 long-term survivors of childhood malignancies. Good psychosocial adjustment was associated with patients' early knowledge of the diagnosis. A high percentage of the survivors, their parents, and siblings felt that the cancer diagnosis should be shared with the child early on.

(Sloper 1996)(436)

In this English study of 98 families of children with cancer, the author held interviews with the main carer and administered self-report questionnaires to mothers and fathers. The majority of parents (84%) were satisfied with the way in which they had been told the diagnosis. Parents particularly commented on the sensitive way in which breaking the news was handled and on the honesty of those involved. They were appreciative of being given hope of successful treatment whilst being realistically appraised of the diagnosis. Parents were dissatisfied when they felt that their informant had appeared abrupt and unsympathetic; where they received conflicting information from different sources; where they were told in a public place, such as a corridor or waiting room; and where one parent was alone at the time. Parents who were told of the diagnosis at district general hospitals were more likely to be dissatisfied or very dissatisfied than those told by general practitioners or at paediatric oncology centres.

83% of families felt they had been given the right amount of information after diagnosis. The majority (92%) felt that the information they received was clear and comprehensible, and their questions were welcomed and answered. All but three parents wanted to know the whole truth however negative. The majority (69%) did not want more information once the initial information had been given; among those who did, the information most often mentioned was long-term effects of the disease and treatments and risks of recurrence. Only one aspect of diagnosis and information was significantly related to parental malaise scores: respondents who felt that they did not understand the information they received were likely to have higher malaise scores.

Many parents noted the importance of having someone to talk to who was not so emotionally involved in the situation. Friends and extended family, particularly parents and siblings, were cited more often than partners as the people parents talked to about their feelings and as being particularly helpful. A minority of respondents (14%) felt that they had no one to talk to about their feelings, and this was strongly related to higher malaise scores. Just under half the families (48%) felt that they not had received one or more types of help they needed. One third of these felt that they needed counselling for themselves; 21% needed more financial help; 17% wanted more follow-up at home; 15% wanted more information, particularly about available services; and 15% wanted more practical help at home. The mean malaise score for respondents indicating a need for counselling was significantly higher than for other respondents.

(Young et al, 2003)(449)

The study investigated the views of young people and their parents on the management of communication about their illness and how they perceived the role of their parents in this process.

The authors invited patients (aged 8-17 years) attending one English paediatric oncology unit, and their parents, to participate in semi-structured interviews about experiences of communication about cancer in young people. Sampling was largely opportunistic. The authors interviewed 13 of 20 families approached, comprising 19 parents (13 mothers, 6 fathers) and 13 young people. Prompt guides were used to help to structure the interviews. Data analysis was based on the constant

comparative method, and the parents' and patients' accounts analysed separately.

Parents described assuming an executive-like role during the period around diagnosis, managing what, when, and how their children were told about their illness. This role was tacitly negotiated with them by doctors: the diagnosis was usually disclosed by doctors to parents first, without the patient present.

Children expressed a range of views about the form of the disclosure: a few thought it was better to hear the news at the same time as their parents, some thought it was more appropriate for their parents to be told first, and others reported no strong feelings either way. In contrast, all but two parents who expressed a preference wanted to be given the diagnosis without their child being present, and before the patient was told. Parents expressed considerable apprehension about "breaking down" in their child's presence, and thought they would be better able to support their son or daughter if they could first "compose" themselves.

Over the course of the illness, some families described adjusting their management of communication away from the "executive" controlling and directive model towards a partnership based model. In other cases, parents described continuing to orchestrate when and what their child was told. The young people differed in the extent to which they were satisfied with the executive style of communication. A few seemed to welcome it. However, the accounts of other patients suggested that they thought communication was constrained by their parents: some referred to the inability or unwillingness of parents to answer their questions; others questioned how the information boundaries had been defined and expressed unease at the perceived disparity between how much information they had been given and what their parents had been told. Notwithstanding these accounts, the young people did not regard their parents' involvement in communication as inappropriate in principle. Young people's accounts showed how their preferences were fluid and depended on context. Almost all the young people at times embraced, or even actively cultivated, their parents' roles as "buffers" to limit their exposure to information. Young people's dependency on their parents as brokers in the communication process arose because they did not, for the most part, see themselves as having direct access to information through their own interactions with health professionals, particularly doctors. The young people saw themselves as occupying a marginal position in consultations, and some thought that their priorities were of little interest to medicine. Consultations were largely carried out between parents and professionals, and seemed to leave the young people without a voice. Some did not see "emotional labour" as a duty of doctors, whereas they did see it as something that nurses undertook, and many felt more at ease talking to nurses.

The study, as the authors acknowledged, did not address the influence of sex, ethnicity, social class, and the nature of the illness on how communication is managed. Opportunistic sampling may pose limitations to the extrapolation of findings to other paediatric settings.

(Patistea and Babatsikou, 2003)(450)

This Greek study addressed the type and amount of information provided to parents who have children with leukaemia. It also examined the sources parents used to increase their knowledge about the disease. Finally, it explored parental satisfaction with the explanations given to them about the medical condition of the child.

A consecutively selected sample of 71 parents (41 mothers and 30 fathers) who had children with leukaemia constituted the study population. The subjects were recruited from the oncology clinic of a Greek university hospital. 89.5% of the parents approached refused to participate. Data were gathered at a mean time of 28.6 (SD = 27.5, r = 3-96) months after the diagnosis of the child's leukaemia. Two questionnaires with closed and open-ended questions were handed to the parents. The questionnaires included socio-demographic data, illness-related information, parents' perceptions of the threat to the child's life, parents' perceptions of the amount of information given to them by the health-care staff about certain bio-medical aspects of the child's leukaemia, and

parents' sources of any other leukaemia-related information.

The sample represented a range of socio-economic levels according to level of education, employment status and place of residence. The two bio-medical areas in which most respondents perceived that they were given the most information were the diagnosis/basic physiology and the existing therapies. In contrast, the disease-related issues on which the majority of the participants reported that they were given the least information included the causes, course and prognosis of the disease. Less than half of the parents (N = 30, 42.2%) commented that they were given some additional information besides that associated with the clinical aspects of the disease: guidelines to obtain fringe benefits (N= 8, 11.3%), other sources of information about the child's condition (N= 8, 11.3%), stress and behaviour management for the sick child (N= 6, 8.4%), existing self-help associations which could offer emotional and practical support (N= 5, 7%), and the management of family conflicts (N= 4.2%). Forty-one parents (57.8%) said that the hospital personnel did not provide them with information other than that concerning the pathophysiology of illness.

The most significant source of information was the medical team, especially physicians. Informal sources of information included relatives, friends, books, medical journals, television and other parents in the same situation. Approximately one third of the subjects expressed satisfaction with the information offered. Only a few parents (N= 12, 16.9%) reported high levels of satisfaction whereas about half (N= 34, 48%) reported low levels. Participants wanted to know more about the cure and causes of the disease, but also to learn more about various familial and psychosocial issues including the function and organisation of the health care system (telling and disciplining healthy siblings, discipline of the child with leukaemia, operational routine of the health care system, management of their own emotional reactions, and family planning).

Statistical analysis did not reveal significant differences between the two genders on any of the variables examined. Mothers and fathers who lived in large cities (over 1,000,000 population) reported that they received more information as compared to those who resided in smaller cities, towns or villages (Kruskal-Wallis 8.6, P=0.013). In addition, parents with higher education level were less satisfied with the amount of information they were offered (x^2 = 21.56, P = 0.010). Finally, the mothers and fathers who said that they received more information about their child's leukaemia also had higher levels of satisfaction (r=0.53, P<0.001). No statistically significant relationships were observed between the respondents' perceptions of the seriousness of illness and (a) the amount of information they were given and (b) their evaluation of it. The stage of the disease (i.e. continuous remission or relapse) did not correlate with any of the dependent variables included in this analysis.

(Dixon-Woods et al, 2001)(434)

The authors examined parents' narratives about the diagnosis of childhood cancer, with the aim of determining how parents felt about the process, how the process affected them, and whether these narratives had implications for early diagnosis and referral of childhood cancers.

The authors undertook semi-structured interviews with 20 parents (response rate = 95%) whose children (aged 4-18 years) had a confirmed diagnosis of cancer or brain tumour. Children's medical records were examined to corroborate parents' accounts and to obtain more precise details of dates, referrals, and investigations. The authors noted the signs and symptoms that parents reported as serious and how they acted on these, their accounts of interactions with health services, and how they perceived the roles of themselves, their children, and health professionals. Data were analysed by the constant comparison method.

Children had been diagnosed roughly 1-36 months before interview (median 11 months). Four families were of South-Asian origin and the remainder white. The families were socially mixed.

Parents were first alerted to their child's illness by a range of signs and symptoms, and by behavioural and affective changes. The signs and symptoms of younger children were first noticed by parents. Parents of older children and adolescents, however, often had to be told of the problem. Early symptoms were often vague, non-specific, and common. Most parents had a wait and see

period in which they monitored symptoms and attempted to manage them with simple remedies, but they tended to feel that if symptoms persisted they should be investigated thoroughly and quickly.

Ten families' accounts of this period before diagnosis included a dispute with doctors. Parents accepted that a few visits to the general practitioner might be necessary before a test was ordered, but were not satisfied if they had had to insist on action being taken by the general practitioner. Parents who had had disputes said that they had to argue with general practitioners and demand investigations; they rejected commonsense diagnoses by general practitioners of their child's condition on the basis of the unusual nature of the symptoms and their intimate knowledge of their child.

Lengthy disputes occurred in seven of the 20 families. In these cases diagnosis was made between 2.5 and eight months after symptoms were first noticed. Parents' accounts of the disputes mainly described the perceived inadequacy of medical response, incompetence or delay in investigation, and doctors' failure to realise that their child's symptoms were serious. Disputes about the importance of children's symptoms continued when parents accessed secondary services.

Parents' reactions to the diagnosis of cancer were affected by their experiences of obtaining the diagnosis. Some parents who had had to struggle to get their child investigated felt vindicated or relieved. At the other extreme, parents whose child was diagnosed within hours or days were shocked and stunned, and described feelings of numbness and disbelief. Some parents who had had disputes felt guilty and self-reproachful because they had not been more effective advocates for their child.

The study had some limitations as acknowledged by the authors: it included only one paediatric oncology unit, and there were few examples of some tumour types that can be prone to delays in diagnosis (cancer types included in this study were leukaemia (N=9), brain tumours [2], and solid tumours [9]). High consistency was nevertheless found between parents' accounts and notes in medical records. The authors made reference to the advice offered by the general practitioner

John Halliday, whose own child died of cancer, and which is included here:
Always be prepared to see a child

If you are unable to find any abnormality after examination always tell the parents you cannot find anything, but are prepared to examine the child again if symptoms persist.

Always take seriously the mother who comes and tells you that although she does not know what is wrong, she knows her child is not right.

Beware of telling a family categorically that there is nothing wrong with their child. Note how often the child is seen. If after a few visits you have found nothing, consider asking a GP colleague or a paediatrician to see the child. A new pair of eyes may spot something you have missed.

(Arksey, 1999)(451)

This paper drew on evidence from a previous study by one of the authors to explore lay perspectives and empowerment in relation to obtaining a diagnosis for childhood cancer.

Over half of the parents of children with cancer (57%) felt that there had been some avoidable delay in getting a diagnosis, in the stage before. The evidence suggested that a substantial number of parents of children with cancer felt their experiences and knowledge were disregarded by doctors in the diagnostic process. Denying the validity of an individual's perceptions had implications for obtaining an accurate diagnosis, which could in turn make access to appropriate health care and treatment problematic. A key issue to emerge from the analysis was the need for additional training in communication skills. The authors also concluded that the underlying problems of attitudes, especially giving weight to the informed views of lay people, is another matter which needs to be addressed.

(Eiser et al, 1994)(452)

In this study, a total of 30 families (28 mothers, 23 fathers, 13 children; response rate = 86%) with a child diagnosed with cancer were interviewed separately about their recall of the period immediately before the diagnosis, and their experiences during the diagnostic interview. Parents were asked to describe in their own words the time before the child was diagnosed and then what happened immediately afterwards. Prompts were sometimes used to elicit information on the diagnostic process (place, personnel involved, information received, questions parents asked, whether or not they had known anyone with cancer before and how this affected their response, presence or absence of the child, and how the decision to inform or not inform the child was taken). The authors undertook content analysis of the interviews.

Children presented with a wide range of symptoms (mean = 3.0, range = 1-7). Parents reported considerable delay between the time when they first sought professional advice about their child and the diagnosis being confirmed (mean =17 weeks, range = one week to 15 months). This mean interval was least for children diagnosed with acute lymphoblastic leukaemia (7.3 weeks) and lymphomas (16.3 weeks). Longer delays were reported for children with solid tumours (20.3 weeks) and brain tumours (35.8 weeks). A total of 35 alternative diagnoses were suggested by general practitioners. One half (N=14) of the mothers felt they were not believed by their general practitioner. Where parents felt they were not believed, they were more likely to blame the general practitioner for failing to make an appropriate diagnosis ($P<0.5$). In addition, parents were more likely to blame the general practitioner as the time to diagnosis increased ($P<0.05$). Sixteen mothers were unprepared for the diagnosis.

In 20 cases, mothers were told the child had cancer by the general practitioner or local hospital before they received fuller information at the oncology unit or regional centre. All but two mothers reported that this initial explanation was incomplete and unsatisfactory. Few parents reported that they specifically asked for information, the rest said that they had not known what to ask, or did not understand and did not wish to show their ignorance. In retrospect, mothers felt they should have been given more information about long-term complications (N=8), side effects or the cause; fathers more often wanted information about prognosis, particularly in statistical terms ("I wanted to know what the odds were"). However, there was little real criticism of the way information was given at either the oncology unit or the regional centre, with many parents recognising that it was a very difficult situation, with no obvious "right way". Both mothers and fathers acknowledged that they were helped in that they went from a situation of no hope (when first told their child had cancer) to one of increasing hope when they reached the specialist centre.

The policy in both hospitals (oncology unit and regional centre) was that children who are old enough (over eight years of age) to understand should be told the diagnosis as soon as possible. The question of what to tell the child was always first raised by the consultant. All but two mothers agreed, referring to the doctor's greater experience. Those two mothers initially preferred that the child should not be told, though quickly realised that this would not be possible. Once children were informed, all mothers expressed relief and none had come to regret agreeing to the child being informed. However, some had reservations about the speed with which children were informed, especially commenting that they need time for themselves before being able to deal with the child's distress.

21 Research recommendations

21.1 Introduction

Guideline development groups are invited to make recommendations for further research. Lack of evidence or poor quality evidence has been a recurring problem in developing recommendations for referral for suspected cancer, and the group is likely to wish to make recommendations on

further research.

NICE requests that research recommendations are made using a standard format. The recommendations are considered by NICE in a systematic process, and those that gain support are raised with research funders. To assist the group, two research recommendations have been suggested in this paper – one for a randomised controlled trial of an educational intervention to improve primary healthcare professionals' ability to detect cancer, and a second for a study to identify the presenting features of cancers in a large population of patients attending primary care services.

The Guideline Development Group has made the following recommendations for research, which result mainly from systematic reviews of questions within the guidance scope. The guideline developers and their advisers regard them as the most important to improving NICE guidance and patient care in the future.

When making these recommendations for research, the guideline developers have considered the potential importance of factors relating to gender, ethnicity and people with special needs.

21.1.1 An RCT of an educational intervention to improve primary healthcare professionals' ability to detect cancer

Table 41 that follows presents a recommendation for this study. Our searches have shown that although there is a growing number of experimental studies to test interventions to improve professional performance, there are very few studies concerned specifically with detection of cancer among people presenting with symptoms and/or to primary health care. Trials of interventions to change the performance of professionals have tended to concentrate on treatment decisions or monitoring routines rather than the process of reaching a diagnosis. Whilst reminder systems, educational outreach or system changes may be suitable when treatment or monitoring are the targeted behaviours, other interventions will almost certainly be needed for the very different clinical task of diagnosis. The educational interventions that might be employed include training in consulting skills, workshops on the features of cancer, possibly educational outreach or computerised decision support. The comparator intervention in an RCT would be either no intervention, educational materials or a basic workshop.

The intervention should be designed to take account of the difficulties primary care professionals face in detecting cancer. These include consulting behaviours (e.g. premature decision on a diagnosis, failure to re-consider a diagnosis, failure to conduct the appropriate examination, failure to take full account of parental concerns), lack of knowledge about the presentation of rare cancers or the significance of some symptoms, and anxieties about the possibility of missing a diagnosis. The RCT should therefore include a stage for development of the educational intervention. The study should consider several cancers, and might evaluate alternative educational interventions for each cancer.

Since primary care professionals encounter only a small number of patients with cancer each year, it would be necessary to consider the use of simulated patients or similar techniques in order to make the conduct of an RCT feasible.

Table 41 Recommendations for the study.

Category	Details
Intervention and control:	Name and type: education to improve primary care professionals' detection of patients with cancer. The control would consist of no intervention (normal practice).
	Formulation, route. N/A

	Dose, frequency. N/A
	Duration of therapy N/A
	Other (for example, surgical procedure)
Study aims:	Efficacy or effectiveness? Efficacy
	Better than or equivalent to other interventions? Better than routine continuing professional development
	Other
Target population:	Diagnosis, stage Primary health care professionals – general medical practitioners, nurse practitioners
	Baseline risk N/A
	Gender -
	Age groups: cancer presenting in unselected primary care patients
	Ethnic groups:
	Exclusions: undergraduates
	Other
Clinical setting:	Community, primary care, outpatient, secondary care, tertiary care: primary health care
	Other (for example, rural or urban)
Outcomes – main measures of benefit and harm/adverse events:	Type of outcome: reduction in delays in suspecting cancer and initiating referral
	Measurement method: interval between first presentation of symptoms and signs, and referral
	Blinding. Required in analysis
	Measurement frequency. N/A
	Total follow-up time. Six months
	Other

21.1.2 The presenting features of cancer in a large primary care population

Cancer is a relatively uncommon diagnosis in primary health care. Some cancers are so rare that a primary healthcare professional will never encounter a new case. Even the more common cancers often present with symptoms or signs that can occur in much more common benign conditions, and it can be difficult to distinguish at an early stage those patients who have cancer from those who do not. The available evidence on the features of cancer presenting is primary care is limited. Many of the studies considered in this guideline are case reports of patients attending secondary care. A small number of studies have been undertaken in primary care, but almost invariably these have involved a limited number of primary care providers and therefore included only small numbers of patients with cancer. Some cancers have been particularly neglected in research. These include gynaecological cancers, upper gastrointestinal cancers, bone cancers and children's cancers. The early detection of these cancers in primary care can be difficult, and a better evidence-base will be needed when these guidelines are updated in several years time.

A case-control study is required that includes a large primary care population in which 50- 100 cases of each of the following cancers would be expected to occur during the study period: gynaecological cancers, upper gastrointestinal cancers, bone cancers and children's cancers. Information about control populations with similar symptoms who were not referred would be collected during the study. In addition, reasons for delayed referral and diagnosis would be explored. General practice record systems would provide some data for such a study, but detailed information about the initial presenting features would be needed. In samples of cases, interviews of the referring professional would be used to obtain more detailed information about the process that led to the decision to refer. The study would also be able to compare the features of patients with and without cancer among those who were referred.

Table 42

Category	Details
Study aims:	Incidence, prevalence, severity To determine the incidence and predictive value of symptoms and signs that distinguish cancer among patients presenting in primary health care
	Causes, aetiology, disease progression
Target population:	Gender M and F
	Age groups. All
	Ethnic groups. All
	Diagnosis, stage of disease. Pre-diagnosis i.e. suspecting cancer and initiating referral
	Co-morbidity. -
	Baseline risk. -
	Exclusions. Nil
	Denominator/geographical context (for example, population based or hospital/primary care trust series). Patients in primary health care
How disease/exposure is defined:	Method, criteria. Disease is determined by final diagnosis after referral/ on follow up.

	Other
Clinical setting:	Community, primary care, outpatient, secondary care. Primary care.
	Other, for example rural or urban
Outcomes – main measure of disease/harm/error:	Name of measure. Predictive value of symptoms and signs (PPV and NPV)
	Measurement method. Observation of symptoms and signs in referred patients, and samples not referred.
	Measurement frequency. Once
	Duration of follow-up Until final diagnosis
Specific methods advised:	Challenge test (drug adverse events). -
	Cohort, case–control, observational. Case-control
	Retrospective/prospective study. Prospective
	Root-cause analysis (errors). -

*Permission to reproduce being sought

21.1.3 The support and information needs of patients when cancer is suspected and referral instigated.

Little or no evidence was found during development of the guideline to inform recommendations about the needs of people suspected of having cancer and at the stage of referral to specialist services. The guideline group had to reply heavily on their own experiences and on extrapolation of evidence from patients after the diagnosis of cancer. The needs and experiences of people who are referred but turn out not to have cancer have been overlooked in research almost entirely. The information about the reason for an urgent referral to be given to patients was extensively discussed among the group and in the comments of stakeholders, but research evidence is silent on this issue.

Table 43

Category	**Details**
Study aims:	To identify the support and information needs of people at the time of referral, when cancer is first suspected.
Target population:	Gender M and F
	Age groups. All
	Ethnic groups. All
	Diagnosis, stage of disease. Pre-diagnosis i.e. suspecting cancer and initiating referral
	Co-morbidity. -
	Baseline risk. -
	Exclusions. Nil

	Denominator/geographical context (for example, population based or hospital/primary care trust series). Patients in primary health care
How disease/exposure is defined:	Method, criteria. Disease is determined by final diagnosis after referral/ on follow up.
	Other
Clinical setting:	Community, primary care,.
	Other, for example rural or urban
Outcomes – main measure of disease/harm/error:	Name of measure. Patients' experiences of referral for suspected cancer, their views on the information they need, and support required.
	Measurement method. Interviews.
	Measurement frequency. Once or twice
	Duration of follow-up Until final diagnosis
Specific methods advised:	Challenge test (drug adverse events). -
	Cohort, case–control, observational. Case-control (i.e. people who are eventually diagnosed with cancer and those who are not)
	Retrospective/prospective study. Prospective
	Root-cause analysis (errors). -

21.1.4 The support and information needs of patients when cancer is suspected and referral instigated.

There is little evidence about the relationship between socio-economic status or ethnicity and diagnostic delay. Much of the evidence that is available is from other countries and its relevance to populations in England and Wales is uncertain. If there is a relationship between socio-economic status or ethnicity and delay, clinical services will need to take steps to reduce the delays experienced by such groups in order to reduce impact on survival.

A study is required to determine whether, and if so to what extent, socio- economic status and ethnicity influence delay. The study should address patient- related and service-related delays. A case-control study in a large population that includes significant numbers of people from ethnic sub-groups is required. A mix of quantitative and qualitative methods will be needed, and the study should seek to generate ideas for potential strategies to address delay (if delays are discovered).

It would be appropriate to limit the study to one or two cancers in the first instance, for example colorectal and children's cancers.

Table 44

Category	Details

Study aims:	To determine whether there is a relationship between socio-economic status or ethnicity and delay in presentation and referral.
Target population:	Gender M and F
	Age groups. All
	Ethnic groups. All
	Diagnosis, stage of disease. Pre-diagnosis i.e. suspecting cancer and initiating referral
	Co-morbidity. -
	Baseline risk. -
	Exclusions. Nil
	Denominator/geographical context (for example, population based or hospital/primary care trust series). Patients in primary health care
How disease/exposure is defined:	Method, criteria. Disease is determined by final diagnosis after referral/ on follow up.
	Other
Clinical setting:	Community, primary care.
	Other, for example rural or urban. Localities selected to include wide socio-economic and ethnic mix.
Outcomes – main measure of disease/harm/error:	Name of measure. Time from onset of first symptom to presentation in primary care, and time from presentation to referral.
	Measurement method. Quantitative and qualitative methods.
	Measurement frequency. Once or twice
	Duration of follow-up. Until final diagnosis
Specific methods advised:	Challenge test (drug adverse events). -
	Cohort, case–control, observational. Case-control (i.e. people who are eventually diagnosed with cancer and those who are not)
	Retrospective/prospective study. Retrospective.
	Root-cause analysis (errors). -

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