Clinical Guidelines for

The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care

This is the original document for reference and is not part of the consultation. Sections with a grey tint are being updated to take account of new evidence on MRI in surveillance.
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Citation:


Information for the Public

A version of the short form of this guideline written for women at risk of familial breast cancer, their families and the public is available from the NICE website (www.nice.org.uk) and from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0562 for a version in English only and reference number N0563 for a version in English and Welsh.)
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1. Key priorities for implementation

Approaches to care

1. Effective care involves a balanced partnership between patients and healthcare professionals. Patients should have the opportunity to make informed choices about any treatment and care and to share in decision making.

2. To ensure a patient–professional partnership, patients should be offered individually tailored information, including information about sources of support (including local and national organisations).

3. Standard written information regarding familial risk and breast cancer risk factors should be developed for use in primary, secondary and tertiary care, to provide consistent advice to women.

Family history and referral

4. When a woman presents with breast symptoms or has concerns about relatives with breast cancer, a first- and second-degree family history should be taken in primary care to assess risk, because this allows appropriate classification and care.

5. Healthcare professionals should respond to women who present with concerns, but should not, in most instances, actively seek to identify women with a family history of breast cancer.

6. Local protocols for the care of women at risk of familial breast cancer should be developed with clear referral mechanisms between primary, secondary and tertiary care, and with appropriate facilities.

Care

7. Access to psychological support and assessment is a key part of the package of care needed for many women covered by this guideline.

8. All women aged 40–49 years satisfying referral criteria to secondary or specialist care (at moderate or greater risk) should be offered annual mammographic surveillance.

9. Mammographic surveillance should only be undertaken after provision of information about its potential advantages and disadvantages for the early detection of breast cancer, and where offered this should be of high quality (equivalent to NHS Breast Screening Programme standard) and audited.

10. Genetic testing is appropriate only for a small proportion of women who are from high risk families.

11. Risk-reducing surgery (mastectomy and/or oophorectomy) is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team.
### Important messages to share with women with concerns

- Most women do not develop breast cancer, and of those who do most will not have a known family history of the disease.
- For most women increasing age is the greatest risk factor.
- The great majority of women with a family history of breast cancer do not fall into a high risk category and do not develop breast cancer.
- The great majority of women with a relative with breast cancer are not at substantially increased risk of breast cancer themselves.
2. Guideline development
2.1 The guideline

The guideline is aimed at all health care professionals providing care to women who present with concerns about the risk of developing breast cancer because of a family history.

The guideline aims to provide recommendations to help health care professionals in primary, secondary and tertiary care.

Guideline development methods are NICE development process, which are described in three NICE Guideline Development Process Manuals, available on the NICE website (www.nice.org.uk).

Key features of the guideline are that:

- it is evidence based, where evidence is available
- in areas where evidence is lacking this is made clear, and the consensus methods used are clearly described
- recommendations are explicitly linked to evidence where it is available
- the recommendations, methods and conclusions in the guideline are explicit and transparent.

The full scope of the guideline is presented in Appendix 22.

2.2 Using guidelines

Guidelines are only one type of information that health care professionals may use when making decisions about patient care. It is assumed that this guideline, like all guidelines, will be used by health care professionals who will also bring to bear their clinical knowledge and judgement in making decisions about caring for individual patients. It may not always be appropriate to apply either specific recommendations or the general messages in this document to each individual or in every circumstance. The availability of resources may also influence decisions about patient care, including the adoption of recommendations.

2.3 Responsibility and support for the guideline

The guideline was commissioned by NICE. The development of the guideline was undertaken by ScHARR, University of Sheffield, a provider partner in the National Collaborating Centre for Primary Care (NCC-PC). The guideline development group (GDG) was convened by the NCC-PC. The guideline development group consisted of relevant health care professionals, patient representatives and guideline developers, including a systematic reviewer. The membership of guideline development group is shown in Appendix 21.
2.4 Scope of the guideline

The scope of this guideline was care, and classification, of women at risk of breast cancer because of family history. The guideline covers women aged 18 years and older. It does not cover women who have breast cancer. It does not cover the care and management of men who may be at risk because of family history. The guideline addresses care in primary, secondary and tertiary care in respect of these women. However, the guideline does not cover in detail some aspects of some interventions that may be relevant, for example it does not address methods of screening in detail as that is outwith the scope. The full scope can be seen in Appendix 22.

2.5 Key clinical questions

The guideline development group identified the potential pathways that women with a family history of breast cancer might take in accessing and moving through health care services. From these pathways they identified potential interventions that might be available and also the decision points where these interventions might have to be considered by women and those involved in their care.

This evidence pathway is presented in Appendix 24, along with the literature search strategies.

2.6 Evidence identification

The development of the clinical guideline took an explicit, systematic approach to evidence identification, consideration and presentation. However it is perhaps worth noting that it is a clinical guideline and is resourced as such rather than a set of exhaustive systematic reviews. The guideline does not set out to undertake comprehensive systematic reviews for each topic area that it covers as this cannot be achieved with the resources available. In this guideline about 30 would have been required. The NICE guideline development process allows the use of existing meta-analyses and systematic reviews where they exist as a basis for evidence statements and recommendations.

The searching provided most of the papers contained in the guideline. This was in spite of the searching for articles that specifically addressed populations with a family history not being straightforward. Many papers addressed breast cancer in populations both with and without family histories and the indexing of papers in databases did not always pick this up, leading to some articles perhaps being missed. We used the expertise available on the group to identify papers that may have been missed as is common practice in NICE and other guideline development and other evidence assimilation processes.

In addition to the guideline scope the GDG identified key clinical questions to be addressed by the guideline these provided a starting framework for considerations of relevance. Late papers have been accommodated in the document and these have been discussed with the GDG to consider what if any impact they have on the recommendations, evidence statements and discussions in the relevant sections.
2.6.1 Search strategies

The search strategies attempted to locate the best available evidence for the interventions identified. It was recognised very early that in many instances this would not be meta-analyses, systematic reviews or RCTs. The searches therefore were wide ranging in the types of study that were searched for.

Searches for studies that included women with a family history of breast cancer, including BRCA1 and BRCA2 carriers were undertaken. However, in many instances studies relevant for family history were not found and therefore studies of general populations of women were also used.

Searches were limited to English language citations.

The databases searched and example search strategies can be found in Appendix 24.

For each intervention the evidence of effectiveness, evidence of harm and cost effectiveness information was sought.

2.6.2 Sifting and reviewing the evidence

Studies retrieved were assessed for their quality and relevance in answering the key clinical questions identified by the clinical working group and the pathways of care exercise.

For studies where our concern is that of what intervention seems to be most effective, then in our assessment of those studies our key concern was the quality of the study in terms of the various aspects of study validity. Firstly, if a study can credibly demonstrate the causal relationship between treatment and outcome then it can be said to have internal validity. Secondly, if the findings can be generalised from the specific study sample to a wider population, then it is said to be generalisable or to have external validity. Thirdly, if the study actually measures what it says it measures then it is said to have construct validity.

Study quality was assessed using modified SIGN checklists.

2.6.3 Synthesising the evidence

Extraction tables and narrative descriptions of studies were used to provide the basis for conclusions about the findings of the body of evidence.

Many meta-analyses and systematic reviews included papers that involved populations of women with a family history and women without a family history, and in many instances did not differentiate in any given conclusions etc. In the guideline if there are papers that were concerned primarily with women with a family history, we have often given a précis of these studies in addition to the meta-analyses/systematic reviews as this population is the one the guideline is primarily concerned with and may have information that is pertinent to this group but lost in the overall findings.

2.6.4 Areas without evidence

The guideline development group used informal consensus methods to derive evidence statements and recommendations in areas where research literature was not available, drawing upon their clinical knowledge and experience. Theses are graded accordingly (D level recommendations).
Although research evidence may be lacking there is a clinical need for this guideline and it is therefore acceptable to present consensus based recommendations for care.

### 2.7 Evidence grading

Once individual papers had been assessed for methodological quality and relevance in terms of our key clinical questions, they were graded according to the levels of evidence currently used by NICE.

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia:</td>
<td>evidence from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib:</td>
<td>evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa:</td>
<td>evidence from at least one controlled study without randomisation</td>
</tr>
<tr>
<td>IIb:</td>
<td>evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III:</td>
<td>evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV:</td>
<td>evidence from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

This classification is most appropriate for questions of causal relationships, and is usually used to assign studies, dealing with causal relationships, to levels of evidence.

In many areas within this guideline other types of evidence have been used. In many areas the best available evidence comes quite far down the hierarchy. In some instances the most appropriate type of study has been used (e.g. cohort), so despite attracting a ‘low’ level of evidence in this hierarchy, it is nonetheless the best and methodologically appropriate evidence. Thus the best evidence might not appear to be very strong but this should be seen in terms of a shortcoming of the grading approach rather than a reflection of the evidence available in many instances.

The literature was synthesised, using a qualitative narrative approach, to produce an evidence report. This also included health economics information. This evidence report, with summary evidence statements, was presented to the guideline development group.
2.8 Derivation and grading of recommendations

The derivation of recommendations usually involves assessment of evidence, processes of interpretation and consensus to arrive at recommendations. The mix of evidence, interpretation and consensus will vary between topic areas. The grading of recommendations takes account of this and therefore variation may occur between different groups presented with the same evidence. Whilst evidence statements can be formulated without reference to the context in which clinicians practise, this is not always the case with recommendations.

Recommendations were graded A to D, using the current NICE approach.

Grading of Recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>directly based on category I evidence</td>
</tr>
<tr>
<td>B</td>
<td>directly based on category II evidence, or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C</td>
<td>directly based on category III evidence, or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D</td>
<td>directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence</td>
</tr>
</tbody>
</table>

The NICE guideline development process requires that recommendations are graded on the basis of the evidence that underpins them. The recommendation grading process does not take clinical importance into account. In some instances a lower than expected recommendation grading may be presented, but this will be as a result of extrapolation of higher level evidence, and may for example reflect different populations or settings presented in the evidence and that found in clinical practice in England and Wales.

A low graded recommendation e.g. a D level recommendation does not therefore mean that it is not an important recommendation it only reflects the level of evidence, using the hierarchy described previously, that underpins the recommendation and is not a reflection of its clinical or policy relevance or importance.

2.9 Cost effectiveness review and analysis

NICE guidelines do not currently require a cost impact to be undertaken, which would model the likely cost of implementing all or some of the recommendations. It is recognised that the issue of resource implications of guideline implementation is a major concern. A pilot study to look at methods of undertaking cost impacts of guidelines is currently being commissioned.
2.9.1 Review

**Identification of papers**

This strategy aimed to identify all relevant studies of cost-effectiveness across the entire scope of the guideline. A literature search was undertaken alongside the clinical literature review. Details of the databases searched and the filters used to identify relevant economic studies are given in Appendix 24. Titles and abstracts were then examined by hand in order to identify cost-effectiveness, cost-utility or cost-benefit studies (CEA, CUA, CBA). Members of the guideline development group provided additional references that had not been identified by the searches.

Studies that did not appear to be CEA, CUA or CBA were not reviewed. This excluded a number of studies that examined only costs. Only primary studies were included except in the area of mammographic surveillance since in this area there were no studies relevant directly to women with a familial history but a large number of studies relating to the cost-effectiveness of surveillance in other women. Consistent with the clinical review, the IARC screening report (IARC 2002a) was used.

**Reviewing the evidence**

Eligible papers were assessed using the Drummond checklist (Drummond et al. 1996) for economic evaluations as a basis for review. A narrative was produced for each paper that reflected these methodological issues and any additional information that was considered relevant to the guideline.

2.9.2 Estimation of cost effectiveness

The scope of the guideline is broad, including the assessment of risk, genetic testing, management strategies including risk reducing surgery, chemo-prophylaxis, and surveillance. Inevitably there are substantial gaps in the economic evidence base. At an early stage the guideline development group identified those areas that they felt were most likely to require additional, primary economic analysis. A decision analytic model was developed as a result of these discussions in order to assess the cost-effectiveness of genetic testing of women at varying degrees of breast cancer risk due to familial history. This model is discussed in more detail in Appendix 20.

2.10 Consensus in recommendations

There may be areas where the group was unable to reach consensus on an area, no matter whether evidence is available or not. Where this has happened it is stated that a consensual recommendation could not be reached, the opposing views are presented and the final decision is left to the user of the guidelines.

Consensus was reached in all recommendations.
2.11 Guideline review

The process of reviewing the evidence is expected to begin 4 years after the date of issue of this guideline. Reviewing may begin earlier than 4 years if significant evidence that affects the guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.
3. Women with a family history of breast cancer
3.1 Introduction

Most women do not develop breast cancer, and of those who do most will not have a known family history of the disease.

Breast cancer is a multifactorial disease which may involve lifestyle, environmental, reproductive as well as genetic factors and as with many other cancers, as yet unknown factors. Even where a woman has a relative with breast cancer it may well be due to chance rather than genetic or shared lifestyle factors.

Some women will have one relative who has had a diagnosis of breast cancer. In many instances these affected relatives will be in the older age range when a diagnosis of breast cancer was given. This type of family history is not that which will increase the risk in women discussed in this document. Rather it reflects that for most women as they get older their risk of breast cancer increases. The family histories that can be considered relevant and pertinent to any increased risk are discussed in the relevant sections where referral criteria are discussed. Therefore it may be helpful to think in terms of relevant (in terms of risk) family histories when the terms family history is used in the guideline.

However for some women with a family history, where there is a cluster of affected family members, there is a considerable degree of worry associated with knowing about the possible increase in risk associated with having a family member who has had breast, or ovarian, cancer. Familial breast cancer typically occurs in women within a family where there have been an unusually high number of family members affected by breast cancer. If there have been more cases of breast or related cancers than would be expected by chance alone, it may be that genes transmitted between generations are sufficient to cause or, more typically, contribute to the development of breast cancer.

In this guideline evidence based information and recommendations for management are presented. An important factor is that of helping concerned women better understand the issues and risks involved. Perhaps even more important is the need to ensure that women are offered appropriate reassurance whenever necessary to prevent unnecessary worry and distress.

3.2 Incidence and prevalence

Breast cancer is the most common cancer in women and accounts for between 18-25% of all female malignancies world-wide (Office for National Statistics 2001, McPherson et al 2000). Although breast cancer incidence and mortality varies considerably around the world, the proportion of women who develop breast cancer is higher in western, developed countries. The lifetime risk (to 85 years of age) of developing breast cancer in more developed countries world-wide has been estimated in the UK at 11% (1 in 9 women) (Office for National Statistics 2001, NHS Cancer Screening Programmes and Cancer Research Campaign 2001). Cancer of the breast is the commonest cancer to affect women in the United Kingdom, accounting for nearly 30% of cases of cancer in women (Office for National Statistics 2001). In 1997 there were 33,100 new registrations of female breast cancer in England and Wales, representing almost 30% of all cancers in women, more than twice as many as for colorectal cancer, the second most common female cancer (Office for National Statistics 2001).
The overall incidence of breast cancer in England in 2000 was 114 per 100,000 female population. Four in five new cases are diagnosed in women over the age of 50, with the peak in distribution of new cases in the 50-54 age group. The 5-year relative survival rate for women diagnosed with breast cancer was 73% for women diagnosed in 1991-95 and 78% for women diagnosed in 1996-99. This means that three quarters of women diagnosed with breast cancer were still alive five years after their diagnosis (all ONS 2003).

The exact causes of breast cancer remain unclear. However, it has been estimated that up to 27% of women may have an inherited predisposition to breast cancer (Peto & Mack 2000). Nonetheless only 3-5% are likely to carry gene faults which conferred a very substantial (>50%) risk of breast cancer (Claus et al 1994; Ford et al 1998). Media reporting often gives the impression that a greater proportion of cases are linked to genetic inheritance. Since breast cancer is relatively common, it can be difficult for women to know whether any case in a relative indicates a familial inheritance or not. As such, questions about possible familial breast cancer may be expressed to (or raised by) general practitioners, symptomatic breast clinics, breast screening services and others. The size of the demand this puts on health services does not appear to have been accurately assessed in the UK.

3.3 The role of family history

Known risk factors for developing breast cancer relate to an individual’s age, lifestyle and environmental factors, reproductive history (for example, early menarche, number of children, late 1st pregnancy), previous benign breast disease and family history (NHS Cancer Screening Programmes and Cancer Research Campaign 2001).

Family history is one of the strongest risk factors for developing breast cancer (Emery et al 2001). Although a woman in the general population aged 70 years of age has a 3% risk of breast cancer in the next 10 years a woman with a BRCA1 mutation has as much as a 15% risk for the next 10 years when aged only 30 years (Ford et al 1998). Whilst the majority of cases of breast cancer arise in women with no apparent family history, between 6-19% of women with breast cancer will have a family history of the disease (Department of Health 2000, Hill et al 1997). This clustering of breast cancer in a family may be due to chance, shared environmental/lifestyle risk factors, or to increased genetic susceptibility.

A large reanalysis of epidemiological data world-wide has found that the probability that women in more-developed countries will develop breast cancer increases according to the number of affected 1st degree relatives (Collaborative Group on Hormonal Factors in Breast Cancer 2001). The probability of a woman aged 20 developing breast cancer by the age of 80 who has no affected relatives is 7.8%, 1 affected relative, 13.3% and 2 affected relatives, 21.1%. Also, the risk of developing breast cancer is greater the younger the relative is when she developed the disease. For example, a woman whose sister developed breast cancer between the ages of 30-39 has a cumulative risk of 10% of developing the disease herself by age 65, but that risk is only 5% (close to the population risk) if the sister was aged 50-54 when breast cancer was diagnosed (McPherson et al 2000). The lifetime risks of breast cancer (to age 80 years), the remaining risk (to 80) and the risk over the next 10 years is shown (Table 1) for the general population (ONS 2001), and for a woman with a mother or sister diagnosed aged 30-39 years (Claus et al 1994 and Collaborative Group on Hormonal Factors in Breast Cancer 2001).

It must be appreciated that the risks derived from the CASH dataset (Claus et al 1994) are from an era when breast cancer was less frequent in the general population (prior to screening and increase in other risk factors such as HRT). At the time of derivation the risks to women with a sister or mother
with breast cancer less than 40 years of age represented a true doubling of lifetime risk. This is reflected to some extent in the lack of increase in the last 20 years of life (from the table), which is unlikely to be true. Nonetheless the table demonstrates the 10 year risks at 40 years of age for the woman with an affected relative being the same or more (using Collaborative Group data) as for the general population a decade later. Indeed recent validation of the risks in a familial screening clinic have shown that the risks are underestimated in the single affected relative category (Amir et al 2003) and use of Collaborative group data may improve risk accuracy in this group. Although lifetime risks are now commonly quoted to 80 years of age (the definition used in these guidelines) these are not available for familial risks beyond 79 years.

Table 1: Lifetime risks of breast cancer\(^1,2\)

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Population - 10 year risk(^3)</th>
<th>Claus - risk next 10 years(^4)</th>
<th>Collaborative Group - risk next 10 years(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.1%</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>30</td>
<td>0.4%</td>
<td>1.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>40</td>
<td>1.5%</td>
<td>2.7%(^7)</td>
<td>4.1%(^8)</td>
</tr>
<tr>
<td>50</td>
<td>2.8%(^6)</td>
<td>4.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>60</td>
<td>2.8%</td>
<td>4.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>70</td>
<td>3.1%</td>
<td>3.5%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Notes:
1. All figures rounded to 1 decimal place
2. Cumulative risk figures for this table are presented in Appendix 25
4. Claus et al 1994, risks for a woman with a sister or mother with breast cancer aged 30-39 years
5. Collaborative Group 2001, risks for a woman with a sister or mother with breast cancer aged 30-39 years
6. Entry to NHSBSP
7. Risk level similar to NHSBSP
8. Collab group risk estimate

From Table 1 it can be seen that the risk estimate that gains entry to the NHSBSP is 2.8%. A similar risk estimate for women with a family history was found from Claus at age 40 (2.7%). The corresponding risk estimate from the Collaborative Group was 4.1%. Therefore a risk estimate between 2.7% and 4.1% was thought by the guideline development group to indicate a risk estimate that would be reasonable to justify as moderate risk, hence a figure of 3% was agreed by the guideline development group.

It has been estimated that for a total population of 1 million with an age and sex structure comparable to that of England and Wales there would be 20-40 families whose family history of breast cancer would indicate that members had a high risk of developing breast cancer (R&D Office of Anglia and Oxford 1998). Furthermore, 4,450 women aged 35-49 would be estimated to be at moderate risk of developing the disease, out of a total of 47,000 women at risk.
Family history, however, is not always a reliable indicator of those with gene mutations. Known genetic gene mutations are implicated in only about 2-5% of all cases of breast cancer (NHS Cancer Screening Programmes and Cancer Research Campaign 2001, Department of Health 2000). It is not yet known how many breast cancer genes there may be, although two breast cancer genes, BRCA1 and BRCA2, have been identified and account for a considerable proportion of very high risk families, that is, those with four or more close relatives who have breast cancer (McPherson et al 2000). Certain populations have been found to have different rates of certain genetic alterations. In the Ashkenazi Jewish community three “founder” mutations (two in BRCA1, one in BRCA2) are relatively common and explain almost all the high risk families due to these genes, and other populations have been found to have higher rates of BRCA1 and BRCA2 alterations (e.g. Norwegian, Dutch and Icelandic people). Breast cancer genes may be transmitted through either sex and some family members may transmit the abnormal gene without developing cancer themselves. However, carrying the gene mutation gives a high lifetime risk of developing breast cancer; it is estimated that the risk is as high as 50% of developing the disease by the age of 50, rising to 85% (for some families) by the age of 70 (R&D Office of Anglia and Oxford 1998). Genetic, or hereditary, breast cancer is usually characterised by early onset, a high incidence of bilateral disease and an association with other malignancies; for instance, inherited factors are thought to contribute to 25-35% of cases diagnosed before the age of 30 (Hill et al 1997). Indeed mutations in the known high risk genes BRCA1, BRCA2 and TP53 have been demonstrated in 20% of a population based sample of women with breast cancer aged 30 years and under (Lalloo et al 2003).

3.3.1 Ovarian and prostate cancers: family history issues

The largest proportion of hereditary ovarian cancer cases originate from families with significant family histories; either of ovarian, breast or both cancers. The majority of these families are due to mutations in BRCA1. Therefore a combination of ovarian cancer and breast cancer or multiple cases of ovarian cancer in families implicates a potentially increased risk of breast cancer. Stratton et al. (1999) in a population study of ovarian cancers found that 3% had probable germ-line BRCA1 mutations and that BRCA1 mutations contribute to 5% of all ovarian cancer cases. It is important, however, to distinguish between epithelial ovarian cancer and the rarer germ cell tumours of the ovary in which there is no clear association with an increased risk of either ovarian cancer or of breast cancer in close relatives. There is also evidence to suggest that it is only certain types of epithelial ovarian cancer that confer an increased risk. Mucinous cancers are not associated with BRCA1 or BRCA2 mutations (Werness et al., 2000) and do not appear to increase risk in case control studies for either breast or ovarian cancer (Shah et al., 1994). Borderline tumours of the ovary are also not associated with a significantly increased risk of either BRCA1 or BRCA2 (Stratton et al 1999; Werness et al., 2000) and do not appear to substantially increase the risk of invasive ovarian cancer in relatives (Stratton et al., 1999).

Prostate cancer can be linked with breast cancer in BRCA2 families. A relative risk of 4-5 fold for early onset prostate cancer has been reported and 2-3% of early onset prostate cancer (<55 years) can be due to BRCA2 mutations (Edwards et al 2003). Nonetheless a history of prostate cancer alone in a family will not substantially increase breast cancer risk and even in addition to breast cancer will only add a small amount to the likely hereditary component.

3.4 Impact on individuals with a family history of breast cancer

Understanding the role of inherited gene mutations in familial breast cancer brought promise of genetic testing for breast cancer susceptibility and targeted risk management and preventative strategies. In response, there has been a rapidly increasing demand for information from women with
a family history of breast (and/or ovarian) cancers. However, the wider implication of having a family history of breast cancer affects an individual at many levels.

Women may want to know the significance of the family cancers for their personal risk and discuss what they can do to reduce it, but not all family members will be at the same state of readiness to seek risk information (Hagoel et al 2000). Obtaining the necessary family pedigree may be distressing due to the need to contact estranged relatives and to raise painful issues. Decisions about having children and aspects of lifestyle can be affected because of a family history, and those found to carry a genetic mutation may experience guilt about passing a gene to a new generation. Therefore risk counselling is strongly advocated to help prepare counselees for their emotional reactions to genetic testing and decisions about disclosure to the family.

Overall, women attending Cancer Genetics Clinics are not found to be more anxious than other women in the population (Brain et al 2000, Cull et al 1999, Thirlaway et al, Lloyd et al 1996) but they have increased breast cancer specific worries (Lloyd et al 1996). Concerns that informing women about a high risk of breast cancer could induce or increase anxiety or depression have not been borne out by research studies. A minority of women who had experienced the diagnosis or death of a mother may experience subsequent psychological problems or unresolved grief; daughters who were adolescents or in early adulthood are particularly vulnerable (Wellisch et al 1992, Hopwood et al 1998, Watson et al 1999).

Women state that the value of mammographic surveillance cannot be underestimated, but access is limited for young women at risk and the benefits are currently being researched. Preventive surgery and chemoprevention trials require careful balancing of the possible effects on fertility, body image, menopausal effects and unwanted side effects, leading to potentially difficult decision making.

Men who may be gene carriers are less likely to be tested than women so that information may not be available to unaffected women at risk, and this, together with men’s own guilt and anxiety, may affect family dynamics (Dudok de Wit et al 1996).

Ethnic minorities and less well-educated women are under-represented in clinic attendees (Wonderling et al 2001). The number of affected relatives, relationships and position in the family may affect motivation for risk counselling and increased public awareness of cancer genes can lead to further pressure on individuals to deal with their risk.
4. Risk assessment and classification (including family history taking) and risk communication

Note:
This section contains the evidence review and evidence statements about risk assessment and classification. The recommendations relating to risk assessment and classification have been presented in the sections that address the primary, secondary and tertiary care management recommendations, as different actions will be required in each of the different settings. However, the evidence base is not split into these different care settings as it was considered as a body of evidence with appropriate recommendations for each setting then being derived.

Throughout the guideline, where risk levels and estimates are presented/discussed, refer to Table 1, Appendix 26 and accompanying text for discussion and explanation.
4.1 Risk estimation

There are breast cancer risks that all women are exposed to (population level); risks that sub-populations (e.g. certain types of family history) are exposed to and the risks for each individual woman. The risks of breast cancer can be expressed in terms of an age-specific risk (e.g. risk over the next five years), or a lifetime risk (e.g. risk to age 80). Another important measure is the chance that a mutation in a high risk breast cancer gene (BRCA1 or BRCA2) may be present.

In many situations, the breast cancer risk to a woman with a family history of the disease can be estimated straightforwardly from epidemiological studies. These indicate that the risk of breast cancer to a woman with a single affected first degree relative is approximately twice the risk to women in general. The risks are higher if there are more affected relatives, or if the relative(s) is affected at a younger age.

With more complex situations, risks can be estimated by applying risk algorithms, although these models can give inconsistent results and have not been thoroughly evaluated.

Different risks apply to women who are carriers of mutations in the known high-risk genes, BRCA1 or BRCA2. The risk to carriers of BRCA1 mutations have been estimated to be 60-80% by age 70, while the risk to carriers of BRCA2 mutations is somewhat lower and for both genes the risks could be lower in a family with an identified mutation, but little family history. In most instances it is unlikely that a family history of breast cancer will be due to known high-risk genes such as BRCA1 or BRCA2 and we are only beginning to appreciate the contribution of other lower risk genes that may account for more breast cancer overall. In the absence of good epidemiological evidence on these other genes use of existing algorithms for calculating risk is still valid and most will take into account the possibility of such genes being involved.

Epidemiological studies indicate that risks associated with a family history are modified by other known breast cancer risk factors, including age at menopause, parity and breast feeding. It is less clear whether such factors also modify the risks in BRCA1 or BRCA2 carriers.

It must also be remembered risks can be expressed in terms of relative risk or absolute risks. Many research papers often give results in terms of relative risks, one group compared to another, which need to be considered in the context of both absolute and relative risks, especially as the relative risks often sound very dramatic/extreme changes in risk level.

4.2 Risk classification

In this guideline recommendations for care are presented in sections that reflect where the care is likely to be delivered, e.g. primary, secondary or tertiary care, rather than in categories of risk level, e.g. low, medium or high. This is done firstly to reflect service provision as much as possible and secondly to try and avoid problems that previously occurred with the use of low, high and medium risk level descriptions.

In the past, risk categories have been broadly described as 1. “low”, 2. “moderate” and 3. “high” risk. During the guideline development process it became clear that while the latter 2 terms (moderate and high) were generally accepted, the term “low” was misleading and in particular not accepted by patient groups and the lay members of the committee. It was considered misleading as these women...
are still at increased risk compared to the general population. Other alternatives were considered, but the group finally felt that definitions should be described on the basis of whether women were cared for in primary, secondary or tertiary care following risk assessment. However it is also recognised that descriptions of women at high and moderate risk will also be necessary in some situations, and that the terms will still be used by many people in the clinical setting. As has been made clear in the relevant sections it is NOT expected that precise risks will be calculated in primary or secondary care, but that health care workers will utilise the algorithms provided. The thresholds for entry to each risk category are based on:

**Near population risk:** Women at or near **population risk** of developing breast cancer (that is, a 10-year risk of less than 3% between age 40 and 50 years and a lifetime risk of less than 17%) are cared for in primary care.

**Moderate risk:** Women at **moderate risk** of developing breast cancer (that is, a risk of 3–8% between age 40 and 50 years or a lifetime risk of 17% or greater but less than 30%) are generally cared for in secondary care.

**High risk:** Women at **high risk** of developing breast cancer (that is a risk of greater than 8% between age 40 and 50 years or a lifetime risk of 30% or greater) are cared for in tertiary care. High risk also includes a 20% or greater chance of a faulty **BRCA1**, **BRCA2** or **TP53** gene in the family.

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**In the context of this guideline**

All affected relatives must be on the same side of the family and be blood relatives of the consultee and each other.

In cases of **bilateral breast cancer**, each breast cancer has the same count value as one relative.

**First-degree relatives:** mother, father, daughter, son, sister, brother.

**Second-degree relatives:** grandparents, grandchildren, aunt, uncle, niece and nephew; half sister and half brother.

**Third-degree relatives:** great grandparents, great grandchildren, great aunt, great uncle, first cousin, grand nephew and grand niece.
4.3 Family history taking

Recommendations

Note: these are repeated in the sections dealing with primary and specialist care

Family history taking and initial assessment in primary care

1. When a woman presents with breast symptoms or has concerns about relatives with breast cancer, a first- and second-degree family history should be taken in primary care to assess risk because this allows appropriate classification and care. (D)

2. Healthcare professionals should respond to women who present with concerns but should not, in most instances, actively seek to identify women with a family history of breast cancer. (D)

3. In some circumstances it may also be clinically relevant to take a family history, for example for women older than age 35 years using an oral contraceptive pill or for women being considered for long-term HRT use. (D)

4. Women should be given the opportunity to discuss concerns about their family history of breast cancer if it is raised during a consultation. (D)

5. A second-degree family history (that is, including aunts, uncles and grandparents) should be taken in primary care before explaining risks and options. (D)

6. A second-degree family history needs to include paternal as well as maternal relatives. (D)

7. Asking women to discuss their family history with relatives is useful in gathering the most accurate information. (D)

8. Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and they should be made available. (C)

9. For referral decisions attempts should be made to gather as accurate information as possible on:
   - age of diagnosis of any cancer in relatives
   - site of tumours
   - multiple cancers (including bilateral disease)
   - Jewish ancestry. (D)
Family history taking in secondary care

10. A family history should be taken when a woman presents with breast symptoms or has concerns about relatives with breast cancer. (D)

11. A third-degree family history should be taken in secondary care where possible and appropriate. (D)

12. Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and risk assessment and they should be made available. (C)

Family history taking in tertiary care

13. A third-degree family history should be taken in tertiary care, if this has not been done previously. (D)

14. For accurate risk estimation the following are required:
   - age of death of affected and unaffected relatives
   - current age of unaffected relatives. (D)

15. In general, it is not necessary to validate breast cancer only histories (via medical records/cancer registry/death certificate). (D)

16. If substantial management decisions, such as risk-reducing surgery, are being considered clinicians should seek confirmation of breast cancer only histories (via medical records/cancer registry/death certificates). (D)

17. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with risk reducing surgery. (D)

18. Abdominal malignancies at young ages and possible sarcomas should be confirmed in specialist care. (D)

Evidence statements

1. Reporting of breast cancer family histories, by women with and without breast cancer, is generally valid. (III)

2. Completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist. (Ib)

3. Poor communication amongst families can impede the collection of family history information. (III)

4. Postal questionnaires and family history assessment tools are useful instruments to support the identification of women at increased risk of breast cancer. (III)
5. *GPs have been found to prefer computerised programs to collect family history information compared to pen-and-paper methods.* (III)

6. *Computer support programmes have been found to produce more accurate pedigrees and more appropriate management decisions.* (III)

4.3.1 Introduction

Drawing a family tree is the first step in investigating a possible inherited predisposition to breast cancer. This will mean asking a woman to tell you about all their close relatives. It is necessary to know what age they have lived to, what tumours they may have had and the age at which these were diagnosed. Thus a family tree is drawn showing the consulting woman with an arrow and drawing out her first degree relatives (mother, father, sisters, brothers, children); her second degree relatives (grandparents, aunts, uncles, nieces, nephews) and in a thorough history third degree relatives (great grandparents, great aunts and uncles, first cousins). While family history of breast cancer in first degree relatives is nearly always correctly given (the cancer can be verified from pathology records or death certificates) this becomes more problematic for more distant relatives and is particularly a problem for abdominal malignancies and sarcomas (Douglas et al 1999). Verification of family history is an essential part of assessment in a cancer genetics clinic.

4.3.2 Research literature evidence

Studies


In a crossover experiment involving a random sample of 36 UK general practitioners, the potential impact of computer support for interpreting family histories of familial breast and ovarian cancer and the effectiveness of two different types of computer programme were evaluated. Eighteen hypothetical cases designed to cover a range of risk levels were managed by each doctor, six each with the following methods of support: RAGS, a computerised decision support system; Cyrillic, an established family history drawing programme designed for clinical geneticists; and pen and paper. Results showed that RAGS produced significantly more appropriate management decisions (median 6) compared to either Cyrillic (median 3) or pen and paper (median 3), with a median difference between RAGS and Cyrillic of 2.5 (95% CI, 2.0-3.0; P<0.0001). Significantly more accurate pedigrees were also taken using RAGS compared to Cyrillic and pen and paper, with a median difference between RAGS and Cyrillic of 1.5 (95% CI, 1.0-2.0; P<0.0001). RAGS took longer to use per case than pen and paper, but was quicker than Cyrillic (P=0.02). Thirty-three doctors (92%) preferred using RAGS overall.


A family history assessment tool (FHAT) for use by clinicians in selecting individuals for genetic counselling underwent a preliminary validation in this Canadian study involving 184 unrelated families at risk of breast and ovarian cancer. Women who were either selected or excluded by the tool were compared to how those same individuals would be assessed using a doubling (22%) of the lifetime risk as estimated by Claus and by BRCAPRO. The number of women who tested positive for BRCA1/2 mutations who would have been selected or excluded by each of the methods was also assessed. The FHAT performed well in selecting patients for referral as compared to using the Claus
or BRCAPRO methods. Both positive and negative predictive values for the FHAT were better than the Claus tables (0.31 and 0.97 v 0.28 and 0.90, respectively). BRCAPRO was more effective in reducing the number of referrals for genetics but would have missed some women selected by the FHAT and found to be mutation-positive.


The reliability of maternal history of cancer information was assessed as part of a US case-control study by comparing the medical records of 214 women with breast cancer and of their controls aged 26-59 years and diagnosed between 1974-1995, with the records of their mothers. In the sample of women, 30% of cases and 17% of controls had a maternal cancer history. For any type of cancer, the proportion documented in the daughter’s medical record was only 56% among cases and 32% among controls, although for breast cancer, the percentage was higher (79% among cases and 57% among controls).


The validity of the family history of breast cancer as reported by the patient was evaluated in a Finnish survey of 288 women with breast cancer. Family history of breast or ovarian cancer was reported by approximately 30% of the patients, with 7-9% classified as breast cancer families. The information reported by the patients proved to be quite accurate, with only about 5-7% of all reported diagnoses among breast cancer families found to be incorrect.

**Emery et al (1999)**

General practitioners’ attitudes towards and use of a computer programme for assessing genetic risk of cancer were explored in a UK qualitative study, using interviews and video recordings of simulated consultations. A purposive sample of 15 general practitioners took part, with each doctor using the Risk Assessment in Genetics (RAGS) programme in 2 consultations in which an actor played a women concerned about her family history of cancer. Results indicated that most of the doctors found the programme easy to use and an appropriate application of information technology, but it affected their control of the consultation, in that they wanted to share the computer screen with the patient but were concerned about the risk of premature disclosure of bad news.

**Leggatt et al (1999)**

In a UK survey in general practice, the feasibility of using a postal questionnaire to identify patients at increased genetic risk of breast or colorectal cancer was assessed. 960 patients aged 35-65 years registered at one practice took part and were sent a questionnaire requesting details of first degree, second degree and more distant relatives known to have had cancer; of these 666 returned the questionnaire. The majority of patients were assessed to be at lower risk (not at sufficiently increased risk of breast or colorectal cancer to be offered surveillance). Twenty-nine patients were assessed to be at higher risk; of these, 14 had previously received genetic advice, although 12 of the remaining 15 patients had never previously discussed their family history with their general practitioner. The authors conclude that a self-completed questionnaire was a useful instrument to identify patients at increased genetic risk.

**Kerr et al (1998)**

Case studies are presented of 5 individuals attending UK and North American family cancer or genetic counselling clinics whose factitious family or personal history resulted in inaccurate risk estimations. Factors which may indicate a false history are a history of benign breast disease, poor
communication within families, long survival with early onset or bilateral disease, a lack of detailed knowledge of the illness and treatment in close relatives, and inconsistencies in the history in repeated consultations. The authors note the importance of verifying family histories because a false family or personal history of breast cancer is not a rare occurrence and has serious implications for risk assessment and management.

Parent et al (1997)

Pathology records were compared with reports of breast cancer events among 125 first-degree relatives provided by 68 women with breast cancer and 37 women without the disease in a Canadian study. Sixty-seven (90.5%) of the reports of the occurrence of breast cancer in relatives by affected women and 32 (97.0%) of those by unaffected women were accurate. Women reporting several affected relatives often over-reported the presence of breast cancer events. The authors conclude that reliance on reports by patients should not critically affect the assessment of breast cancer risks for family members.

Green et al (1997)

Forty-six women attending a UK genetics clinic for familial breast/ovarian cancer took part in interviews as part of a longitudinal qualitative study which assessed the process of communicating family history between family members. Nearly all the women reported affected maternal, rather than paternal, relatives which may indicate lack of awareness. Thirty-six (78%) of the 46 women approached at least one relative for information before going to the clinic, with mothers, if they were still alive, being the key figures in supplying family information. Although most women contacted at least one relative regarding counselling, most named a relative with whom they did not feel able to communicate on this subject. The communication process was impeded by factors such as divorce, adoption, family rifts and large age groups between siblings.

Theis et al (1994)

The validity of information relating to family histories of cancers reported by 165 Canadian women with breast cancer was assessed using questionnaires and interviews. Results showed that questionnaire and interview reports agreed with records for 82-96% of reports on first-degree and 48-80% on second-degree relatives. In terms of reported cancer sites, these were generally accurate in first-degree relatives (breast 99%, ovary 100%, prostate 85% and colon 93%). Reports for second-degree relatives were accurate for prostate cancer but only for 85% of breast and 72% of colon cancers. The authors conclude that in a similar population, use of the questionnaire alone should provide adequate data for identifying families which need to undergo further genetic investigation.


Lalloo et al examined the correlation between frequency and penetrance of BRCA1, BRCA2 and TP53 mutations in young women (30 and under) with a diagnosis of breast cancer and family history. They found that 17 of 36 familial cases had a BRCA1, BRCA2 or TP53 mutation compared with three of 63 non-familial cases. They also found that TP53 accounted for 4% of patients diagnosed with breast cancer at a young age, rather than the usual reported rate of 1%. Their conclusions were that family history was important to ensure that those women who need altered management (eg TP53 carriers with the high risk of radiation induced tumours) were identified.
4.3.3 Family history taking: (psychosocial outcomes)

Qureshi et al (2001)

A UK randomised controlled trial was conducted to assess the psychological impact of a family history-screening questionnaire used in general practice. Individuals who had not had a health check within the previous 2 years were randomised to an intervention (receiving a health check and a self-administered family history questionnaire; n=50) or to a control group (health check only; n=50). Of the 100 patients, 76 of them were followed through to the 3-month end point. Results showed that at both 1 and 2 weeks after the health check, anxiety was higher in the intervention group than the control group ($F=6.4; df=1,73; P=0.014$), but at 3 months, there was no significant difference between the groups. These results would suggest that the family history questionnaire led to short-term psychological distress, but this did not persist.


The psychological impact of completing a cancer family history questionnaire and receiving an assessment of personal genetic risk of breast or colorectal cancer was evaluated in this UK survey. A total of 604 patients registered with a single general practice returned baseline (before completion of the questionnaire) and follow-up (4-6 weeks after receipt of their risk assessment) measures of anxiety and cancer worry. Patients were assessed to be either not at significantly increased risk (lower risk group; n=568) or at potentially increased risk; of the latter group, 25 patients were subsequently confirmed to be at significantly increased risk (higher risk group) and 11 deemed not to be at significantly increased risk (false positive group). There were no differences between the 2 time points for any of the groups except for the lower risk group, where perceptions of personal risk of developing cancer showed a small reduction ($P<0.001$). For both the higher risk group and the false positive group, baseline responses showed that their pre-existing breast cancer risk perception was higher than that of the lower risk group ($P<0.001$ and $P=0.003$, respectively). The authors conclude that completion of a cancer family history questionnaire and receipt of risk assessment does not make patients more anxious or worried about cancer.

Winter et al (1996)

To determine the impact of breast cancer risk notification on family members, 376 male and female relatives of 160 breast cancer patients were contacted as part of a US epidemiological follow-up study. Participants were surveyed to assess prior knowledge of family history of cancer, issues relating to study participation and concerns regarding developing cancer. Results showed that 24% of blood relatives were not aware of their family history of breast cancer, and more blood relatives (76%) than non-blood relatives (62%; $P<0.01$) were aware of their family history. Forty-three (12%) of participants expressed concerns about taking part in a large genetic follow-up study. Level of concern about developing cancer was high across all participants (range 50-78%), with males being as concerned as females and non-blood relatives only slightly less concerned than blood relatives. The authors conclude, however, that risk notification does not appear to have a significant detrimental impact on family members.

4.3.4 Summary of evidence relating to recording and assessing family history

A number of studies have been identified which relate to the recording and assessment of family history in women with a family history of breast cancer, although generally, study design lacks rigour.
Four studies have assessed the accuracy of the family histories provided by women with and without breast cancer and have found that reporting of breast cancer family histories is generally reliable (Theis et al, 1994; Parent et al, 1997; Eerola et al, 2000; Husson et al, 2000). Case studies have shown, however, the importance of verifying family histories as a false family history has serious implications for patient management (Kerr et al, 1998). Another study found poor communication amongst families can impede the collection of family history information (Green et al, 1997).

Two studies have evaluated methods of identifying patients at increased genetic risk of breast and other cancers suitable for referral for genetic screening (a postal questionnaire and a family history assessment tool), both of which appeared to be useful instruments (Leggatt et al, 1999 and Gilpin et al, 2000, respectively). A computer support programme for interpreting family histories of breast and ovarian cancer was found to produce more accurate pedigrees, more appropriate management decisions and was preferred by doctors, in comparison to other methods (Emery et al, 2000); doctors found, however that it affected their control of the consultation (Emery et al, 1999).

In terms of evidence relating to psychosocial aspects of recording and assessing family history of breast cancer, 2 surveys have found that collecting family histories and notifying family members about their cancer risk does not appear to cause anxiety (Winter et al, 1996; Leggatt et al, 2000). An RCT, however, found that completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist (Qureshi et al, 2001).

4.3.5 Comment

Family history can be by far the most significant factor in predisposition. About 4-5% of breast cancer is thought to be due to inheritance of a highly penetrant dominant cancer predisposing gene (Newman et al 1988, Claus et al 1994). However, these type of genes may only account for about 20% of the familial risk as up to 27% of breast cancer is attributable to heritable factors from twin studies (Peto & Mack 2000). If a woman inherits a fault in one of these genes her lifetime risk of breast cancer may be as high as 80-85%. Hereditary factors may play a part in a proportion of the rest, but these are harder to pin down. There are no external markers of risk (no phenotype) to help identify those who carry a faulty gene, except in very rare cases such as Cowden's disease (Nelen et al 1996) and Peutz Jegher disease. In order to assess the likelihood of there being a predisposing gene in a family, it is necessary to assess the family tree. Inheritance of a germ line mutation or deletion of a predisposing gene causes the disease at a young age and often, if the individual survives, cancer in the contralateral (opposite) breast. Some gene mutations may give rise to susceptibility to other cancers, such as ovary, colon and sarcomas (Malkin et al 1990, Leach et al 1993, Papadopoulos et al 1994, Nicolaides et al 1994). Multiple primary cancers in one individual or related early onset cancers in other relatives are, therefore, suggestive of a predisposing gene. To illustrate the importance of age it is thought that over 25% of breast cancer under 30 years is due to a mutation in a dominant gene, whereas less than 1% of the disease over 70 years is so caused (Claus et al 1994). The important features in a family history are therefore:

- age at onset
- bilateral disease
- multiple cases in the family (particularly on one side)
- other related early onset tumours.
- number of unaffected individuals (large families are more informative).

There are very few families where it is possible to be sure of dominant inheritance, but where 4 relatives in the same direct lineage (all related in first degree to at least one other affected individual) have early onset or bilateral breast cancer the risk of inheriting a gene for their offspring is close to 50%. Epidemiological studies have shown that about 80% of gene carriers develop breast cancer in their lifetime. Therefore, unless there is significant family history on both sides of the family, the
maximum risk counselled is 40-45% (reflecting the 50% chance of inheriting a gene conferring an 80% risk). Breast cancer genes can be inherited through the father and a dominant history on the father's side of the family would give at least a 20-25% lifetime risk to his daughters. It is important to recognise however, that most family histories of breast cancer are not due to a mutation in BRCA1, BRCA2 or TP53 genes. Some are due to lower penetrance genes which have not yet been discovered and some are simply due to chance, given that breast cancer is a common disease.
4.4 Risk assessment tools

Recommendations

Note: this is are repeated in the section dealing with tertiary care

1. Computerised risk-assessment models can be helpful aids to risk assessment, but can be misleading and should not yet totally replace careful clinical assessment of family trees with a manual approach. (D)

Evidence statements

1. Existing computer models (Gail, Claus, BRCAPRO) underestimate in a family history setting in terms of breast cancer risk prediction, although the manual Claus tables produce risks close to those seen in a screened familial risk population. (III)

2. One US study found that BRCAPRO predicted BRCA 1 & 2 mutation status better than genetic counsellors. (III)

3. The degree of correlation between different risk models is relatively poor. (III)

4.4.1 Research literature evidence

Evidence has been identified from the literature concerning methods of predicting individual risk of developing breast cancer in women with a family history of breast cancer. The evidence relates to a number of risk assessment models and a number of studies, which have reviewed or compared these models. The models can be divide into those that predict

a) Breast cancer risk over time

b) The chances of an individual or family carrying a BRCA1 or BRCA2 mutation

c) Both the above

Four guidelines have also been identified for genetic risk assessment and management of women with a family history of breast cancer.

4.4.2 Breast cancer risk assessment models

BRCAPRO (Berry et al 1997)

BRCAPRO is a mathematical model, which has been developed to calculate the probability that a woman with a family history of breast and/or ovarian cancer carries a BRCA1 or BRCA2 gene mutation. The model applies Bayes’ theorem to predict risk, using estimates of BRCA1 mutation frequencies in the general population and age-specific incidence rates of breast and ovarian cancers

The classification and care of women at risk of familial breast cancer
in mutation carriers and non-carriers, with probability based on the cancer statuses of all 1\textsuperscript{st}- and 2\textsuperscript{nd}-degree relatives.

\textbf{Claus et al 1994}

The Claus model uses a mathematical approach to model the likely inheritance of breast cancer genes in the population studied (known as segregation analysis). The genetic model that best fitted the data was that of a rare allele (or alleles) associated with high penetrance. Non genetic factors are not taken into account in this model.

This statistical model uses data from the Cancer and Steroid Hormone Study (CASH), which was a US population-based case-control study of 4,730 white breast cancer cases and 4,688 age-matched controls aged 20-54 years. Data on breast cancer occurrence in 1\textsuperscript{st}-degree relatives and age at onset were obtained from participants, with an aim of determining whether these data supported the existence of an inherited breast cancer susceptibility gene. The data supported the existence of a rare autosomal dominant allele which increased predisposition to breast cancer. The Claus model provides breast cancer risk estimates in tabular form at 10-year increments between the ages of 29 and 79 years, based on which relatives were affected with the disease and age at diagnosis.

\textbf{Gail et al 1989}

The Gail model is a risk assessment model which focuses on non-genetic risk factors, with limited information on family history.

Data from 2,852 white breast cancer cases and 3,146 white controls aged between 35 and 79 years who took part in the Breast Cancer Detection Demonstration Project (BCDDP) are used in this statistical model. The model estimates the probability of a woman of a given age and set of risk factors developing breast cancer over a specified time interval, the risk factors being age at menarche, age at 1\textsuperscript{st} live birth, number of affected 1\textsuperscript{st}-degree relatives, and number of previous breast biopsies. The Gail model has been evaluated in 3 populations and has been adapted for use in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-BCPT).

Further risk assessment models estimations which have not been identified by our searches are mentioned by McTiernan et al (1997) and Tischkowitz et al (2000). These papers are not presented in the review but are listed in references (Ottman et al (1983), Anderson et al (1985), Taplin et al (1990), Houlston et al (1992), Murday (1994), National Surgical Adjuvant Breast and Bowel Project (1992)).

\subsection*{4.4.3 Reviews/comparisons of risk assessment models}

\textbf{Amir et al (2003)}

Amir et al assessed the goodness of fit and discriminatory value of the Tyrer-Cuzick, Gail, Claus and Ford models. This was assessed using data from 1933 women taking part in a family history evaluation and screening programme. The observed/expected ratios (for breast cancer) were: Gail 0.48 (0.37-0.64); Claus 0.56 (0.43-0.75); Ford 0.49 (0.37-0.65) and Tyrer-Cuzick 0.81 (0.62-1.08). ROC curves were calculated and showed: Gail 0.735; Claus 0.716; Ford 0.737 and Tyrer-Cuzick 0.762.

The authors concluded that the Tyrer-Cuzick model is the most consistently accurate for prediction of breast cancer, and the others all underestimate risk.

This study looked at the relative performance of eight cancer risk counsellors compared with BRCAPRO in identifying likely to carry a BRCA gene mutation. Pedigrees with a proband affected by breast or ovarian cancer having a gene sequence that was unequivocal were used (148 pedigrees). The study found that the counsellors and BRCAPRO had similar results in terms of sensitivity (counsellors 94% [range 81-98%], BRCAPRO 92% [range 91-92%]). BRCAPRO had better findings in terms of specificities (counsellors 16% [range 6-34%], BRCAPRO 32% [range 30-34%]). It was also found that BRCAPRO had better results in terms of ROC curves (counsellors 0.671 [range 0.620-0.717], BRCAPRO 0.712 [range 0.706-0.720]). The better findings in terms of specificities meant that BRCAPRO was thought to have slightly better overall discrimination.

McTiernan et al (2001)

The lifetime and 5-year breast cancer risk estimates of the Gail and Claus models were compared in this US study of 491 women aged 18-74 years with a family history of breast cancer. Women were recruited between 1996-1997 from the general population, with additional samples of Ashkenazi Jewish, African-American and lesbian women. About one-quarter of women were assigned the ‘high’ risk category according to the Gail model (>1.7% risk of developing breast cancer in the next 5 years). Estimation of average lifetime risk was 13.2% using the Gail model and 11.2% using the Claus model. Estimates of the 2 models were moderately correlated (r=0.55) with the Gail model producing higher estimation than the Claus model for most women. The authors conclude that in women with a family history of breast cancer, it may be preferable to present both Claus and Gail estimates.

Tischkowitz et al (2000)

This study compared lifetime risk estimations of developing breast cancer in 200 women attending a UK breast cancer genetic assessment clinic, using 3 different risk assessment methods which are currently being used in the UK; the Claus model, the ‘Houlston/Murday’ method and a qualitative method. Women were assigned a ‘high’ (>20%) or ‘low/moderate’ (<20%) lifetime risk according to each method. Comparison of the 3 models found significant differences in terms of women’s allocation to the moderate or high risk categories (chi-squared=73.3, 2 df, P<0.00001). Only 108 (54%) of women were allocated the same risk category with all 3 methods. The authors conclude that these 3 methods provide inconsistent risk estimations for breast cancer.

McTiernan et al (1997)

This review compared the breast cancer risk assessment models of Ottman et al, Anderson et al, Taplin et al, Claus, Gail, and the NSABP-BCPT adaptation of the Gail model in terms of populations used for estimates, risk factors included, estimation methods, and applications of the method. Each method was also tested with particular ranges of patient characteristics to compare estimates of breast cancer probability across the different methods. The authors note that a direct comparison of the different risk assessment methods is difficult because the models include different sets of risk factors; some do not specify the total number of 1st-degree relatives with breast cancer; some are derived from small sample sizes and have wide confidence intervals; and some do not account for competing causes of death. McTiernan et al concluded:

- the validity of risk estimation from any of the methods is questionable, with each having particular strengths and weaknesses:
- the Gail model may be a valid predictor for postmenopausal women attending regular mammographic surveillance, although it overestimates breast cancer risk by 30-50% in premenopausal women.
- the Taplin method may be useful for a qualitative classification of populations.
- the Gail and NSABP-BCPT models may provide the best available risk estimates in women without a family history of breast cancer, or for women with a history of atypical benign breast disease.
- no models have been developed for other racial or ethnic groups than white women, apart from the NSABP-BCPT model, which can predict risk in African-American women, although it has not been tested for validity.
4.5 Risk communication

Recommendations

Note: these are repeated in the section dealing with tertiary care

Risk communication in tertiary care

1. Women should be offered a personal risk estimate but information should also be given about the uncertainties of the estimation. (D)

2. When a personal risk value is requested, it should be presented in more than one way (for example numerical value if calculated and qualitative risk). (D)

3. Women should be sent a written summary of their consultation in a specialist genetic clinic, which includes their personal risk information. (D)

Evidence statements

1. There is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood. (IV)

2. Risk communication improves the accuracy of the woman’s perceived risk. (IV)

3. Qualitative studies have indicated that in women who attended genetics clinics, many found personal risk information useful. (IV)

4. There is some evidence that numerical risk values are preferred over risk categories. (IV)

5. The use of a written summary of the consultation reinforces risks information and enhances recall. (IV)

4.5.1 Introduction

Women attending cancer genetics clinics want to discuss their family history, cancer risks and risk management options. However, they may feel unprepared for the consultation due to unfamiliarity with the process and content of genetic counselling, and have unrealistic expectations about access to genetic testing or mammographic surveillance (Hallowell et al 1997c). Lay beliefs about inheritance may interfere with assimilation of risk information and awareness of the family history may result in a fixed perception that risk is high (Richards 1999). Retention and recall of risk values will also depend on the salience of the information for counselees; risk reduction and access to breast screening may take precedence (Hallowell 1997a&b, Richards 1999).
4.5.2 Research literature evidence

Studies

Sachs et al (2001)

In a Swedish qualitative study, participant observation in 45 consultation sessions between clinicians and potential patients was conducted at a hereditary cancer clinic to explore the communication of genetic information. A main theme of the sessions was the numerical discussion of risk. Problems for clinicians are described in terms of the process of translating scientific knowledge into clinical management. Problems in providing information include unclear aims of the consultations; mixing types of background information and probabilities; recognising how low predictive values are; and difficulties in communicating the relationship between probability and conclusions. Problems in communication about genetic risk of cancer relate to dilemmas arising from the uncertainty of the nature of the information itself, and in communicating information in a format that can be interpreted by patients.

Schapira et al (2001)

A US qualitative study used 4 focus groups involving a total of 41 women aged between 40-65 years to evaluate responses to various formats used in the communication of breast cancer risk. Frequency and probability formats with and without the use of graphic displays were explored; these formats are both based on the likelihood of an event being assigned a value of between 0 and 1. Results found that graphic discrete frequency formats using highlighted human figures were preferable compared to continuous probability formats using bar graphs, in that identical numerical risks were perceived as less when presented with bar graphs compared to highlighted human figures. The authors conclude that risk formats should be chosen to optimise patients’ understanding and ability to use the information effectively, rather than for the purposes of persuasion.


The key findings of 75 published papers, research reports (including case studies) and clinical protocols relating to the communication of risk for familial cancer are presented in this review. On review of the evidence, the authors found that there was no clear evidence about how to sensitively and effectively communicate cancer risk information to individuals and families at risk for familial cancer, as well as those who are not, or about how to ensure that the probabilistic nature of risk estimates is accurately communicated and understood. There is also uncertainty about how to communicate the error-proneness of genetic tests; and strategies currently used to communicate cancer risk have not been adequately evaluated. The authors conclude that risk communication strategies need to be developed and tested to meet the information needs of the general public.


To investigate women’s perceptions and use of written summaries of genetic consultations, 40 UK women (mean age 40 years, range 22-59) with family histories of breast and/or ovarian cancer took part in face-to-face interviews. The majority of women regarded a written summary of their genetic counselling session as valuable, with 92% saying that it facilitated their recall and/or understanding of the information provided in the consultation. Eight-five percent of women said that they had used, or intended to use, the summary to facilitate the communication of genetic information to their relatives. The authors note, however, that the summaries may lead women to perceive themselves as
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‘bearers of bad news’, may have implications for medical confidentiality, or may generate an inappropriate demand for genetic counselling.

Hallowell et al (1997a & b)

In this UK study, the presentation of probabilistic information used during genetic consultations at a cancer family history clinic is described, and women’s attitudes about, and preferences for, different types of breast cancer risk information formats are explored. The 46 women (mean age of 40 years; range 22-59, SD=8.8) reported a total of 132 female relatives affected by breast or ovarian cancer (mean 2.9, range 1-8) and a further 77 male and female relatives affected by other cancers. Clinic counsellors used a wide variety of qualitative and quantitative formats to describe women’s risk of inheriting a genetic mutation or developing cancer; quantitative formats used were proportions, percentages, ratios, odds against and as comparisons with population risks. Results showed that women were positive about the way their cancer risk had been described. 73% preferred risks to be described using quantitative formats, with little difference in preference between percentages, proportions or population comparisons. In over 40% of cases, risk information was not presented in the women’s preferred quantitative format during the consultation.

This UK study used questionnaires and interviews to evaluate women’s recall of numerical risk information following genetic counselling for breast and/or ovarian cancer. Forty-six women took part in the study with a mean age of 40 years (range 22-59, SD=8.8). Results found that many of the women had difficulty in recalling the probabilities used to describe their risk of developing cancer and that recall failure increased with time. Recall accuracy was incorrect in 17/32 women (53%) and 6/32 (19%) had no recall at 6 weeks post-genetic counselling; at 12 months post- counselling, 11/25 women (44%) had incorrect recall and 11/25 (44%) had no recall. The authors suggest that women who failed to recall risk information may not have memorised their risk estimate because they had received written confirmation of their risk; or recall failure may be due to women regarding a numerical risk estimate as less important than having their pre-counselling risk perceptions confirmed or refuted.

4.5.3 Summary of evidence relating to breast cancer risk communication for women with a family history of breast cancer

Evidence relating to the communication of breast cancer risk in women with a family history of breast cancer is limited, relates to mainly qualitative research studies and has addressed various aspects concerning how cancer risk is communicated in this population of women.

Two studies have evaluated different risk information formats (Hallowell et al, 1997a,b; Schapira et al, 2001), and 7 further studies have investigated women’s recall of risk information and whether written summaries have aided this, and the observed problems which clinicians encounter in translating scientific knowledge into their clinical management at a hereditary cancer clinic (Hallowell et al, 1997a,b; Hallowell et al, 1998; Sachs et al, 2001, Cull et al 1999, Evans et al 1994, Hopwood et al 1998, Watson et al 1999). A literature review of studies which have assessed the process of risk communication for familial cancer has concluded that there is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood.

4.5.4 Comment

The transfer of risk information is not straightforward. There is a high degree of uncertainty in the information given in genetic counselling, with respect to the risk of inheriting a predisposing gene, of
gene penetrance and hence of developing cancer (Richards 1999). This uncertainty reflects the state of knowledge but is in direct contrast to the needs of counselees, who seek precise information (van Zuuren et al 1997, Julian-Reynier et al 2003 in press). Information can be provided in a number of ways and evidence is conflicting as to the optimal method of risk communication. Categorical risks are criticised for being open to wide interpretation and numerical values may be more difficult for some to understand. Whatever the difficulties, use of numerical risk information may be unavoidable, as this forms the basis for offering risk management (e.g. risk reducing surgery or mammographic surveillance) and decision making about preventive strategies (Fisher 1999 and others).

There has been evaluation of the effectiveness of risk counselling on women’s risk accuracy. The apparent precision of numerical information to guide risk management appeals to geneticists and counsellors, but the influence of risk accuracy on health care behaviour and lay beliefs is less clear. Aids to risk communication, such as summary letters, audiotapes and videotapes have shown limited benefit (Cull et al 1998, Evans et al 1994, Hallowell & Murton 1998, Watson et al 1998,) but other strategies, such as visual displays are being evaluated.
5. Approaches to care and information giving
5.1 Approaches to care and information giving

Recommendations

1. Effective care involves a balanced partnership between patients and healthcare professionals. Patients should have the opportunity to make informed choices about any treatment and care and to share in decision making. (D)

2. To ensure a patient–professional partnership, patients should be offered individually tailored information, including information about sources of support (including local and national organisations). (D)

3. Tailoring of information should take into account format (including whether written or taped) as well as the actual content and form that should be provided (see Box 1). (D)

4. Standard information should be evidence based wherever possible, and agreed at a national level if possible (NICE's Information for the Public provides a good starting point). (D)

5. Standard information should not contradict messages from other service providers, including commonly agreed information across localities. (D)

5.1.1 Evidence

These recommendations are based on the consensus of the guideline development group, and reflect good clinical professional practice. They may seem self-evident but it was thought worthwhile to reiterate them.

The last decade or so has seen the burgeoning development of genetic risk assessment and family history clinics (FHCs) to deal with the increasing demand for advice by women concerned about their family history of breast cancer. While these clinics were originally centrally based in a few major centres, the demand is such that management of women needs to be carried out in local units. In some areas, a system of triage has developed with most women managed in primary care, those women meeting referral criteria are assessed in local units and “high” risk women are referred to the regional cancer genetics centre. This approach has been endorsed by the Harper report and more recently the NHS Cancer plan (Sept 2000).

In practice initial assessment of a woman will usually take place in primary care. The decision will be made as to whether to offer an appointment to be assessed in a local family history clinic usually at secondary care level. At secondary care level an assessment will be made and if the woman is felt to be at ‘high risk’, she may be offered referral to a genetics department. There is therefore a triage system based on 3 levels of care. Women in primary care depending on their family history may meet a threshold for assessment in secondary care to discuss options for surveillance and reducing breast cancer risk, but not meet criteria for assessment in a genetics centre. Most women will be managed in primary care and informed that they are not at substantially increased risk and are unlikely to benefit from early mammography or genetic testing. In some cases women may still require referral to or discussion with secondary care if they remain anxious or if the family history is unclear. There thus exist 3 categories of risk:
1. Women who can be managed and reassured at primary care level
2. Women who meet thresholds for referral to secondary care
3. Women who meet threshold for referral to tertiary care

There are likely to be women who do not fall neatly into a particular category. This may be because of doubts over the type of cancers or age at which they occurred. These women can be discussed between primary care and secondary care and between secondary care and a genetics department. Women should also be informed that their risk can change with changes in their family history. For instance if a new breast cancer occurs then the risk may need to be reassessed.
Box 1 Information provision

Standard written information for all women
- risk information about population level and family history levels of risk, including a definition of family history
- the message that if their family history alters their risk may alter
- breast awareness information
- lifestyle advice regarding breast cancer risk, including information about
  - HRT and oral contraceptives
  - lifestyle including diet, alcohol, etc
  - breastfeeding, family size and timing
- contact details of those providing support and information, including local and national support groups
- the message that to help provide support and understanding of the issues discussed, women should be informed prior to appointments that they can bring a family member/friend with them to appointments
- details of any trials or studies that may be appropriate for the women to consider taking part in

For women cared for in primary care:
- standard written information (as above)
- advice to return to discuss any implications if there is a change in family history change or breast symptoms develop

For women being referred to secondary care:
- standard written information (as above)
- information about the risk assessment exercise that will take place and advice about how to obtain a comprehensive family history if required
- information about potential outcomes depending on the outcome of the risk assessment including referral back to primary care, management with secondary care or referral to a specialist genetic service and what may happen at each level

For women being referred back to primary care
- standard written information (as above)
- detailed information about why secondary or a specialist genetic service are not needed
- advice to return to primary care to discuss any implications if there is a change in family history change or breast symptoms develop

For women being cared for in secondary care:
- standard written information (as above)
- details of the risk assessment outcome, including why they are not being referred to a specialist genetic service
- details of surveillance options including risk and benefits

For women being referred to tertiary care:
- standard written information (as above)
- details of the risk assessment outcome including why they are being referred to a specialist genetic service
- details of surveillance options including risk and benefits
- details of what should be expected in a specialist genetic service, including counselling and genetic testing

For women being cared for in tertiary care:
- standard written information (as above)
- information about hereditary breast cancer
- information about genetic testing, both predictive testing and mutation finding, including details of what the tests mean and how informative they are likely to be, and the likely timescale of being given the results
- information about the risks and benefits of risk reducing surgery when it is being considered, including both physical and psychological impact
5.2 Breast awareness and examination

Recommendations

1. Women at increased risk of breast cancer should be ‘breast aware’ in line with Department of Health advice for all women (see www.cancerscreening.nhs.uk/breastscreen/breastaware.pdf). (D)

Evidence statement

1. There is a lack evidence for a high risk population that either clinical breast examination or self-examination is useful as the sole surveillance modality. (III)

5.2.1 Research literature evidence

No evidence was identified for the effectiveness of either clinical or self-breast examination as the sole screening modality in women with a family history of breast cancer and/or BRCA1/2 mutations.

A recent Cochrane Review which examined the evidence for regular self-examination or clinical examination for early detection of breast cancer (for women in general), concluded that trials did not suggest a beneficial effect of screening by breast examination, and may in some instances cause harm (Koster & Gotzsche 2003).

Furthermore, the Department of Health issued advice that clinical breast examination was not an appropriate screening technique in February 1998. The reference is PL/CMO/98/1.
6. Care of women in primary care
6.1 Care and management approach – primary care

Recommendations

Family history taking and initial assessment

1. When a woman presents with breast symptoms or has concerns about relatives with breast cancer, a first- and second-degree family history should be taken in primary care to assess risk, because this allows appropriate classification and care. (D)

2. Health care professionals should respond to women who present with concerns, but should not, in most instances, actively seek to identify women with a family history of breast cancer. (D)

3. In some circumstances it may also be clinically relevant to take a family history, for example for women older than age 35 years using an oral contraceptive pill or for women being considered for long-term HRT use. (D)

4. Women should be given the opportunity to discuss concerns about their family history of breast cancer if it is raised during a consultation. (D)

5. A second-degree family history (that is, including aunts, uncles and grandparents) should be taken in primary care before explaining risks and options. (D)

6. A second degree family history needs to include paternal as well as maternal relatives. (D)

7. Asking women to discuss their family history with relatives is useful in gathering the most accurate information. (D)

8. Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and they should be made available. (C)

9. For referral decisions attempts should be made to gather as accurate information as possible on:
   ♦ age of diagnosis of any cancer in relatives
   ♦ site of tumours
   ♦ multiple cancers (including bilateral disease)
   ♦ Jewish ancestry. (D)
Primary care management

10. Women can be cared for in primary care if the family history shows only one first-degree or second-degree relative diagnosed with breast cancer at older than age 40 years, provided that none of the following are present in the family history:
   ◆ bilateral breast cancer
   ◆ male breast cancer
   ◆ ovarian cancer
   ◆ Jewish ancestry
   ◆ sarcoma in a relative younger than 45 years of age
   ◆ glioma or childhood adrenal cortical carcinomas
   ◆ complicated patterns of multiple cancers at a young age
   ◆ paternal history of breast cancer (two or more relatives on the father’s side of the family) (D)

11. Women who do not meet the criteria for referral should be cared for in primary care by giving standard written information (see Box 1). (D)

Referral from primary care

12. Before a decision on referral is made, primary care professionals should note that a woman outside the 40-49 year age group who is estimated to be at moderate risk (e.g. she has only one relative with breast cancer diagnosed at any age, or she has two relatives diagnosed with breast cancer older than an average age of 50 years) will not generally be offered additional mammography. (D)

13. Women outside the 40-49 year age group may be referred for risk counselling and advice on risk management or consideration for prevention trials. Advice should be sought from the designated contact in secondary care about appropriateness of referral. (D)

14. Women who meet the following criteria should be offered referral to secondary care: (D)
   ◆ one first-degree female relative diagnosed with breast cancer at younger than age 40 years
   or
   ◆ one first-degree male relative diagnosed with breast cancer at any age
   or
   ◆ one first-degree relative with bilateral breast cancer where the first primary was diagnosed at younger than age 50 years
   or
   ◆ two first-degree relatives, or one first-degree AND one second-degree relative, diagnosed with breast cancer at any age.
   or
   ◆ one first-degree or second-degree relative diagnosed with breast cancer at any age AND one first-degree or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative)
   or
   ◆ three first-degree or second-degree relatives diagnosed with breast cancer at any age.
15. Advice should be sought from the designated secondary care contact if any of the following are present in the family history in addition to breast cancers in relatives not fulfilling the above criteria:

- bilateral breast cancer
- male breast cancer
- ovarian cancer
- Jewish ancestry
- sarcoma in a relative younger than age 45 years
- glioma or childhood adrenal cortical carcinomas
- complicated patterns of multiple cancers at a young age
- paternal history of breast cancer (two or more relatives on the father’s side of the family). (D)

16. Discussion with the designated secondary care contact should take place if the primary care health professional is uncertain about the appropriateness of referral because the family history presented is unusual or difficult to make clear decisions about, or where the woman is not sufficiently reassured by the standard information provided. (D)

17. Direct referral to a specialist genetics service should take place where a high risk predisposing gene mutation has been identified (e.g. BRCA1, BRCA2 or TP53). (D)

**Information for women who are being referred**

18. Women who are being referred to secondary or tertiary care should be provided with written information about what happens at this stage (see Box 1). (C)

**Information and ongoing support for women who are not being referred**

19. Support mechanisms (e.g. risk counselling, psychological counselling, and risk management advice) need to be identified and should be offered to women not eligible for referral and/or surveillance on the basis of age or risk level who have ongoing concerns. (D)

**Support for primary care**

20. Support is needed for primary care health professionals to care for women with a family history of breast cancer. Essential requirements for support for primary care are:

- a single point and locally agreed mechanism of referral for women identified as being at increased risk
- educational materials about familial breast cancer
- decision-support systems
- standardised patient information leaflets
- a designated secondary care contact to discuss management of ‘uncertain’ cases. (D)
6.1.1 Introduction

Several studies have reported on a wide range of issues relating to the management of women with a family history of breast cancer in primary care. These are described in detail in other relevant sections of the document (see family history taking, patient education and information). The evidence from these has informed the recommendations in this chapter.

The number of primary care consultations where family history of breast cancer is raised by women is relatively infrequent. A recent study reported that it may be of the order of 5/1000 consultations, which averages out at about 0.6 per clinician per month (Women’s Concerns Study Group 2001). The same study illustrated that if list size and consultation rates were taken into account then an extrapolation of data might mean that for each 1000 women (aged 16 years or over) on a practice list, about 15 per year will raise the issue of family history of breast cancer. They also point out that about 10 times that number will consult for contraceptive advice and three times that number will consult for menstrual disorders. They also found that clinicians were 6.6 times more likely to raise the issue of family history of breast cancer than patients.

The provision of more genetics services, including risk assessment, in primary care to allow more appropriate referrals and use of specialist services is an important issue in the management of women with a family history of breast cancer. However studies have shown that many GPs lack required knowledge and confidence to take on this work. Studies have also shown however that the provision of educational materials to GPs can significantly improve referral decisions for patients with a family history of breast cancer and improve confidence (Watson et al 2001, Watson et al 2002).

6.2 Patient education/information in primary care

6.2.1 Introduction

Women may have a hazy notion of their personal breast cancer risks, and of the significance of their family histories. A perceived high risk may be attributed to cancers in the family that are not associated with a possible genetic predisposition, causing unnecessary anxiety and demands for surveillance. Approximately 25% of referrals to Cancer Genetics Clinics are made for women who are not at increased risk of breast cancer (Wonderling et al 2001): these women, if not offered an appointment for referral, will require reassurance and explanation of the family history. In addition, women may lack information and express concerns about the oral contraceptive (OC) pill, HRT and other possible risk factors because there has been breast cancer in the family. Women with a significant family history may feel unprepared for a genetics consultation.

6.2.2 Research literature evidence

Studies

Andermann et al (2002)

In this UK study, an evidence-based information leaflet was developed after assessing the information needs of women with a family history of breast cancer, and was subsequently evaluated in a primary care setting. Information leaflets and questionnaires were sent to 190 women referred to a family cancer clinic for breast/ovarian cancer. One hundred and forty-four women returned the questionnaire (response rate of 76%); women had a mean age of 42 years (SD=8.8), were mostly white (98%) and well educated, with 83% having a mother or sister diagnosed with breast cancer.
Results showed that over 90% of women felt that the leaflet was easy to read and understand, was written in a caring way and was comprehensive. 80% felt that the leaflet was relevant and between 60-70% agreed that it helped them talk to doctors and to family members and was reassuring. Some women, however, felt that the leaflet should not be a substitute for talking to a health care professional.


In a UK qualitative study, women’s views of GP consultations about family history of breast cancer were investigated using 72 telephone interviews and a further 20 face-to-face interviews with a subsample of 20 women. Participants were women from 18 GP practices (mean age 49 years; range 34-76 years) who had experienced a primary care consultation in which breast cancer family history was mentioned, as reported by the clinician. Results found that family history of breast cancer was rarely the main focus of consultations. Women’s understanding of familial risk and disease was often lacking and they expressed a need for clarification, explanation and information. The authors’ conclude that the GP’s main role in relation to family history and cancer risk is to provide appropriate reassurance for the majority of patients not at increased risk.

Andermann et al (2001)

A survey of 128 UK women with a family history of breast cancer (mean age 38 years; SD=10.0) referred by their GP to secondary care (genetics or breast clinic) was carried out to explore women’s views, expectations and experiences of the process. 90% of women wanted their GP to provide them with information and 87% wanted their GP to discuss their risks of developing breast cancer, and for most women these needs had not been met. Women often had unrealistic expectations of what they might expect from a secondary care referral, particularly in terms of genetic testing. 11% of women had returned to their GP within 1 month of attending the secondary care appointment to discuss family history and what had happened at the specialist clinic. Study results indicate that women want information and want to discuss their family history concerns in a primary care setting. Information provision in primary care is even more important for women who are not referred, as this may be their only source of information and advice.


The role of information, support and communication needs was evaluated in this Canadian qualitative study involving 55 at-risk women with at least one first-degree relative with breast cancer. Results showed that information, support and communication were important factors in enabling women to adjust to their personal risk of breast cancer, articulated as a 3-phase process: ‘living the breast cancer experience’ through the relative’s experience; developing a risk perception; and ‘putting risk in its place’. However, despite the importance of information and support, most women were dissatisfied with the amount and type of information they received and felt isolated and unsupported, and communication both within the family and with health care professionals was poor. The authors conclude that women’s needs could be more effectively addressed by measures that identify at-risk women, assess their specific needs, and provide them with support and accurate, individualised information.

6.2.3 Summary of evidence relating to patient information in a primary care setting for women with a family history of breast cancer

Evidence from two qualitative studies and one survey has shown that women with a family history of breast cancer have unmet needs for information, support and reassurance either in the primary care...
setting (Chalmers et al, 1996; Grande et al, 2002), or whilst awaiting specialist genetics consultations having been referred by their GP (Andermann et al, 2001). The GP’s role in providing information and reassurance was seen to be extremely important for these women, particularly for those who are not referred to secondary care, as the GP may be their only source of information and advice.

A further study which developed and evaluated a research-based leaflet for women with a family history of cancer for use in a primary care setting found that it was effective in meeting women’s information (Andermann et al, 2002).

6.2.4 Comment

Primary care professionals have an important part to play in the care of women with concerns about their family history of breast cancer. Issues about family history of breast cancer are often raised by primary care professionals in routine consultations (Hyland et al 2001) but women may not be given the opportunity to discuss concerns they have about their risk of breast cancer (Grande et al 2002). Although the case is not yet made for screening all women for a family history of breast cancer, primary care professionals should be alert to the fact that women may have concerns about their family history which they wish to have addressed.

Taking an adequate family history that covers first and second degree relatives on both sides of the family is central to providing women with an initial assessment of their risk in primary care. Patients may be uncertain about the details of their family history on initial questioning but can often obtain this information by asking family members; this enables a more accurate assessment of their risk in primary care.

The majority of women with a family history of breast cancer will not be at substantially increased risk. In these circumstances, primary care professionals should discuss the woman’s risk of breast cancer and advise her about breast awareness, relevant lifestyle factors and the NHS National Breast Screening Programme. Women who are at significantly increased risk of breast cancer should be offered referral for a more detailed discussion of their risk. Women who are referred about their risk of breast cancer often have unrealistic expectations of the outcome of referral (Andermann et al 2001). Primary care professionals therefore have an important role in preparing women and providing them information about what to expect from referral and supporting them afterwards with the ongoing management of their breast cancer risk.
7. Care of women in specialist (secondary and tertiary) care

Note:

Service configurations will vary by locality. However we have presented recommendations for settings that are likely to be found in most localities.
7.1 Specialist care - care and management approach

Recommendations

Care of women in secondary care (such as a breast care team, family history clinic or breast clinic which can be shared between trusts)

1. Care of women in secondary care (such as a breast care team, family history clinic or breast clinic which can be shared between trusts) should be undertaken by a multidisciplinary team. It should include the following:
   - written protocols for management
   - central, standardised resources
   - mammographic surveillance available to standard of NHS Breast Screening programme
   - access to a team offering risk reducing surgery
   - standardised written information
   - designated/lead clinicians
   - a designated contact for primary care
   - a designated contact in tertiary care
   - audit
   - clinical trials access
   - access to psychological assessment and counselling
   - information about support groups and voluntary organisations
   - administrative support. (D)

Family history taking in secondary care

2. A family history should be taken when a woman presents with breast symptoms or has concerns about relatives with breast cancer. (D)

3. A third degree family history should be taken in secondary care where possible and appropriate. (D)

4. Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and risk assessment and they should be made available. (C)

Management in secondary care

5. Women who meet the following criteria should be offered secondary care and do not require referral to tertiary care: (D)
   - one first-degree relative diagnosed with breast cancer at younger than age 40 years
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or
♦ two first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 50 years

or
♦ three first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 60 years

or
♦ a formal risk assessment (usually carried out in tertiary care) or a family history pattern is likely to give risks of greater than 3–8% risk in the next 10 years for women aged 40 years, or a lifetime risk of 17% or greater but less than 30%

provided that none of the following are present in the family history:
♦ bilateral breast cancer
♦ male breast cancer
♦ ovarian cancer
♦ Jewish ancestry
♦ sarcoma in a relative younger than 45 years of age
♦ glioma or childhood adrenal cortical carcinomas
♦ complicated patterns of multiple cancers at a young age
♦ very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father’s side of the family) (D)

6. Women whose risk is less than that in the cases above (Recommendation 5) can be referred back to primary care:
♦ with appropriate information being offered (see Box 1), and
♦ support mechanisms (e.g. risk counselling, psychological counselling, and risk management advice) need to be identified and should be offered to women not eligible for referral and/or surveillance on the basis of age or risk level who have ongoing concerns. (D)

Surveillance

7. Mammographic surveillance should not be available for women younger than age 30 years. (D)

8. For women aged 30-39 years of age satisfying referral criteria for secondary or specialist care, mammographic surveillance should be carried out:
♦ only as part of a research study (ethically approved) or nationally approved and audited service (D)
and
♦ individualised strategies should be developed for exceptional cases, such as:
♦ women from families with BRCA1, BRCA2 or TP53 mutations (C)
♦ women with equivalent high breast cancer risk (D)

9. Support mechanisms (e.g. risk counselling, psychological counselling and risk management advice) need to be identified and should be offered to women not being offered mammographic surveillance who have ongoing concerns. (D)
10. All women satisfying referral criteria to secondary or specialist care (at moderate risk or greater) should be offered mammographic surveillance from age 40 years. (C)

11. For women aged 40–49 years at moderate risk or greater, mammographic surveillance should be:
   ♦ annual
   ♦ to NHS Breast Screening Programme standards
   ♦ audited
   ♦ part of the NHS Research and Development Health Technology Assessment programme evaluation of mammographic surveillance of women younger than age 50 years with a family history wherever possible
   ♦ only undertaken after provision of written information about the positive and negative aspects of surveillance (D)

12. For women aged 50 years and older, surveillance should be:
   ♦ as part of the NHS Breast Screening Programme, screened every 3 years (C)
   ♦ more frequent mammographic surveillance should take place only as part of a research study (ethically approved) or nationally approved and audited service (D) and
   ♦ individualised strategies should be developed for exceptional cases, such as:
     ♦ women from families with BRCA1, BRCA2 or TP53 mutations (C)
     ♦ women with equivalent high breast cancer risk (D)

13. If ongoing assessment of surveillance efficacy for women younger than age 50 years subsequently shows it is not cost effective, surveillance should be stopped. (D)

14. Before decisions on surveillance are made, written patient information and discussion should be offered. This should:
   ♦ reflect the possible reduced sensitivity of mammographic detection of the younger age group with dense breasts and the increased potential for further investigations (C)
   ♦ discuss the potential advantages and disadvantages of breast surveillance for early detection of breast cancer, including
     ♦ radiation risks (C)
     ♦ the possible psychological impact of a recall visit (D)

15. On the basis of current evidence, MRI and ultrasound should not be used in routine surveillance practice but may have a role in problem-solving mammographically detected abnormalities. (D) (Note: several studies have already been presented at major cancer meetings and will report in the next two years. This recommendation should be reviewed when they become available)

**Referral to tertiary care**

16. Women who meet the following referral criteria should be offered a referral to tertiary care. (D)
   ♦ At least the following female breast cancers only in the family
   ♦ two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative)
or
- three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative)

or
- four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative)

or
- **Families containing one relative with ovarian cancer at any age and, on the same side of the family**
  - one first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years

or
- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years

or
- another ovarian cancer at any age

or
- **Families containing bilateral cancer (each breast cancer has the same count value as one relative)**
  - one first-degree relative with cancer diagnosed in both breasts at younger than an average age 50 years

or
- one first-degree or second-degree relative diagnosed with bilateral cancer AND one first or second degree relative diagnosed with breast cancer at younger than an average age 60 years

or
- **Families containing male breast cancer at any age with, on the same side of the family, at least:**
  - one first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years

or
- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years

or
- **A formal risk assessment has given risk estimates of**
  - a 20% or greater chance of a gene mutation being harboured in the family

or
- a greater than 8% risk of developing breast cancer in the next 10 years

or
- a 30% or greater lifetime risk of developing breast cancer

17. Clinicians should seek further advice from a specialist genetics service for families containing any of the following, in addition to breast cancers:
- Jewish ancestry
- sarcoma in a relative younger than 45 years of age
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♦ glioma or childhood adrenal cortical carcinomas
♦ complicated patterns of multiple cancers at a young age
♦ very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father’s side of the family) (D)

18. The management of a high-risk woman may take place in secondary care if she does not want genetic testing or risk-reducing surgery and does not wish to be referred to a specialist genetics service. (D)

19. Following initial consultation in secondary care, written information should be provided to reflect the outcomes of the consultation (see Box 1). (D)

Care of women in tertiary care

20. Care of women referred to tertiary care should be undertaken by a multi-disciplinary team. In addition to having access to the components found in secondary care it should also include the following: (D)

♦ clinical genetic risk assessment
♦ verification for abdominal malignancies and possible sarcomas

Family history taking in tertiary care

21. A third-degree family history should be taken in tertiary care, if this has not been done previously. (D)

22. For accurate risk estimation the following are required:

♦ age of death of affected and unaffected relatives
♦ current age of unaffected relatives. (D)

23. In general, it is not necessary to validate breast cancer only histories (via medical records/cancer registry/death certificates). (D)

24. If substantial management decisions such as risk-reducing surgery, are being considered, and no mutation has been identified, clinicians should seek confirmation of breast cancer only histories (via medical records/cancer registry/death certificates). (D)

25. Where no family history verification is possible, agreement by a multi-disciplinary team should be sought before proceeding with risk reducing surgery. (D)

26. Abdominal malignancies at young ages and possible sarcomas should be confirmed in specialist care. (D)
Risk assessment tools

27. Computerised risk assessment models can be helpful aids to risk assessment, but can be misleading and should not yet totally replace careful clinical assessment of family trees with a manual approach. (D)

Risk communication in tertiary care

28. Women should be offered a personal risk estimate but information should also be given about the uncertainties of the estimation. (D)

29. When a personal risk value is requested, it should be presented in more than one way (for example numerical value if calculated and qualitative risk). (D)

30. Women should be sent a written summary of their consultation in specialist genetic clinics, which includes their personal risk information. (D)

Risk reducing surgery

31. In services offering risk reducing surgery the following should be available:
   - facilities to verify family history and clinical genetic risk assessment
   - mammography before surgery
   - psychological assessment and counselling
   - information about support groups
   - onco/plastic skills (D)

32. If risk-reducing surgery is being considered, and no mutation has been identified, clinicians should seek confirmation of family history (via medical records/cancer registry/death certificates). (D)

33. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with risk-reducing surgery. (D)
7.2 Surveillance (secondary care)

Recommendations

Note: these are repeated in the section dealing with Specialist care - care and management approach

Surveillance

1. Mammographic surveillance should not be available for women younger than age 30 years. (D)

2. For women aged 30–39 years of age satisfying referral criteria for secondary or specialist care, mammographic surveillance should be carried out:
   - only as part of a research study (ethically approved) or nationally approved and audited service (D) and
   - individualised strategies should be developed for exceptional cases, such as:
     - women from families with BRCA1, BRCA2 or TP53 mutations (C)
     - women with equivalent high breast cancer risk (D)

3. Support mechanisms (e.g. risk counselling, psychological counselling and risk management advice) need to be identified and should be offered to women not being offered mammographic surveillance who have ongoing concerns. (D)

4. All women satisfying referral criteria to secondary or specialist care (at moderate risk or greater) should be offered mammographic surveillance from age 40 years. (C)

5. For women aged 40–49 years at moderate risk or greater, mammographic surveillance should be:
   - annual to NHS Breast Screening Programme standards
   - audited
   - part of the NHS Research and Development Health Technology Assessment programme evaluation of mammographic surveillance of women younger than 50 with a family history wherever possible
   - only undertaken after provision of written information about the positive and negative aspects of surveillance (D)

6. For women aged 50 years and older, surveillance should be:
   - as part of the NHS Breast Screening Programme, screened every 3 years (C)
   - more frequent mammographic surveillance should take place only as part of a research study (ethically approved) or nationally approved and audited service (D)
and

♦ individualised strategies should be developed for exceptional cases, such as:
  ♦ women from families with BRCA1, BRCA2 or TP53 mutations (C)
  ♦ women with equivalent high breast cancer risk (D)

7. If ongoing assessment of surveillance efficacy for women younger than age 50 years subsequently shows it is not cost effective, surveillance should be stopped. (D)

8. Before decisions on surveillance are made, written patient information and discussion should be offered. This should:

  ♦ reflect the possible reduced sensitivity of mammographic detection of the younger age group with dense breasts and the increased potential for further investigations (C)
  ♦ discuss the potential advantages and disadvantages of breast surveillance for early detection of breast cancer, including
    ♦ radiation risks (C)
    ♦ the possible psychological impact of a recall visit (D)

9. On the basis of current evidence, MRI and ultrasound should not be used in routine surveillance practice but may have a role in problem-solving mammographically detected abnormalities. (D) (Note: several studies have already been presented at major cancer meetings and will report in the next two years. This recommendation should be reviewed when they become available)

Evidence statement

1. Mammographic surveillance for women 50-69 years reduces mortality from breast cancer in this group. (III)

2. Mammographic surveillance is less sensitive in younger women, women with a family history of breast cancer and in BRCA1/2 mutation carriers. (III)

3. There is a lack of research into the psychosocial impact of breast screening in women with a family history of breast cancer. (IV)

4. One paper described a negative effect of a false positive result in women with a family history, but the effect appeared to be short-term. (IV)

5. There is some evidence that young women, especially those with low levels of cancer worry and perceptions of low personal vulnerability, may be less likely to adhere to a screening programme. (IV)

6. The small number of studies and lack of scientific rigour in most studies exploring relationships between perceived risks, screening behaviour and modifying factors (e.g. perceived barriers) means that research results should be viewed cautiously. (IV)

7. There are insufficient intervention studies to draw conclusions about the mediating effects of psychosocial factors (e.g. perceived risk accuracy) on screening compliance. Two studies, including a randomised trial, failed to show evidence to support interventions to improve screening adherence. (II)
7.2.1 Comment

Several studies have presented at major cancer meetings and will report in the next two years.

An HTA funded evaluation is addressing the issue of mammographic screening in women aged 40-44. This study includes an economic evaluation.

7.2.2 Research literature evidence

7.2.2.1 Mammography

Studies


This study is an update report on the efficacy of early diagnosis and treatment of high-risk breast cancer groups at dedicated clinics in Norway, Scotland, England and Holland, which provide genetic counselling and follow-up surveillance including mammographic and clinical examination at least annually. Results for 249 women in whom breast cancer was diagnosed showed that 20% of women had carcinoma in situ, 54% had infiltrating cancer without spread and 26% had cancer with spread. 36 women had BRCA1 mutations and 8 had BRCA2 mutations. Presence of BRCA1 mutation was associated with infiltrating cancer, high grade and lack of oestrogen receptor (P<0.05 for each characteristic). 5-year survival for BRCA1 mutation carriers was 63% versus 91% for non-carriers (P=0.04). 21 of these mutation carriers had undergone risk reducing oophorectomy; all but one relapse occurred in the 15 women who had kept their ovaries (P<0.01), and no relapse occurred in those who had been oophorectomised within 6 months of diagnosis (P=0.04). It was concluded that current screening protocols appear satisfactory for most women with a family history of breast cancer, but alternative strategies such as MRI, chemoprevention or risk reducing surgery may be needed for BRCA1 mutation carriers.


251 BRCA1/2 mutation carriers aged 24-79 years who underwent surveillance (monthly BSE, CBE 2-4 times per year and annual mammography) or preventive surgery took part in this US prospective follow-up study (mean follow-up 24.8 months) to evaluate the impact of genetic counselling and testing on risk-reduction strategies and cancer incidence. Results found that genetic counselling and testing increased the frequency of cancer surveillance by physical examinations and imaging studies and led to risk-reducing operations, resulting in the diagnosis of early-stage tumours. More frequent surveillance was recommended in this high-risk group.

Brekelmans et al (2001)

This Dutch retrospective/prospective follow-up study presented the first results of surveillance (monthly BSE, yearly mammography and 6-monthly CBE) in 1,198 women comprising 449 moderate and 621 high-risk women and 128 BRCA1/2 mutation carriers. MRI was also carried out in the case of dense breast tissue, with additional ultrasound with or without fine needle aspiration (FNA) when indicated. After a median follow-up of 3 years, 35 breast cancers were detected with
detection rates for moderate and high-risk women and BRCA1/2 mutation carriers of 3.3 (95% CI, 1.1-8.6), 8.4 (5.4-13.2) and 33 (17-63) per 1,000 person-years, respectively. The ratio of observed versus expected breast cancers in an age-matched average risk population was 2.7, 7.0 and 23.7, respectively. Results relating to tumour stage and sensitivity were less favourable in BRCA1/2 carriers and in women aged less than 40 years. The authors conclude that the results indicate the possibility of identifying young women at high risk for breast cancer.

Goffin et al (2001)

In a research letter, the authors describe a Canadian study which examined the sensitivity of mammography in a retrospective cohort of 161 Ashkenazi Jewish women diagnosed with invasive breast cancer aged less than 65 years, who were tested for BRCA1/2 mutations. Results found that breast cancers less than or equal to 2cm in size occurring in BRCA1/2 mutation carriers were statistically significantly less likely to be detectable than similar sized cancers in non-carriers (46% vs 89%; P<0.001). The authors conclude that these results support the evidence that mammography is insensitive in detecting breast cancer in BRCA1/2 mutation carriers, and that alternative forms of early detection are likely to be beneficial in this high-risk group.

Gui et al (2001)

This UK data review of women with a family history of breast cancer aimed to select women for screening according to predicted risk, and to assess the value of annual CBE in addition to annual mammography. Women were divided into one group of 1,500 women at standard risk (lifetime risk less than 1:6) and a second group of 1,078 women at moderate/high risk (lifetime risk greater than or equal to 1:6). 31 cancers were detected, 12 in group I and 19 in group II; median age at diagnosis in group II was 45 years (range 26-66) compared with 54.5 years (range 38-63) in group I (P=0.03). Compared to breast cancer incidence in the normal population, standardised incidence ratio in group II was significantly higher at 2.8 (95% CI, 1.7-4.2); the incidence ratio of women in group I was similar to that of the general population (1.1; 95% CI, 0.6-1.8). 26/31 (84%) of cancers were palpable, of which 14 (54%) were not visible on mammography. Results support screening programmes for women with a family history of breast cancer, selected according to predicted risk, and justify screening from an earlier age than offered by the NHSBSP, with CBE in addition to mammography.

Law et al (2001)

Cancer detection rates and dose levels in the NHSBSP are used to compare numbers of cancers detected with numbers predicted to be induced by the screening process itself in this data analysis. Results showed that the numbers detected exceeded those induced by a large margin in women aged over 50 years. This margin was found to be reduced in younger women but remained positive to the age of 40 years. The authors also found that in younger women with a family history of breast cancer, the margin of benefit over risk was sufficient down to the age of 40 years, although they advise caution in annually screening women below the age of 35 years.

Myles et al (2001)

Early results are presented on the effectiveness of a UK mammography programme in 2,998 women aged 19-71 with a moderate family history of breast cancer in terms of test and programme sensitivity and sojourn time. Results found that 50 breast cancers were diagnosed, with an observed incidence rate of 4.46 per 1,000 person-years compared to an expected rate of 3.75 per 1,000 person-years. Screen-detection rates at first and subsequent screenings were 5.00 and 4.93 per 1,000, respectively, and interval cancer incidence in the first year following a negative screen was 0.91 per
1,000 person-years. Screening test sensitivity was estimated as 83% and programme sensitivity as 70%. Early indications suggest that the programme is likely to be effective.


This Dutch follow-up study of 294 women at moderate (15-25%) breast cancer risk aged 22-75 years (mean age 43) and 384 women at high (>25%) risk aged 20-74 years (mean age 43) who underwent physical examination, mammography and MRI in a subgroup of women, aimed to assess whether surveillance of these women resulted in detection of breast cancer at an earlier stage than in symptomatic women with a family history. 26 breast cancers were detected which were significantly more often found in an early stage than the 24 breast cancers found in the symptomatic women with a family history referred during the study period (P=0.018). MRI detected 3 occult breast cancers in the subgroup of women. The authors conclude that starting surveillance at an earlier stage may result in higher detection rates.


In a cross-sectional US study of 389,533 women aged 30-69 years, performance of mammography was compared in women with a 1st degree family history of breast cancer and women of similar age without a history. Results found that for women in both groups, the sensitivity of mammography increased as women got older (P=0.001). Sensitivity was similar for each decade of age regardless of family history. The PPV of mammography was higher in women with a family history than in those without (P=0.001). The authors conclude that the sensitivity of mammography is primarily influenced by age, and that cancer detection rates in women who have a 1st degree relative with a history of breast cancer were similar to those in women a decade older without a history.

Macmillan (2000)

A retrospective review of data from 8,783 women aged less than 50 years with a significant family history of breast cancer who underwent breast screening (mammography, CBE and ultrasound) at 22 UK Breast Units was conducted. Results found that median age at diagnosis was 43 years; cancer incidence was 11.3/1000/year, with the rate of cancer detection 4.78/1000 at prevalent screening and 4.52/1000 at incident screening; and interval cancers presented at a rate of 2.45/1000. Rates of cancer detection and incidence were similar to those of the NHSBSP for women aged 50-64 years, and provide evidence to suggest that screening young women with a family history of breast cancer is effective and a survival benefit can be expected.


As part of the Swedish Two-county RCT, this study compared the effectiveness of mammography in 29,179 women aged 40-74 years with and without a family history of breast cancer. Results showed that a significantly higher proportion of high-risk mammographic patterns was observed in association with family history among women aged 40-49 years. Interval cancers were higher in women with a family history; and in older women with a family history, mean sojourn time was shortened (1.89 years compared to 2.70). Results suggest that annual screening for women aged 40-49 years with a family history of breast cancer is reasonable; and screening interval may need to be shortened to 1 year in women aged over 50 years with a family history of breast cancer.


Data from a Canadian nested case-control study was used to assess whether mammographic density was associated with women at increased risk due to family history of breast cancer. Of 354 women
with incident breast cancer and 354 matched controls aged between 40-59 years, mammographic densities were compared in terms of 3 criteria of family history. Relative risks for women with at least one affected 1st-degree relative were 11.14 (95% CI, 1.54-80.39); at least 2 affected 1st or 2nd-degree relatives, 2.57 (95% CI, 0.23-28.22); and for any affected 1st or 2nd degree relative, 5.43 (95% CI, 1.85-15.88). It was concluded that mammographic density may be strongly associated with breast cancer risk among this group of women.


In this UK follow-up study of cancer detection rates, 1,371 women aged less than 50 years with a family history of breast cancer underwent annual CBE and biennial mammography. Twenty-nine cancers (23 invasive and 6 in situ) were detected or presented as interval cancers in this group of women, giving a relative risk for invasive cancer of 5 when compared with age-matched women in the UK. Cancer screening detection rates were similar to those of women aged 50 years or more in the NHSBSP, although a higher proportion of in situ cancers was detected. The authors suggest that young women with a family history of breast cancer may benefit from regular breast screening due to early detection of in situ lesions.


This study reported on results of a UK screening service (annual mammography) of 1,259 women aged less than 50 years with a family history of breast cancer. Seven prevalent, 7 incident and 2 interval cancers were detected. Twelve invasive cancers were detected, giving a ratio of 1.42 (95% CI, 0.73-2.48). The number of invasive cancers expected to occur if this high-risk group had not been screened was 8.45 (in 2,722 person years at risk). The authors conclude that overall cancer detection rates were similar to those in older women in the NHSBSP; and that the number of cancers detected was greater than expected in this population.

Law (1997)

Data relating to the numbers of cancers detected and induced in UK breast screening programmes in terms of single view/two-view screening, different intervals and age ranges, and in women with a family history of breast cancer were reviewed. Results indicate that the numbers of women in the NHS Breast Screening Programme (NHSBSP) where the risk of breast cancer induction exceeds that of breast cancer detection is very small and likely to be generally acceptable. Benefits have yet to be established in women aged 40-47 years. In women with a family history of breast cancer, radiation susceptibility needs to be taken into account as compared to increased breast cancer risk. The author suggests caution in screening below the age of 30 years, or below 40 years if family history groups are showed to have an increased susceptibility to ionising radiation.

Chart et al (1997)

1,044 women at increased risk of breast cancer who underwent breast surveillance (mammography, CBE, and breast self-examination (BSE)) were followed-up in this Canadian study in order to evaluate the role of breast screening practices. Breast cancer was diagnosed in 24 patients (mean age 47 years), 12 in the high-risk group, 4 in the moderate-risk group and 8 in the group at slightly increased risk. Of the 24 women, 17 reported a family history of breast cancer. The authors conclude that surveillance of women at increased risk may be useful in detecting breast cancer at an early stage.
Kerlikowske et al (1996)

To determine factors influencing the sensitivity of first screening mammography, 28,271 women aged 30 and over took part in this US cross-sectional study. Results showed that sensitivity of mammography was highest among women aged 50 and older who have primarily fatty breast density (P<0.01). Sensitivity was lowest in women younger than 50, and was particularly low when the screening interval was about 2 years, or when women had a family history of breast cancer.

Sætersdal et al (1996)

This Norwegian follow-up study involving 537 women aged between 20-76 years (mean 43 years) with a family history of breast cancer aimed to evaluate whether breast screening techniques (clinical breast examination (CBE), mammography and/or ultrasonography, and fine needle aspiration) were suitable to identify women at risk of breast cancer. Results showed that a high number of breast cancers occurred in women with a family history of breast cancer, with 8 carcinomas and 5 cases of atypical hyperplasia found, compared with 1.6 and 0.3 expected, respectively. The authors conclude that the breast screening methods used were suitable to identify women with a family history of breast cancer, and that early diagnosis and treatment are likely to be of benefit in this group of women.


This paper looked at the long-terms impact of surveillance on death from breast cancer, using data from two Swedish counties. They examined the data about deaths from breast cancer diagnosed in the 20 years before screening was introduced (ie 1958-77), and those with breast cancer diagnosed in the 20 years after the introduction of screening (ie 1978-97). The paper looked at deaths from breast cancer and all-cause mortality. They calculated raw unadjusted relative risks of death from breast cancer (1978-97 compared with 1958-77), they then estimated relative risks adjusted for age, changes in incidence of breast cancer in the later period relative to the earlier period, and bias from self selection for attendance or non-attendance at screening where appropriate. They also estimated relative risks for all-cause mortality and for all-cancer mortality in women with breast cancer adjusted for age and incidence. Their findings were that in women aged between 40-69, after adjustment for age, changes in incidence and self-selection bias, there was a reduction in breast cancer mortality of 44% (stat significant) exposed to screening. There was also a significant reduction in the overall age group (40-69) of women exposed and not exposed to screening. They say that this is explained by the rapid introduction of population-based screening in these two counties, the tailoring of screening intervals to age of the women invited to screening, and very high rates of attendance. The reduction in deaths in women in the 40–69-year age-group not exposed to screening was 16%, and the reduction in the never-screened 20–39-year age-group was 27%. Their overall conclusion was that mammography screening is contributing to substantial reductions in breast cancer mortality in the two Swedish counties examined.

### 7.2.2.2 Comparison of different breast screening techniques

Note: The findings of an ongoing HTA trial about MRI, which may help clarify its effectiveness, are awaited. [This section is being updated to take account of new evidence on MRI for surveillance.]
Studies

Hou et al (2002)

This Taiwanese study compared mammography, sonography and CBE carried out on a single day in 935 women aged over 35 years who had a family history of breast cancer. Twenty-one breast cancers, 16 of which were invasive and 5 non-invasive cancers, were detected. Of the cancers, 19 (16 invasive and 3 non-invasive cancers) were detected by sonography, whereas only 11 invasive cancers were detected by mammography and 7 by physical examination. The sensitivity of sonography was 90.4% which was higher than mammography (52.4%) and physical examination (33.3%), or a combination of both techniques (66.7%). Results suggest that sonography was more accurate for screening than mammography and CBE, identifying 7 additional cancers, in this cohort of women at high risk of breast cancer due to family history.

Warner et al (2001)

196 women aged 26-59 years who had BRCA1/2 mutations or strong family histories of breast or ovarian cancer underwent mammography, ultrasound, MRI and CBE on a single day in this Canadian screening study. Six invasive and 1 non-invasive breast cancers were detected; 5 of the invasive cancers occurred in mutation carriers and the sixth occurring in a woman with a previous history of breast cancer. The prevalence of invasive or non-invasive breast cancer was 6.2% in the 96 mutation carriers. MRI detected all 6 invasive cancers, whereas only 3 were detected by ultrasound, 2 by mammography and 2 by CBE. It is concluded that MRI may be superior to mammography and ultrasound in women at high risk of hereditary breast cancer.

O’Driscoll et al (2001)

Ultrasound and mammography were compared, particularly in terms of specificity, in this UK pilot study of 149 women with a mean age of 42 years who were at moderate risk of breast cancer due to family history. All but one of the mammograms were normal; in this case both mammography and ultrasound showed a lesion which when biopsied was found to be a fibroadenoma. One core biopsy was carried out on both mammographic and ultrasound criteria and 9 biopsies were carried on ultrasound criteria alone. Biopsy results were 7 fibroadenomas; 2 areas of fibrocystic change; and 1 adenoid cystic carcinoma, which would not have been otherwise diagnosed. PPV for biopsy was 10%. It is concluded that screening with mammography and ultrasound may be beneficial in women at increased risk of breast cancer due to family history.

Stoutjesdijk et al (2001)

In this Dutch retrospective study, the sensitivity of MRI was compared to that of mammography in a cohort of 179 women with a family history of breast cancer aged 21-71 years, to determine whether MRI has a role in the early detection of breast cancer in this population. Thirteen cancers were detected, or which all were detected by MRI, although 7 were not detected by mammography. For the whole cohort, the area under each curve (AUC) for mammography was 0.74 (95% CI, 0.68-0.79) and for MRI was 0.99 (95% CI, 0.98-1.0). For a subset of 75 women who had both MRI and mammography, the AUC for mammography was 0.70 (95% CI, 0.60-0.80) and for MRI was 0.98 (95% CI, 0.95-1.0). The authors conclude that MRI was more accurate than mammography in annual screening of women with a family history of breast cancer.

This prospective German study compared MRI to mammography and ultrasound in 192 asymptomatic and 6 symptomatic women suspected or proved to carry a BRCA mutation. Fifteen breast cancers were identified; in 9 of the 192 asymptomatic women and in all 6 of the symptomatic women. Four of the 9 cancers in the asymptomatic women were detected and correctly classified with mammography and ultrasound combined; all 9 cancers were correctly classified by MRI. The sensitivities of mammography, ultrasound and MRI in 105 of the asymptomatic women were 33%, 33% (mammography and ultrasound combined, 44%) and 100%, respectively, with PPVs of 30%, 12% and 64%, respectively. The authors conclude that the accuracy of MRI is significantly higher than that of mammography and ultrasound in high-risk women.


In this Dutch study, MRI in addition to normal surveillance (mammography, CBE, ultrasound and FNA) was evaluated in 109 women, mean age of 42 years, who had a more than 25% risk of breast cancer due to genetic predisposition. MRI was performed in these women because over 50% dense breast tissue was seen at mammography and no suspect lesion had been detected. Results showed that MRI detected 3 breast cancers occult at mammography, whereas 2 cancers were expected. MRI was false-positive in 6 women, with no false-negative results. The extra cost of breast MRI in addition to mammography and physical examination was €13,930 per detected cancer, compared to €9000 for the detection of one breast cancer patient in the Dutch national screening programme. It is concluded that MRI appears successful in screening young women at high risk of breast cancer, as it appears to advance detection of cancers still occult at mammography and physical examination; however, the cost may be prohibitive.

7.2.2.3 Radiation risks in mammography

The risks and benefits of using ionising radiation to screen for breast cancer in the context of the NHS Breast Screening Programme (NHSBSP) were considered in a recent report (NHSBSP Publication 54, 2003). We were interested in any evidence about differential risks associated with those with a family history and those in the younger age groups. As the report notes adequate information on which to provide sound estimates of risk is somewhat lacking. The report used information from North American women populations (from women who were given high doses of radiation for medical purposes (mainly for TB and postpartum mastitis in the 1930s and 1940s)) who have been followed for many decades. They present estimates of lifetime risk of radiation induced breast cancer for UK women in the context of mammography doses as follows (screening ages are shown in bold):

<table>
<thead>
<tr>
<th>Age at exposure (years)</th>
<th>Lifetime risk (per million per mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
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<td>18</td>
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<td>18</td>
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<td>30</td>
<td>18</td>
</tr>
<tr>
<td>35</td>
<td>17</td>
</tr>
</tbody>
</table>
They also point out that they have used a dose and dose rate effectiveness factor (DDREF) of 2 to arrive at these risk estimates, however other agencies such as the US Environmental Protection Agency advocate a DDREF of 1 for breast cancer – which would mean a doubling of risks presented in this table.

The report also points out that:

it is unclear to what extent radiation risks may differ between women with a family history of breast cancer and other women. However, particularly for exposures at older ages for which radiation risks are lower, it is unlikely that genetic susceptibility would have a major impact on the average population risks used in this report. (p.6)

### 7.2.3 Summary of evidence for effectiveness of breast screening in women with a family history of breast cancer and/or BRCA1/2 mutations

There is evidence from a number of studies that surveillance, and other integrated programmes of mammography, clinical breast examination and ultrasound, are effective in detecting breast cancers in women with a family history of breast cancer and/or BRCA1/2 mutations, although in general, study design is not rigorous. There is no evidence that breast screening reduces mortality from breast cancer in this high-risk group of women.

A number of studies have observed that surveillance is less sensitive in younger women, women with a family history of breast cancer and in BRCA1/2 mutation carriers (Kerlikowske et al, 1996; Kerlikowske et al, 2000; Goffin et al, 2001).

Data reviews have indicated that the risk of radiation-induced breast cancer is small compared to the benefits of breast cancer detection, and that the margin of benefit over risk is also sufficient in women with a family history of breast cancer down to the age of 40 years (Law, 1997; Law et al, 2001).

In terms of comparative evidence for breast screening techniques in women with a family history of breast cancer and/or BRCA1/2 mutations, there is some evidence that MRI is more sensitive in detecting breast cancer than mammography or combined breast screening techniques (Kuhl et al, 2000; Tilanus-Linthorst et al, 2000; Stoutjesdijk et al, 2001; Warner et al, 2001). Numbers of women taking part in these studies was, however, small.

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>16</td>
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<tr>
<td>45</td>
<td>15</td>
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<tr>
<td>50</td>
<td>14</td>
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<td>12</td>
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<td>60</td>
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<tr>
<td>65</td>
<td>8.0</td>
</tr>
<tr>
<td>70</td>
<td>6.1</td>
</tr>
<tr>
<td>75</td>
<td>4.2</td>
</tr>
<tr>
<td>80</td>
<td>2.5</td>
</tr>
<tr>
<td>85</td>
<td>1.2</td>
</tr>
</tbody>
</table>
7.2.4 Evidence for the efficacy of breast cancer screening in the general population of women

A recent review of the efficacy of breast cancer screening in the general population of women (IARC 2002a) has evaluated the research evidence as follows:

- There is sufficient evidence for the efficacy of screening women aged 50-69 years by mammography as the sole screening modality in reducing mortality from breast cancer.
- There is limited evidence for the efficacy of screening women aged 40-49 years by mammography as the sole screening modality in reducing mortality from breast cancer.
- There is inadequate evidence for the efficacy of screening women under 40 or over 69 years by mammography in reducing mortality from breast cancer.
- There is inadequate evidence for the efficacy of screening women by clinical breast examination in reducing mortality from breast cancer.
- There is inadequate evidence for the efficacy of screening women by breast self-examination in reducing mortality from breast cancer.

7.2.5 Evidence of cost-effectiveness of mammographic screening [This section is being updated to take account of new evidence on MRI in surveillance.]

No specific studies were identified that examined the cost effectiveness of mammographic screening in women with a familial history of breast cancer. A recent handbook on breast cancer screening, IARC (2002), provides an overview of published cost-effectiveness studies relating to mammographic screening in the general population from which two relevant issues are raised. Firstly, it is stated that screening of women below the age of 50 yrs is, in the general population, unlikely to be as cost-effective as increasing the frequency of screening for older women. Secondly, the latter option is associated with substantially less uncertainty due to the unproven health benefits of screening younger women. The report states that, in relation specifically to screening high-risk women, this same uncertainty applies.

7.2.6 Surveillance: patient information and uptake

Several studies have looked at patient information (including risk information) in relation to use and uptake of mammography in women with a family history.

McCaul et al (1996)

This meta-analysis synthesised data from 54 studies which evaluated the association between risk perception and/or family history of breast cancer and mammography uptake (quality assessment of studies was not reported). In terms of family history, 17 or 19 studies reported positive associations between family history and screening behaviour, with a mean weighted effect size of $r=0.27$ ($P<0.001$). Correlations between perceived breast cancer risk and screening behaviour were positive in 18 of 19 studies, with a mean weighted effect size of $r=0.16$ ($P<0.001$). Studies which compared women who did or did not have a history of breast problems showed that those with a positive history were more likely to have been screened ($P<0.001$), and studies that measured breast cancer worry
showed that greater worry was associated with high screening levels (P<0.01). The authors conclude that increasing perceptions of personal vulnerability may increase mammography screening.

Schwartz et al 1999

This trial investigated the efficacy of breast cancer risk counselling with that of a general health education control intervention among women with a family history of breast cancer. Participants were identified by relatives who were under treatment for breast cancer. For those who agreed to participate and after a baseline interview, they were randomised to either the breast cancer risk counselling or the general health education group. Participants did not know which group they were assigned to until the intervention session began. Participants were followed up one year after for a (blinded) interview. Eligible participants were women aged 40 and over with a family history of breast cancer in at least one first-degree relative. The paper reports the findings based on the women who completed a counselling session and completed the 12 month follow up interview (n=430), from 508 who attended counselling). The treatment groups did not differ in their use of mammography at baseline or at follow up, suggesting that risk counselling did not lead to increased mammography use. The paper reports a significant group by education interaction. When they looked at the 2 education strata (described as high/low levels of education) they found that among less well educated participants, those receiving risk counselling showed reduced mammography use relative to the general health education group (OR=0.44, 95% CI=0.23,0.89). There was no group effect among the more educated participants.

Lindberg et al (2001)

430 US women with a family history of breast cancer aged between 15-78 years were surveyed to evaluate the association between general anxiety, risk perception, screening-related anxiety and breast screening compliance in terms of pap smears, mammograms and performing breast self-examination. Results showed that neither general nor screening-specific anxiety were found to be related to women’s compliance with screening practices; however, significant associations were observed between women’s anxiety regarding breast self-examination and their actual performing it (R=0.21), with higher anxiety associated with poorer compliance. The authors conclude that breast self-examination appears to be the only procedure for which compliance is negatively associated with anxiety.


Breast screening uptake in 461 women aged <30->50 years with a family history of breast cancer took part in this Australian survey. A significantly lower percentage (56%) of women aged <30 years were vigilant in terms of mammography recommendations, compared to older age groups of women (P=0.0001). Results also found that the degree to which health outcomes are perceived to be under personal control was associated with monthly or more frequent breast self-examination (P=0.0037); and that women with moderately high breast cancer anxiety had the highest percentage reporting breast self-examination, compared to women with low, moderately low, and high anxiety levels (P=0.044).

Bastani et al 1999

This study looked at the mailing personalised risk notification and other materials to women with at least one first degree relative and its impact on use of mammography. They present results from 753 women who were followed up throughout the study (from 2500 in random sample, 902 completed baseline interview and 753 completed follow up interviews at approximately 1 year after baseline). Over a third of women were related to each other. Information obtained at baseline information was
used to create a personalised risk notification letter for each woman and indicated a level of risk (slightly, moderately or substantially higher) compared to other women of her age (using an adaptation of Gail risk algorithm). The major outcome of interest was receipt of a screening mammogram between the baseline and follow up. Prior to baseline interview 55% of women in both intervention and control groups reported having a screening mammogram in the 12 months prior. In the interval between baseline and follow up, 58% of the control group and 65% of the intervention group obtained a mammogram. This was a 10.2% increase for the intervention group and 2.5% increase in the control group, around an 8% intervention group advantage. There was an interaction of age in the intervention. There was no significant intervention effect on women aged under 50 yrs and. There was a fairly large intervention effect on women aged 50-64 yrs of age and those aged 65 yrs and over.


The impact of psychological distress and personality construct of consciousness on mammography utilisation was assessed in this US survey of 200 women with a family history of breast cancer aged between 40-84 years. Analyses controlling for potential confounders of physician recommendation for mammography, decisional balance and perceived risk found that distress was negatively associated with mammography uptake in women with a family history of breast cancer who were low in conscientiousness (OR=0.31; 95% CI, 0.10-0.96). Distress was not significantly related to mammography utilisation in highly conscientious women (OR=2.79; CI, 0.73-10.72).


213 women aged between 26-72 years who had at least one relative with breast or ovarian cancer took part in a longitudinal US survey to assess factors which predicted mammography uptake. Results found that only age and cancer worry were significant predictors of greater mammography utilisation (P<0.02 and P<0.04, respectively). The authors suggest that moderate levels of cancer worry facilitate, rather than undermine, mammography adherence.


The psychological effects of false-positive mammography in 35 women with and 87 women without a family history of breast cancer aged between 50-64 years who had taken part in the UK National Health Service Breast Screening Programme were evaluated in this survey. Results showed that recall because of false-positive mammograms caused significant adverse psychological effects, with women more likely to be have borderline or clinically significant anxiety at recall than at baseline (P<0.05), screening (P<0.0001), first follow-up (P<0.005) or at final follow-up (P<0.02). However, for women with a family history, these adverse psychological effects appear to be transient (less than 5 weeks).

Drossaert et al (1996)

This Dutch survey of women aged 50-69 years compared women with (389) and without (3295) a family history of breast cancer with respect to risk perception, breast cancer anxiety and early detection behaviour. 54% of women with and 57% of women without a family history were unaware that having a 1st-degree relative with breast cancer increases breast cancer risk. Women with a family history felt significantly more susceptible to breast cancer than women without (P<0.001); perceived that they had a higher breast cancer risk (P<0.001); and were significantly more anxious about breast cancer (P<0.001). Although women with a family history had higher risk perceptions,
no significant differences were observed between women with or without a history in terms of monthly breast self-examination and adherence to a breast screening programme.

Curry et al (1993)

In this study the effect of obtaining risk information from women and providing generalised or personalised risk information on participation in mammography screening. Participants were women aged 50 and above who were enrolled with a health maintenance organisation. Different invitations were issued and data was collected from some groups that allowed personalised risk information to be gathered and reflected in the type of invitation they received. They were randomised to 1. no risk factor questionnaire + general invitation (n=440); 2. no risk factor questionnaire + general risk invitation (n=447); 3. risk factor questionnaire + general risk invitation (n=595); 4. risk factor questionnaire + personal risk invitation (n=594). Overall, their findings did not show increased screening participation with the addition of general risk information or risk assessment and feedback regarding personal risk factors. However, for women with a family history (defined as one or more first-degree relatives with breast cancer) the invitation to screening that included personalised risk information was associated with higher rates of participation amongst these women (personalised feedback (group 4) was more closely associated with significantly higher participation that general feedback (group 3), 66.7% vs. 42.9%, P=0.005).

7.2.7 Summary of evidence for uptake and psychosocial outcomes of breast screening in women with a family history of breast cancer

In terms of evidence for uptake of breast screening practices in women with a family history of breast cancer, results were inconsistent. One meta-analysis (McCaul et al, 1996) and one survey (Diefenbach et al, 1999) found that increasing perceptions of personal vulnerability to breast cancer and moderate levels of cancer worry, respectively, may increase mammography screening. However, 2 surveys (Drossaert et al, 1996; Lindberg et al, 2001) found that anxiety in women with a family history of breast cancer did not affect breast screening compliance. A further survey (Schwartz et al, 1999) found that distress in women with a family history of breast cancer who were low in conscientiousness was associated with a lower uptake of mammography. Older women were more likely to adhere to mammography (Diefenbach et al, 1999) and, conversely, women aged <30 years were less likely to adhere to mammography recommendations than older women (Meiser et al, 2000).

One survey (Gilbert et al, 1998) found that recall because of false-positive mammograms caused significant adverse psychological effects, although for women with a family history of breast cancer, these effects appeared to be short-term.

7.2.8 Comment

From Table 1 (page 18) it can be seen that the risk estimate that gains entry to the National Health Service Breast Screening Programme (NHSBSP) is 2.8%. A similar risk estimate for women with a family history was found from Claus at age 40 (2.7%). The corresponding risk estimate from the Collaborative Group was 4.1%. Therefore a risk estimate between 2.7% and 4.1% was thought by the guideline development group to indicate a risk estimate that would be reasonable to justify as moderate risk, hence a figure of 3% was agreed by the guideline development group. These risk estimates are used as the basis for recommendations about who should receive mammographic surveillance and from what age.
7.3 Genetic counselling (tertiary care)

Recommendations (tertiary care)

1. Women meeting criteria for referral to tertiary care should be offered a referral for genetic counselling regarding their risks and options. (C)

2. Women attending genetic counselling should receive standardised information beforehand describing the process of genetic counselling, information to obtain prior to counselling session, the range of topics to be covered and brief educational material about hereditary breast cancer and genetic testing. (D)

3. Predictive genetic testing should not be offered without adequate genetic counselling. (C)

Evidence statements

1. Genetic counselling is associated with decreased anxiety, cancer worry and improvements in risk accuracy and knowledge, in the short term. (III)

2. Genetic counselling is not associated with increased anxiety. (III)

3. There is no difference in anxiety reduction and satisfaction between genetic counsellors compared to clinical geneticists. (IV)

4. Many women who mistakenly perceive their risk as high can be reassured that they are at not at such high levels of risk and need no further interventions. (IV)

5. Many women who consider taking a predictive test for BRCA1/2/TP53 are enabled by genetic counselling to make an informed choice about whether or not to proceed with the test. (IV)

7.3.1 Introduction

Genetic counselling describes the consultation between an individual (or individuals) with a family history of breast cancer and a person trained in genetic aspects of the risk of occurrence of breast cancer in the family. (Eeles & Murday, 1996).

Genetic counselling involves skills development for 5 main aims:

1. to help the counselee comprehend the medical facts, and specifically the way heredity contributes to the disorder
2. to provide information about the personal risk of cancer, according to how much the counselee wishes to know
3. to discuss the available options for risk management
4. to choose a personal course of action that seems most appropriate in view of the level of risk, family goals, ethical and religious standards
5. to help the individual adjust to the risk and its implications

The outcomes of cancer genetic counselling (both for risk assessment and genetic testing) have largely been assessed in terms of the accuracy of counselee’s risk perceptions, mental health, attitudes to and psychosocial outcomes of genetic testing and to a lesser extent, health care behaviour.

Although most new attendees may want personal risk information, a range of motivating factors have been shown with need for reassurance, information about cancer detection and prevention strategies, and psychological support also being deemed important, if not more important. Lack of knowledge of inheritance and of what to expect at the consultation may leave women feeling unprepared and dissatisfied because it was not possible to give a clear risk estimate. Lay beliefs about the cause of cancer and past experiences of cancer in the family will influence both the process and outcome of genetic counselling. Women often have inaccurate perceptions of personal and population risks prior to genetic counselling and overestimation may cause increased anxiety and unrealistic expectations of access to surveillance, genetic testing and cancer prevention.

7.3.2 Research literature evidence

One meta-analysis and one systematic review have been identified from the literature which evaluates the impact of genetic counselling in women with a family history of breast cancer.

Meta-analyses, systematic reviews and re-analyses


Twelve studies which have evaluated the impact of genetic counselling on psychological distress, accuracy of perceived risk and breast cancer screening behaviours in women with a family history of breast cancer were included in this meta-analysis (included studies did not appear to undergo systematic quality assessment). Psychological distress was decreased in all studies post-counselling, although analysis of the combined results did not quite reach statistical significance (P=0.052). In terms of the impact of genetic counselling on generalised anxiety, the average effect size across all studies showed a statistically significant decrease (P<0.01). Genetic counselling was also found to improve the accuracy of perceived risk (P<0.01). Findings from studies which have evaluated the impact of genetic counselling on other outcomes were briefly summarised, reporting inconsistent results of impact on anxiety about developing breast cancer and impact on breast cancer screening. Three studies which measured the impact of genetic counselling on breast cancer genetics, however, found significant increases in knowledge. The authors conclude that genetic counselling leads to statistically significant decreases in generalised anxiety and improved accuracy of perceived risk. Psychological distress was also decreased, although this reduction did not quite reach statistical significance.


The impact of genetic counselling for familial breast cancer on risk perception and psychological morbidity was assessed in this systematic review (included studies did not undergo quality assessment). Results showed that in studies which evaluated risk perception after genetic counselling, improvements were observed consistently in the accuracy of perceived breast cancer risk, although between 22-50% of women still overestimated their risk. In one meta-analysis, genetic
counselling was found to significantly improve risk perception (P<0.01). In terms of impact of genetic counselling on psychological outcomes, studies showed varied results, with some showing some reduction in psychological morbidity and some showing no change. Results of the meta-analysis for this outcome indicated a non-significant trend of reduction in psychological distress (P=0.52), although a significant decrease in generalised anxiety was observed (P<0.01). The authors conclude that genetic counselling does not appear to have an adverse effect on psychological outcomes and appears to reduce generalised anxiety. Counselling also appears to be effective in improving the accuracy of breast cancer risk perception, although many women continue to overestimate their risk. The authors note, however, that only a few RCTs were included in the review, that follow-up was short, and that studies lacked data on other outcomes.

**Additional studies**

Additional studies not included in the meta-analysis or systematic review were also identified. Brief details are included in Appendix 4.

### 7.3.2.1 Patient information issues

**Brain et al (1999)**

Brain et al 1999 used a questionnaire study to look at the reasons for attending Family History Clinics. The study consisted of 833 respondents (which represented a response rate of 83%). The questionnaire used a 10 item scale. They reported that the main reasons given were: personal risk (29%), knowledge of family history (19%), risk to family members (13%), to reduce worry (11%), issues related to genetic testing (including access to testing) (10%). They reported important differences in psychological profile of women with different motivations, unrelated to family history. For example those women with a high risk perception, had a greater wish for testing, and less perceived barriers, and greater consideration of prevention. They concluded that there was likely to be wide variation in motivations for attendance requiring a multidisciplinary approach.

**Hallowell et al (1997c)**

This observational study also used questionnaires and interviews. They reported that 65% of women felt unprepared for the consultation. Twenty eight percent felt they could not be given an accurate risk estimate as a result. They recommended that an information leaflet including the following information should be used (description of genetic counselling as practised locally; indicate if partner or significant other should attend; describe the topics to be covered; indicate what information the counselee should bring to the session; brief epidemiological facts about population risk, proportion of cases that could be considered genetic, illustration of dominant inheritance, breast cancer genes, implications of testing).


This study gathered data from daughters of breast cancer patients. It used a 30-item information needs tool. From 125 women approached, 97 responded (77.6%). Their median age was 32. They reported that 63% of respondents got information from their mothers, which increased over time. Seventy four per cent sought information from other sources. They concluded that whilst mothers are an important information source about cancer they can also be a blocking factor, therefore health professionals also need to be involved in health information provisions about familial breast cancer.
Julian-Reynier (1996)

This was a questionnaire survey that investigated women’s’ clinic expectations and risk perceptions. It used a 150 item questionnaire prior to consultation. The respondents were 206 unaffected attendees in 6 cancer genetics centres. They reported that: 87.% wanted information for themselves; 50% wanted information that they could give to their children; 25% wanted information for their siblings; 33.5% wanted preventive information; 45% wanted risk and preventive information. They concluded that the main reason for attending was for information on prevention. They also concluded that medical pathways are more effective than self-referral to reach those at risk.

7.3.3 Summary of genetic counselling evidence

One meta-analysis and 1 systematic review have been identified which have evaluated the impact of genetic counselling on psychological morbidity and breast cancer risk perception. Results from both studies consistently show that counselling does not have an adverse effect on psychological morbidity, with results in the meta-analysis indicating a statistically significant decrease in generalised anxiety. Both studies also showed that counselling improved accuracy of perceived breast cancer risk perception, with a statistically significant improvement observed in the meta-analysis. Studies included in the systematic review, however, showed that many women still overestimated their risk of breast cancer. Studies with longer-term follow-up and improved study design are required to confirm these findings.
7.4 Genetic testing (tertiary care)

Recommendations

1. All high risk women should have access to information on genetic tests aimed at mutation finding. (D)

2. Pre-test counselling (preferably two sessions) should be undertaken. (D)

3. Discussion of genetic testing (predictive and mutation finding) should be undertaken by someone with appropriate training. (D)

4. High-risk women and their affected relatives should be informed about the likely informativeness of the test (the meaning of a positive and a negative test) and the likely timescale of being given the results. (D)

Mutation tests

5. Tests aimed at mutation finding should first be carried out on an affected family member, where possible. (D)

6. Women from families with a 20% or greater chance of carrying a mutations such as BRCA1, BRCA2 or TP53 should have access to testing. (D)

7. The development of a genetic test for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the appropriate gene (such as BRCA1, BRCA2 or TP53). (D)

8. A search/screen for a mutation in a gene (such as BRCA1, BRCA2 or TP53) should aim for as close to 100% sensitivity as possible for detecting coding alterations and the whole gene(s) should be searched. (D)

Evidence statements

1. There are over 500 different mutations in BRCA1 that have been reported. (IIb)

2. BRCA1/2 mutations account for the great majority of multiple case families with combinations of both breast and ovarian cancer and male and female breast cancer. (IV)

3. BRCA1/2 mutations account for less than one third of the inherited component of female breast cancer only families. (III)

4. There is some evidence to suggest that families that receive no results from a BRCA1/2 search/screen show some increased anxiety at a year. (III)
5. Normal practice in the UK is that all reported predictive testing is carried out within a protocol that has at least two sessions of genetic counselling. Shorter protocols have not been studied. (IV)

6. Once a mutation has been identified in a family this should provide near complete certainty about who has or has not inherited the high risk in the family. This allows unaffected individuals to undertake predictive genetic testing. (IV)

7. Tests aid women with decision making with regard to risk reducing interventions (e.g. surgery) and surveillance, but may also give them greater certainty about the risks to themselves and their family. (IV)

8. There is limited evidence which shows that about half of women who have a positive (high risk) predictive test for BRCA1 & 2 undertake risk reducing surgery. The uptake in non-carriers is very low. (III/IV)

9. Thus far, there have been no results from large prospective well designed studies on the results of BRCA1/2 predictive testing. (IV) (note: the outcomes of the CR-UK study are awaited).

10. A negative predictive test for BRCA1/2 has been shown to reassure women in studies with short term follow-up. (IV)

11. A positive predictive test (high risk) result may lead to higher levels of psychological morbidity compared to a negative result, but is not increased over baseline. (IV)

12. Tests aid women with decision making with regard to risk reducing interventions (e.g. surgery) and surveillance but may also give them greater certainty about the risks to themselves and their family. (IV)

13. BRCA1 & 2 testing in the UK has not identified particular hot spots or founder mutations. Mutations in BRCA1 & 2 are generally spread throughout the whole gene. (IV)

14. There are ethnic populations within the UK which have strong founder mutations such as the Jewish population. (IV)

15. Direct sequencing achieves high levels of sensitivity when used to identify sequence alterations. However, there are a number of other substantially cheaper options with virtually identical sensitivity such as MLPA, FAMA, DHPLC and DF. (III)

16. Techniques other than direct sequencing may need to be used to detect deletions. (III)

7.4.1 Introduction

7.4.1.1 Breast cancer genes

At least five genes are known to be associated with an inherited breast cancer risk. It is important to emphasise that these genes are not the only cause for familial breast cancer; it has been estimated that these genes explain perhaps 20% of the increased familial risk of breast cancer. The remainder may be due to other genes or to other factors.

Of the known genes, BRCA1 and BRCA2 are most common. Carriers of mutations in these genes have a high lifetime risk of breast cancer (variously estimated, depending on the context, of 65-85% for BRCA1 and 40-85% for BRCA2). Both genes also confer a high risk of ovarian cancer (around
40-50% for BRCA1, 10-25% for BRCA2) as well as more moderately increased risks of other cancers. BRCA1 and BRCA2 mutations explain a considerable proportion of very high risk families (that is, families with four or more close relatives with breast cancer), particularly if there is also a family history of ovarian cancer or of male breast cancer. Mutations in these genes are however rare in the general population, and probably only account for about 2% of breast cancer cases overall.

Mutations in the TP53 gene predispose to a very high risk of breast cancer, such that the majority of women are affected before the age of 50. Mutations in this gene also predispose to a range of other cancers including sarcomas in childhood and brain tumours, and mutations are therefore usually identified when these cancers occur together in families, a syndrome known as Li-Fraumeni syndrome. Mutations in TP53 are significantly rarer than BRCA1 or BRCA2 mutations.

Mutations in the PTEN gene are responsible for Cowden’s syndrome, a very rare inherited disorder associated with an increased risk of breast cancer. Mutations in two other genes, ATM and CHEK2, are associated with moderate risks of breast cancer; clinical genetic testing for these genes has not been implemented.

7.4.1.2 Genetic Testing

Several hundred different mutations in BRCA1 and BRCA2 have been identified, and these occur almost throughout their sequence. Although some mutations are found in multiple families, there is no one predominant mutation in the U.K. (as, for example, in the case of Cystic Fibrosis). Consequently, screening for BRCA1 and BRCA2 mutations requires screening the entire coding sequence.

A different situation pertains in the Ashkenazi Jewish community. In this population, three “founder” mutations (two in BRCA1, one in BRCA2) are relatively common and explain almost all the high risk families due to these genes. Consequently, a much simpler and more sensitive and specific test based on these mutations is available in this population.

Since mutations are uncommon unless there is a strong family history of breast and/or ovarian cancer, genetic testing is mostly targeted on such families For genetic testing to be maximally informative, testing is usually carried out first on an individual affected with breast or ovarian cancer, who is likely to carry a mutation if one is present in the family. If a mutation is identified, other individuals in the family may be offered a “predictive” genetic test to determine whether or not they carry the mutation. Since this test is based on a single mutation, it is much more straightforward than the initial screen. In the absence of prior mutation finding in a family member, genetic testing is usually inconclusive.

There are several different types of sequence alteration in BRCA1 and BRCA2. The most common alterations seen in high risk families are those that are predicted to cause a truncated protein. These mutations are known to be associated with increased cancer risk and are the basis of most genetic testing. Many other alterations are also found, however, particularly those substituting a single amino-acid (so called ‘missense mutations’). A few of these (particularly in BRCA1) are known to be associated with cancer risk and are used in predictive testing, but the risks associated with most missense changes are either low or not known, and these are not utilised clinically.

Sequencing of the entire coding regions of BRCA1 and BRCA2 can detect reliably most, but not all, the relevant mutations. In particular, sequencing is not able to detect various large rearrangements of part or all of the gene sequence. These alterations explain approximately 20% of BRCA1 mutations (they are rare in BRCA2). Techniques for detecting large rearrangements have been developed but are relatively laborious and not in widespread use. Since sequencing is relatively expensive for these genes, most laboratories in the U.K. rely on other techniques for screening. The sensitivities of these
techniques (compared to full sequencing) for detecting deleterious mutations vary but are probably in the range 60-90%.

7.4.2 Research literature evidence

7.4.2.1 Genetic testing

Evidence for the effectiveness of different genetic testing techniques, with reference to specific populations and detection rates, is summarised in Appendix 6.

One systematic review and a set of draft practice guidelines have also been identified from the literature.


This Canadian technology report includes a review of current genetic testing methods in terms of their predictive ability. The review suggests the use of PTT as an attractive method to apply early on in genetic testing, and the use of PCR-SSCP-MHX analysis as a cost-effective alternative to conventional methods in the detection of germline mutations in BRCA1. DDF is also discussed for detecting all BRCA1 sequence variants, in that it has been found to be more sensitive than SCA. The report, however, does not recommend any one genetic testing technique.

Mueller et al (2001)

Based on reports of workshops run by the European Molecular Genetics Quality Network (EMQN) and the Clinical Molecular Genetics Society (CMGS), these draft practice guidelines concern the molecular analysis of hereditary breast and ovarian cancer. The draft guidelines discuss the various mutation detection techniques, but state that it is not possible to establish a single recommended technique, as testing methods used depend largely on local preferences and facilities.

7.4.2.2 Genetic testing – psychosocial aspects


In an Australian cohort study, 90 women with a family history of breast and ovarian cancer who had undergone genetic testing for BRCA1/2 mutations (30 carriers and 60 non-carriers), and 53 women with a similar family history, but who were not offered testing due to having no living affected relative available for blood sampling, were compared in terms of psychological impact of genetic testing. The mean age of the total sample was 40 years. Results found that mutation carriers had a significantly higher level of breast cancer distress 7-10 days (P=0.005) and 12 months (P=0.045) post-test result compared to women who were not offered testing. Non-carriers showed a significant decrease in state anxiety 7-10 days post-result (P=0.024) and in depression 4 months post-result (P=0.024) compared to women who were not offered testing. Data indicate that non-carriers derive psychological benefits from genetic testing, and women testing positive may anticipate a sustained increase in distress following test disclosure, although no other adverse psychological outcomes were observed.
Tercyak et al (2001)

Paper incomplete – awaiting a full copy.

Lodder et al (2001)

Attitudes and psychological functioning in the weeks before and after genetic test result disclosure were measured in 28 men (mean age 47, range 29-67) who were at 25% or 50% risk of being a BRCA1/2 mutation carrier, and 23 of their partners, in this Dutch study. Results found that pre-test distress in men and their partners was low. Many men and partners expected the test result to be problematic for their children, but not for themselves. Distress was particularly low in men without daughters and in those who were optimistic. Most men reported that they did not actively avoid the issue of mutation carrier status. Four of the 28 men were eventually identified as mutation carriers. High distress was reported post-test result in one mutation carrier and 3 non-mutation carriers. A large variation in psychological reactions was observed in the 4 mutation carriers, for example, feelings of guilt. Low pre-test distress was not found to necessarily indicate avoidance of the issue.


21 unaffected women aged between 22-62 years (mean age 36) who were eligible for mutation searching in their family in that they had a living affected relative willing to give a blood sample, took part in a UK survey to describe the short and longer-term psychological consequences of waiting for genetic testing results. Mutation searches were initiated in 15 of the 21 families, and 2 received their results within 12 months. For the 13 families still waiting, anxiety and distress were within normal ranges at all time-points. Reduced cancer-related worries were reported at the 6- and 12-month post-search offer follow-ups compared with earlier assessments, but an increase in general anxiety was experienced at the 12-month follow-up. Changes in anxiety over time were not observed in those where mutation searches were not initiated. The authors conclude that there may be long-term psychological costs of offering tests for which results are likely to be delayed.

Bottorff et al (2000)

In a Canadian qualitative research study, 20 women who did not meet the eligibility criteria for genetic testing and 10 of their referring physicians took part in interviews to describe experiences of failing to qualify for testing. Three main themes emerged in the interviews with the women: they had deep concerns about their breast cancer risk, despite their ineligibility; they believed that the genetic test was simple and would provide a definitive answer; and they experienced anger and frustration relating to the lack of information they had received. Interviews with the physicians found that they were concerned that women did not understand the implications of genetic testing.

Lodder et al (1999)

General and cancer-related distress was studied in a Dutch survey of 85 healthy women (mean age 38) with a 25% or 50% risk of BRCA1/2 mutation carrier status and 66 of their partners (mean age 39) during the 6-8 week period between genetic counselling/blood sampling and disclosure of the test result. Results found that mean pre-test anxiety and depression rates were similar to those in the normal Dutch population. Most women and partners coped well during this period, although some were quite distressed. Distress was more likely to occur in at-risk carriers who expected problems to increase after an unfavourable test result; were considering prophylactic mastectomy if they were found to be a mutation carrier; were unoptimistic; tended to suppress their emotions; were aged less than 40 years; and were familiar with the serious consequences of having a family history of cancer.

In a US prospective cohort study, 327 adult members (106 males and 221 females) from 33 BRCA1/2 hereditary breast and ovarian cancer families were studied to identify individuals who were at risk for adverse psychological effects of genetic testing. Participants had a mean age of 45 (range 18-84 years) and were identified as mutation carriers, non-carriers, or decliners of genetic testing. Cancer-related stress at baseline was strongly predictive of depression in participants who declined testing. Depression rates increased in decliners from 26% at baseline to 47% at 1-month follow-up, whereas depression rates in non-carriers decreased and in carriers showed no change (OR for decliners versus non-carriers=8.0; 95% CI, 1.9-33.5; P=0.0004). These significant differences in depression rates were still evident at the follow-up (P=0.04). The authors conclude that in BRCA1/2-linked families, individuals with high levels of cancer-related stress who decline genetic testing may be at risk for depression.


Intentions and emotional reactions to the process of BRCA1 testing were studied in a US qualitative study. Participants were 181 individuals (46 males and 135 females) with a mean age of 42 years (range 19-84 years) from 14 families with a history of breast/ovarian cancer. Results of genetic testing were made available 1-5 years after blood sampling, with 78 of 181 participants found to be positive for the BRCA1 mutation. Reasons given for seeking testing were concerns about the risk to their children and about surveillance/prevention options. As might be expected, those with positive results had more emotional responses of sadness, anger or guilt, compared to responses of relief in those who had received negative results.

Croyle et al (1997)

60 women (mean age 47, range 19-83 years) from a large family of Northern European descent at high risk of breast and ovarian cancer were studied in this US survey in terms of short-term psychological responses to BRCA1 mutation testing. Testing found that 25/60 women were mutation carriers. At 1-2 week post-test follow-up carriers had significantly higher levels of test-related distress compared to non-carriers (P<0.001). The highest distress levels were observed among carriers with no history of cancer or cancer-related surgery.

Lerman et al (1996)

In a US prospective observational study, 279 adult males and females from families with BRCA-1 linked hereditary breast and/or ovarian cancer were studied with an aim to identify predictors of utilisation of BRCA1 genetic testing and to evaluate outcomes of participating in the testing programme. The mean age of participants was 43 years, all were white, and 67% were female. Results found that, after disclosure of test results, non-carriers of BRCA1 mutations showed a significant reduction in depression compared to carriers (P<0.001) and those who declined testing (P<0.001). Functional impairment was also reduced in non-carriers compared to carriers (P=0.001) and decliners (P=0.004). The authors conclude that for some high-risk individuals who receive test results, there may be psychological benefits.


Data were reported in a UK study of 32 unaffected individuals (17 females, 15 males) from 2 families with a >95% probability of linkage to the BRCA1 cancer gene, in order to investigate the psychosocial impact of genetic testing. Uptake of testing was 41% overall. Fourteen of the 32 participants provided psychological data. This showed that state anxiety levels were not unusually
high (means ranged from 30.3-35.8). There was an indication that an unanticipated unfavourable test result could cause subsequent psychological distress. At 12-month follow-up, none of the sample (including the 3 identified gene mutation carriers) had experienced problems with insurance or employment.

7.4.3 Summary of evidence for psychosocial outcomes relating to genetic testing in women with a family history of breast cancer and/or BRCA1/2 mutations

In terms of evidence for attitudes towards, and uptake of, genetic testing, identified studies generally lack rigorous design. The majority of studies are surveys carried out in the US, and some have small study samples.

Overall results, however, would indicate that expected and actual uptake of genetic testing in healthy men and women with a family history of breast and/or ovarian cancer is fairly high, indicating the acceptability of such programmes. Factors which appeared to positively influence uptake of genetic testing included a family history of breast/ovarian cancer, relief of uncertainty, older age, greater perceived risk, concerns about risks to children, cancer worry and need to learn more about surveillance options. Perceived risks of genetic testing included costs, anxiety about the possibility of a positive result, concerns about health insurance and the availability and demands of genetic testing programmes.

Overall, the evidence for psychosocial outcomes relating to genetic testing, again, lacks rigorous design, comprising mainly of surveys and observational studies, some with small study samples. Findings for these studies indicate that, as would be expected, individuals who are found to be BRCA1/2 mutation carriers on disclosure of test results tend to have higher levels of psychological morbidity compared to non-carriers at post-test follow-ups (Lerman et al, 1996; Croyle et al, 1997; Meiser et al, 2002). There was some evidence that high-risk individuals who decline genetic testing were more vulnerable to an increase in depressive symptoms (Lerman et al, 1996; Lerman et al, 1998). Although most individuals cope well during the waiting period between blood sampling and results in terms of psychological functioning, some women and their partners experience increased anxiety and distress (Lodder et al, 1999; Broadstock et al, 2000). One qualitative study revealed the concerns of women deemed ineligible for genetic testing, in terms of their continued worries about their breast cancer risks despite their ineligibility and their frustration at the lack of information received (Bottorff et al, 2000).

Psychological aspects have been summarised in Appendices 7 and 8.
7.4.6 Cost-effectiveness of genetic testing studies

Grann et al. (1999)

This is a US study that models the cost-effectiveness in terms of additional costs per life year saved of genetic testing of Ashkenazi Jewish women for BRCA1/2 gene mutations. A Markov model was constructed and analysed using Monte Carlo simulation. Costs were reported in 1995 US dollars and discounted at 3% per annum. Four prophylactic strategies were available for women testing positive: mastectomy and/or oophorectomy, or surveillance and cost-effectiveness results presented separately depending on the treatment strategy adopted.

Parameter values were taken from existing literature. No account was taken of costs associated with lost productivity.

Results with 95% confidence intervals derived from Monte Carlo simulation were as follows:

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost per life year gained (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined surgery</td>
<td>$20,717 (9507 – 46998)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>$29,970 (15333 – 65281)</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>$72,780 (23014 – 240275)</td>
</tr>
<tr>
<td>Surveillance</td>
<td>$134,273 (82838 – 267605)</td>
</tr>
</tbody>
</table>

These base case figures were based on a cost of $450 but a sensitivity analysis used a figure of $2,400. This increases the cost per life year gained in excess of $65,000 for each treatment strategy. Furthermore, it must be recognised that no quality adjustment of health gains was made.

Tengs et al. (1998) & Tengs and Berry (2000)

The first of these papers is a decision analysis that calculates the health implications of genetic testing in terms of additional life expectancy and QALYs. It is an outcomes study only, not an economic analysis, but is presented here since the second, cost-effectiveness analyses builds on it. The study attempts to synthesise evidence relating to likelihood of developing cancer with/without BRCA1/2 gene, error rate in genetic test, likelihood of prophylactic surgery, quality of life and length of life.

The alternative prophylactic strategies considered are mastectomy, mastectomy and oophorectomy, oophorectomy and no prophylactic measure.

There was a large range of data sources used which cannot be evaluated without reference to the original studies. Some estimates were made by a panel of cancer experts. Quality of life estimates associated with different states were also assumed.

Results show that, taking quality of life into account, a 30 year old (with the preferences described in the base case) would benefit from allowing a test to inform her decision. This is dependent on the pretest probability of carrying BRCA1/2. For example, at 0.5 the test is useful in helping women decide between oophorectomy vs. mastectomy and oophorectomy and generates an expected QALY gain of 0.45.

A range of sensitivities were explored. The general conclusion from these analyses is that women of “average” risk would not benefit substantially from testing but that women of “moderate to high” risk with no more than moderate concern about the quality of life implications of prophylactic surgery could benefit substantially from testing.

The second paper is a US cost-utility analysis based on a Markov decision model which compares testing vs. no testing. It builds upon the decision analysis presented in Tengs et al (1998) but updates several of the values. Principally, estimates are drawn from existing literature. A societal perspective
The classification and care of women at risk of familial breast cancer

is taken and sources used are a range of recently published evidence, government databases, company websites and a survey of breast cancer experts. Results are reported in 1998 US $’s and a discount rate of 3% applied to both costs and benefits.

Results are presented for different pre-test risks of BRCA1 and BRCA2 mutations. In the base case analysis, testing women with average population risk does not appear cost-effective ($1.6m per QALY). However, the ICER falls rapidly as the risk level rises and is well within conventionally accepted boundaries even for women of only a slightly elevated risk (p= 0.05 BRCA1, 0.05 BRCA2).

Base case results for low risk women $1,600,000 per QALY
- Slightly higher risk $34,000
- Moderate risk $15,000
- High risk $3500 to $4900

The sensitivity analysis revealed that this is sensitive to the penetrance of breast and ovarian cancers (lifetime probability of BRCA1 carriers developing cancer) although in “high risk” women (p=0.5 BRCA1) this does not take results above conventional cost-effectiveness thresholds. Altering the quality of life impact of mastectomy and oophorectomy could change the optimal strategy following a positive test but did not substantially alter the ICERs relating to testing.

Increasing the cost of the test from $2580 to $5000 takes the ICER beyond $50,000 for women at slightly increased risk.

Sevilla et al. (2002)

This study examines the cost-effectiveness of numerous alternative genetic testing techniques. These techniques were direct DNA sequencing (DS), denaturing high performance liquid chromatography (DHPLC), single-strand conformation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), heteroduplex analysis (HA), fluorescent assisted mismatch analysis (FAMA) and the protein truncation test (PTT). A total of twenty strategies were assessed. The motivation for the analysis is that the gene patent owner (Myriad genetics) may wish to restrict testing to the DS method only.

Comparisons are made in terms of cost per mutations diagnosed in a hypothetical population of 10,000 individuals with a 15% chance of harbouring the mutation. This was altered in sensitivity analyses.

Costs are presented in 2002 Euros. Direct costs were based on studies in three French laboratories.

Results indicate that, 15 of the 20 strategies can be eliminated on the basis of dominance, including DS. FAMA → DS F and FAMA → DS 21 detect as many mutations as the DS method and are less costly. Of the approaches which are not dominated, ICERS are as follows;

<table>
<thead>
<tr>
<th>Strategy</th>
<th>ICER (Euros)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT11 + HA21 → DS F</td>
<td>971 euros</td>
</tr>
<tr>
<td>PTT11 + DHPLC21 → DS F</td>
<td>1873 euros</td>
</tr>
<tr>
<td>DHPLC → DS F</td>
<td>9669 euros</td>
</tr>
<tr>
<td>FAMA11 + DHPLC21 → DS F</td>
<td>18140 euros</td>
</tr>
<tr>
<td>FAMA → DS F</td>
<td>163173 euros</td>
</tr>
</tbody>
</table>

Summary: cost-effectiveness of genetic testing studies

It is difficult to draw definitive conclusions from the available data. It does appear however, as might be expected that testing of women at ‘higher’ risk is more cost effective than women at moderate or
average risk. However there is lack of data, including test costs and accurate costs for other interventions.

7.4.7 Genetic testing: patient information issues

Cameron & Diefenbach (2001)

This study assessed the impact of information about the psychosocial consequences of genetic testing for breast cancer susceptibility or interest in and beliefs about genetic testing, and where these effects vary by levels of wider cancer worry or perceived cancer risk. Women were randomly assigned to read one of four messages consisting of standard information along with information about either psychosocial advantages, potential disadvantages, or the advantages and disadvantages or no additional information. One hundred and eighty women, aged 18 to 25 years, took part in the study. Twenty nine percent (n=52) reported one or more relatives who had developed breast cancer. Interest in genetic testing was highest in the group receiving the message containing only standard information. Levels of interest in testing were significantly lower in response to messages that contained information about advantages, disadvantages or both. Messages that included information about test disadvantages led to lower (significantly) beliefs about the positive benefits of testing compared to standard information alone. Elevated levels of cancer worry independently predicted greater interest and higher testing benefits beliefs whereas risk perceptions did not.

Green et al (2001a)

This study compared face to face education and counselling by a genetic counsellor with education by an interactive computer program. The study assessed the impact of each on knowledge of breast cancer genetics and intent to undergo genetic testing. Participants were English speaking women aged 18 years and older with a first-degree relative diagnosed with breast cancer. Seventy two self-referred women were randomised to individualised counselling from a genetic counsellor (counselling group, n=29), education from an interactive computer programme followed by individualised counselling (computer group, n=29) and 14 were controls. Unadjusted mean scores for knowledge were higher in the computer group than the counsellor group (both higher than control group), but when adjusted for demographic differences they became equivalent. Intent to undergo genetic testing was influenced by intervention. Prior to any educational intervention, 69% indicated that they were ‘likely’ to undergo testing if a genetic test were offered to them (that day). Following genetic counselling (counselling and control groups), or computer plus counselling (computer group) only 44% stated that they were ‘likely’ to do so. The reduction in intent to undergo testing was similar between computer, counsellor or control group (not statistically significant).

Green also looked at the preferences of these women for the computer programme or individualised counselling (Green et al 2001b). They reported that most participants preferred individualised counselling, in particular they preferred the counsellors for addressing their own specific concerns, being sensitive to their feelings and helping them to make decisions. Participants were neutral or preferred the computer for its convenience, time efficiency and for the provision of factual information, and they liked that the computer was user-controlled and private.

Schwartz et al (2001)

This study investigated whether a brief educational booklet about BRCA1/2 testing would influence knowledge, attitudes and interest in testing among Ashkenazi Jewish women from the general population. Following baseline interview, participants were randomised to either genetic testing educational print materials (GTE, n=203) or standard breast carcinoma education (BCE, n=203). The paper is concerned with 391 participants who completed both baseline and follow-up telephone interviews. These were Ashkenazi Jewish women aged 18-83 years of age, 21% had a family history
of breast or ovarian cancer in at least one first-degree relative and 7% had a personal history of cancer. GTE materials led to significant increases in knowledge (relative to BCE materials) and perceived importance of the cons of testing. The GTE intervention did not lead to statistically significant decreases (relative to the BCE intervention), of the perceived pros of testing and testing intentions. GTE materials also led to decreased interest in obtaining a BRCA1/2 test. The authors argue that the use of print materials may be useful in providing preliminary education about BRCA1/2 testing for low-risk individuals. By increasing knowledge and decreasing interest it may allow genetic counselling programmes to concentrate on individuals who are at elevated risk and those who may need further counselling among low-risk individuals.

**Lerman et al 1997**

Lerman et al conducted a randomised trial to evaluate the effects education and education and counselling in decision making for BRCA1 testing. They compared an education only intervention (consisting of structured protocols that addressed issues including individual risk factors, patterns of inheritance/susceptibility, benefits of testing, limitations of testing, risks of testing and limitations of options for prevention) with education plus counselling (non directive counselling, about 75-90 minutes, that addressed issues including experience of cancer in the family, psychosocial impact, anticipated impact of test results, outcomes of deciding not to be tested, coping resources and skills, intentions re communicating findings to family members) with waiting list (control) condition. The paper presents the findings from 400 women who provided data at both baseline and one month follow-up period. Participants were either patient referrals, recruited through a living affected first degree with either breast or ovarian cancer, or self referral who were informed about the programme wither by health care professionals or by leaflets in health care facilities.

The educational approach led to significant increase in knowledge and a small but significant decrease in perceived personal risk of having a BRCA1 mutation. Findings also showed that counselling, but not education, was better than control in increasing the perceived importance of the limitations and risks of BRCA1 testing and in decreasing the perceived importance of the benefits of BRCA1 testing. Neither educational or counselling approaches produced statistically significant changes in intention to have BRCA1 testing. The authors discuss several aspects of their findings. They argue that is the primary goal is to increase knowledge and understanding then the education only approach could be deemed as effective as the education plus counselling approach. However if the view that informed decision making also has to include a reasoned evaluation of alternative choices (both benefits and dis-benefits) then this only appeared to have been achieved by the use of the education plus counselling approach.

**Summary: genetic testing - patient information issues**

The papers discussed suggest that the provision of information about the advantages (and in particular) the disadvantages about the genetic testing can improve knowledge which often lead to a reduction in interest in having a genetic test undertaken, or a reduction in uptake if offered. Two papers also appear to present findings that show that face to face counselling/discussion was preferred and may be more useful in allowing informed decision making to take place.
Recommendations

1. Bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team. (D)

2. Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk. (D)

3. Women considering bilateral risk-reducing mastectomy should have genetic counselling in a specialist cancer genetics clinic before a decision is made. (D)

4. Discussion of individual breast cancer risk and its potential reduction by surgery should take place and take into account individual risk factors, including the woman’s current age (especially at extremes of age ranges). (D)

5. Family history should be verified where no mutation has been identified before bilateral risk-reducing mastectomy. (D)

6. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing mastectomy. (D)

7. Pre-operative counselling about psychosocial and sexual consequences of bilateral risk-reducing mastectomy should be undertaken. (D)

8. The possibility of breast cancer being diagnosed histologically following a risk reducing mastectomy should be discussed pre-operatively. (D)

9. All women considering bilateral risk-reducing mastectomy should be able to discuss their breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills. (D)

10. A surgical team with specialist oncoplastic/breast reconstructive skills should carry out risk reducing mastectomy and/or reconstruction. (D)

11. Women considering bilateral risk-reducing mastectomy should be offered access to support groups and/or women who have undergone the procedure. (D)

Evidence statements

1. Risk reducing mastectomy reduces the risk of breast cancer. (III)

2. There are case reports of breast cancer in women who have had sub-cutaneous mastectomy (nipple/areola sparing), and total mastectomy. (IV)
3. Total mastectomy is likely to be more effective than sub-cutaneous mastectomy (nipple/areola sparing) in reducing the incidence of breast cancer. (IV)

4. Risk reducing mastectomy will not prevent the development of all breast cancers. (III)

5. At risk reducing mastectomy some women are found to have cancer. (IV)

6. Various observational studies report a risk reduction for breast cancer of about 90% in populations of those considered as moderate or high risk and BRCA1 or BRCA2 gene carriers. (III)

7. The majority of women undergoing risk reducing mastectomy are happy with their decision. (IV)

8. For many women, cancer worry decreases after risk reducing mastectomy. (IV)

9. A small proportion of women express regret about their decision for bilateral risk reducing mastectomy and would not choose this option again. These women were more likely to have had the option of risk reducing mastectomy raised by a clinician rather than by themselves. (IV)

10. The effectiveness of preoperative counselling has not been formally evaluated. (IV)

7.5.1 Introduction

Bilateral mastectomy may be used as a risk reducing measure in women at increased risk of breast cancer due to their family history. The aim of surgery is to remove the majority of the ‘at risk’ breast tissue with a corresponding reduction in breast cancer risk. This type of major intervention is one that will need considerable discussion and the women concerned may need time to consider this in detail to allow them to reach an informed decision that they are comfortable with.

7.5.2 Research literature evidence

7.5.2.1 Risk reducing mastectomy studies (effectiveness)

Meijers-Heijboer et al (2001)

The incidence of breast cancer after a mean follow-up of 3 years was compared in a Dutch prospective cohort study involving 76 women with BRCA1 or BRCA2 mutations who had undergone bilateral risk reducing mastectomy (total simple, including nipple), and a control group of 63 women with BRCA1 or BRCA2 mutations who underwent surveillance.

No cases of invasive breast cancer were observed in the women who had undergone risk reducing bilateral mastectomy whereas in the surveillance group, 8 invasive breast cancers were detected. Proportional hazards analysis showed that risk reducing mastectomy significantly (P=0.003) reduced the incidence of breast cancer (hazard ratio = 0.95% confidence interval, 0-0.36), although the length of follow-up is short. The authors do not report on postoperative complications.
Hartmann et al (1999)

This retrospective US cohort study studied the incidence of, and risk of death from, breast cancer after a median follow-up of 14 years among 639 women who had a family history of breast cancer and who had undergone bilateral subcutaneous or total risk reducing mastectomy. In the mastectomy group, women were divided into high (n=214) or moderate risk (n=425) subgroups, with most women in each subgroup having undergone subcutaneous mastectomy (89% and 90%, respectively). In the high risk group, the expected number of cases of breast cancer was determined, with 403 sisters of the high risk women used as controls to calculate the expected age-specific breast cancer rate. The Gail model was used to predict the expected incidence of breast cancer in the moderate risk women.

Study results show a reduction in the risk of breast cancer of 89.5% (P<0.001) in moderate risk women who had undergone risk reducing mastectomy, and in the high risk women, a reduction in risk of between 90-94%. All 7 breast cancers in the moderate and high risk groups developed in women who had undergone bilateral subcutaneous mastectomy, although the study was not sufficiently powered to detect a difference between this technique and total mastectomy. Postoperative complications were not reported. The incidence of death from breast cancer was nil in moderate risk women who had undergone risk reducing mastectomy, giving a risk reduction of 100% (95% confidence interval; 70-100). The number of deaths from breast cancer in the high risk women who had undergone risk reducing mastectomy was 2, giving a risk reduction of between 81-94%.

Other identified studies of relevance (extraction tables not provided)

Two US studies and 1 Dutch study were identified which used decision analysis to estimate, respectively: the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 or BRCA2 mutations (Schrag et al (1997); the effect of risk reducing oophorectomy and mastectomy in terms of survival, quality of life and cost-effectiveness in women with BRCA1 and BRCA2 women (Grann et al (1998)); and the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 mutations (van Roosmalen et al (2002). All 3 studies estimate life expectancy gains as a result of both types of risk reducing surgery in BRCA1 and/or BRCA2 women. However, as the findings of these studies are based on modelling techniques, the cohort studies summarised above will take precedence in terms of providing more robust evidence.

Hartmann et al (2001) carried out blood sample analyses on 176 of the 214 high-risk women who participated in their earlier US retrospective cohort study of bilateral risk reducing subtotal and total mastectomy. They analysed blood specimens to identify women with BRCA1 and BRCA2 mutations in order to estimate the carriers’ probabilities of developing breast cancer. Results identified 26 women with alterations in BRCA1 and BRCA2, of whom none had developed breast cancer after a median of 13.4 years of follow-up. The authors conclude that risk reducing mastectomy is associated with a substantial reduction in incidence of subsequent breast cancer not only in women identified as having a high risk based on family history of breast cancer, but also in known BRCA1 and BRCA2 mutation carriers.

Pennisi et al (1989) published a statistical analysis of US registry data for 1500 women at high risk of breast cancer who had undergone risk reducing subcutaneous mastectomy. Their analysis found that of the 1500 women, 6 (0.4%) developed breast cancer, although 30% of women were lost to follow up over a mean period of 9 years. They conclude that risk reducing subcutaneous mastectomy is effective in reducing the incidence of breast cancer in high risk women. However, these results reflect a statistical data analysis only.
7.5.2.2 Risk reducing mastectomy studies (psychosocial outcomes)

**Bebbington Hatcher & Fallowfield (2003)**

This paper presents the results of qualitative interviews with sixty women who opted for bilateral risk reducing mastectomy and twenty who declined. The women had been referred to centres because of a family history. Those who underwent surgery interviewed pre-operatively and then at 6 and 18 months post-operatively. Those who did not undergo the surgery had an initial interview and then another interview 18 months later. Findings from the interviews were discussed in terms of anxiety; surgery; reconstruction; sexual impact; information; gene testing; support. In these categories there were both positive and negative experiences described by those interviewed. In terms of conclusions the authors argued that there was a clear need for information written specifically for this group of women. They also argued that many of the women needed emotional support. The interviews discussed

**Bebbington Hatcher et al (2001)**

The authors compared psychological and sexual morbidity in 2 cohorts of UK women (total number 154) with a family history of breast cancer who either chose or declined bilateral risk reducing mastectomy, with psychosocial questionnaires administered preoperatively and at 6 and 18 months. The authors do not report on surgical status (whether subcutaneous or total mastectomy was carried out), although 81% of women received implants. Results showed that women who underwent risk reducing mastectomy showed a reduction in psychological morbidity from baseline to 6 and 18 months (P<0.001), whereas in women who declined risk reducing surgery, no comparably significant reduction was observed (P=0.11). Similarly, a reduction in anxiety from baseline to 18 months was observed in women who chose risk reducing mastectomy (P=0.001), compared to no significant reduction in anxiety over time in women who declined risk reducing surgery (P=1.00). Findings also showed that risk reducing mastectomy did not have a detrimental impact on body image or sexual functioning, with no differences in the median score of 4.0 (range 0-30) and no change over time (median change 0, 95% CI, 0-1; P=0.84). However, the authors reported differences between the 2 groups in terms of coping strategies and risk perceptions, notably that women who choose surgery have a higher perception of their breast cancer risk. The authors do not measure the effect of presurgical counselling on psychological morbidity.


In this questionnaire survey based on Hartmann et al’s study (Hartmann et al 1999), the authors evaluated satisfaction and psychosocial function in 572 US women with a family history of breast cancer who had undergone bilateral risk reducing mastectomy, with a mean follow-up of 14.5 years. Most women (89%) had undergone subcutaneous mastectomy with reconstruction. Findings showed that 70% of women reported that they were either satisfied or very satisfied with their risk reducing mastectomy; 74% reported a reduction in emotional concern about developing breast cancer; and 67% stated that they would be likely to choose a risk reducing mastectomy again. Levels of satisfaction were not influenced by age, length of time since surgery, whether women were in the high or moderate risk group, or whether surgery had involved a simple or subcutaneous mastectomy. For some women, however, risk reducing mastectomy was associated with adverse psychosocial effects: 36% reported diminished or greatly diminished satisfaction with their body appearance; and adverse effects were reported in terms of emotional stability (9%), stress (14%), self-esteem (18%), sexual relationships (23%) and feelings of femininity (25%). 18% of women said that they would be unlikely to undergo risk reducing mastectomy if they had the choice again. The authors do not report whether women received counselling prior to surgery.

Postoperative mental health and body image concerns were evaluated in 52 UK women with >1:4 lifetime risk of breast cancer who, following multidisciplinary counselling within a strict confidential protocol, had undergone risk-reducing mastectomy with a mean follow-up of 11 months. Most women underwent risk reducing mastectomy and reconstruction using a tissue expansion technique and implants. Data collected from questionnaires and interviews showed that most women experienced only minor changes in body image and low levels of psychological distress, and both appeared stable over time. Mean scores were fairly similar for women who underwent risk reducing mastectomy with reconstruction compared to those who had no reconstruction. The authors note, however, that some women (7 of 45 interviewed) required further psychiatric support; these women were more likely to have had surgical complications.


Satisfaction with bilateral risk reducing mastectomy (simple, including nipple) and immediate breast reconstruction (IBR) was evaluated in 15 Swedish women with an average lifetime risk of breast/ovarian cancer of >20%. All the women received genetic and surgical counselling, but no psychological evaluation or support. Data from semi-structured interviews which mostly took place at least 1 year post-surgery showed that none of the women regretted having risk reducing mastectomy, with the major benefit perceived as risk reduction. Most women thought that the cosmetic results were better than expected. ‘Unexpected’ findings included the emotional consideration of loss of breasts and the need to ‘mourn’; how breasts would be changed by surgery; and the importance of support from, and for, partners and family. The authors conclude that risk reducing mastectomy and IBR are well-accepted interventions with good cosmetic results. However, in this respect multidisciplinary team support, including psychological input, is mandatory for women undergoing risk reducing mastectomy.


Ten UK women with a family history of breast cancer who had undergone risk reducing mastectomy, and their partners, took part in a qualitative research study (semi-structured interviews) between 6 weeks and 3 years post-surgery. Of the 10 women, two were confirmed as gene carriers (BRCA1/BRCA2), with 4 having living 1st-degree female relatives with breast cancer; 9 women had undergone breast reconstruction, although type of surgical technique (subcutaneous or total mastectomy) was not reported. Data analysis revealed past suffering and multiple loss due to the family history of breast cancer as being central to women’s decision making. Their partners’ key experience was one of ‘riding it through’. The authors found that attitudes towards risk reducing mastectomy were largely favourable, probably due to the pre-surgical psychological consultations. They suggest that: discussion/preparation with a multidisciplinary team of health professionals may be a prerequisite; support groups should be available; and that risk reducing mastectomy is best offered by specialist services.


In this questionnaire survey, 370 US women who had undergone bilateral risk reducing mastectomy with a mean follow-up of 15 years were asked to report their satisfaction with their surgery. A family history of breast cancer (defined as at least one 1st-degree relative diagnosed with breast cancer) was reported by 59% of women. 75% of women had undergone reconstructive surgery, although type of surgery (subcutaneous or total) was not reported by the authors. 95% of women reported no regrets with their decision to have risk reducing surgery. Twenty one women (5%), however, reported regrets, 10 of whom had major regrets. Regrets were reported in 7.5% (19/255) women where the risk reducing mastectomy decision was initiated by their physician, compared with 2% (2/108) women where the decision was initiated by themselves (P<0.05). No significant differences were
found in the level of regret between women who had preoperative psychological counselling, or who had a family history of breast cancer, and those who did not. The majority of women (84%) reported cosmetic results of their risk reducing mastectomy, regardless of reconstructive status, as excellent or acceptable, although 16% of women found their cosmetic results to be unacceptable. Three women were diagnosed with breast cancer post-bilateral risk reducing mastectomy (surgical technique not reported). The authors conclude that overall satisfaction with risk reducing mastectomy is high; that the most important factor that predicts an unfavourable outcome following risk reducing mastectomy is a physician-initiated discussion; and that bilateral risk reducing mastectomy does not provide 100% guarantee against development of breast cancer.

**Stefanek et al (1995)**

One objective of this study was to examine satisfaction with bilateral risk reducing mastectomy (surgical technique not specified), with or without breast reconstruction, among 14 US women with at least one 1st-degree relative diagnosed with breast cancer who underwent risk reducing surgery after counselling. Data from a questionnaire which was mailed to women a mean of 9 months post-surgery found that satisfaction with risk reducing mastectomy was very acceptable, with all 14 women reporting being ‘quite a bit’ or ‘very much’ satisfied with the decision to undergo surgery. The majority of women who underwent reconstruction (n=11) also reported similar satisfaction levels, although 3 women who had silicone implants reported cosmetic results as ‘worse than expected’. The authors note, however, that the sample was small; and that women reported strong family and friend support, and had undergone risk counselling pre-surgery, without which the high degree of satisfaction with risk reducing mastectomy may not have been found.

7.5.3 Effectiveness of surgical techniques in risk reducing mastectomy

No evidence has been identified which compares the effectiveness of total versus subcutaneous risk reducing mastectomy in terms of reducing the incidence of breast cancer.

Case reports in the literature show that neither total nor subcutaneous risk reducing mastectomy are 100% effective in preventing breast cancer (Goodnight et al, 1984; Eldar et al, 1984; Ziegler et al, 1991; Willemsen et al, 1998).

In a case series of women with a family history of breast cancer or a BRCA1/BRCA2 mutation who underwent total risk reducing mastectomy (including nipple/areolar complex), there was no evidence of disease after a median follow-up of 2.5 years (range 1-5.9 years) in 79 women with no previous history of breast cancer, ovarian cancer or ductal carcinoma in situ, (Contant et al, 2002).

7.5.4 Summary: risk reducing mastectomy research

The overall findings from 2 observational studies and 3 decision analysis studies suggest that risk reducing subcutaneous/total mastectomy has a beneficial effect in terms of significantly reducing the risk of breast cancer in women with a family history of breast cancer, or with BRCA1 and BRCA2 mutations. One of the observational studies found that risk reducing mastectomy was also associated with a reduction in breast cancer mortality in women with a family history of breast cancer.

Results from 7 studies which evaluated various psychosocial outcomes after risk reducing mastectomy, two of which had lengthy follow-up periods, show that risk reducing mastectomy is associated overall with fairly high levels of satisfaction and reduced anxiety and psychological morbidity amongst women who undergo this procedure. A number of the studies suggest that the provision of pre-surgical multidisciplinary support was likely to have had a bearing on these findings. A minority of women, however, do express regrets and experience adverse psychosocial events following their surgery.
There is no clear evidence on the optimal surgical technique for risk reducing mastectomy.

7.5.5 Cost effectiveness of risk reducing surgery

This section looks primarily at the cost effectiveness of surgery, however it also considers available evidence about Tamoxifen. It should be noted that papers addressing cost effectiveness reflected the uncertainties found in papers addressing clinical effectiveness.

**Grann et al. (1998)**

This US study is a Markov model that compares no prophylaxis (surveillance) vs. mastectomy and/or oophorectomy in BRCA positive women (aged 30 years in the base case) in terms of cost per QALY. Markov states were good health, breast cancer, ovarian cancer and death and the model was run for 50 cycles of one year each. Costs are reported in 1995 US dollars and excluded costs relating to earnings. A discount rate of 3% was applied to costs and benefits.

Data were primarily drawn from existing literature. Expert opinion was used to develop other assumptions required in the model. QALY values for each health state were based on time trade off values elicited from a convenience sample of the general public (n=54).

Combined surgery is more effective than prophylactic mastectomy, which in turn is more effective than oophorectomy, in terms of improvement in survival. Combined surgery extends length of life by 3.3 years in the low risk model (defined as 40% breast cancer risk, 6% ovarian cancer risk by age 70yrs) and by 6 years in the high risk model (85% breast cancer risk, 63% ovarian cancer risk). The combined strategy is the most effective intervention when assessed in terms of QALYs but this is only a positive gain for those groups at high and medium cancer risk. For lower risk groups, the negative impact of any type of prophylactic surgery outweighs the expected health gains from reduced cancer risk.

Base case cost effectiveness results indicate that combination surgery is cost saving compared to surveillance. A series of one-way sensitivity analyses were performed and revealed that the results are particularly sensitive to the effectiveness of surgery in reducing cancer risk and the quality of life adjustments for relevant health states. The latter is particularly important given the small size of the sample used to derive QALY scores.

**Grann et al. (2000a)**

This paper compares chemoprophylaxis with tamoxifen, raloxifene, or oral contraceptives, with prophylactic surgery in terms of cost per QALY. It is a Markov model with Monte Carlo simulation based on a simulated cohort of 30 yr old women who tested positive for the BRCA1/2 genetic mutations.

The paper covers 7 alternative strategies: surveillance, each of the three drug strategies, each of the two surgical procedures (mastectomy and oophorectomy) and the two surgical procedures combined.

The model was run for 50 years with each transition including the probability of breast cancer, ovarian cancer and death.

Where the model required assumptions these were supplied by clinical oncologist opinion.

Incidences of breast cancer and ovarian cancer in each decade of age among BRCA1/2+ women came from Struweing et al. (1997).

Cost data took a US perspective: medicare payments (1998) for surgical procedures. Costs of dying from cancer with cancer from SEER-HCFA (1992-1994) and costs of dying without cancer from other literature. All costs are shown in 1998 dollars. No indirect costs on loss of earnings are included.

QALYs were calculated from a study of preferences, Grann et al. (1999), using TTO methods. These gave preference weightings for chemo prevention, surgery and normal surveillance. Preference weightings for the chemo prevention were applied to all drug prophylaxis strategies. Time in either of the cancer states were rated according to the weighted average of the weightings of nonmetastatic and metastatic disease.

The base case analysis showed Tamoxifen to be a clearly cost-effective option relative to routine surveillance. All other strategies were cost saving relative to routine surveillance, except Mastectomy and oophorectomy at 50 years. Tamoxifen generates ICERs of $898, $1639 and $3249 per QALY gained when prophylaxis begins at age 30, 40 and 50 respectively. Cost per life year gained is higher at $1879, $4511 and $32891 respectively.

The results are particularly sensitive to the incidence of breast cancer amongst carriers of BRCA mutations, the effectiveness of Px.

**Grann et al. (2000b)**

This paper is a US decision analysis of Tamoxifen in a hypothetical cohort of patients similar in risk to those in the Breast Cancer Prevention Trial (BCPT). It is a Markov model run with 500 Monte Carlo simulations. Endpoints used are survival and TTO values to generate QALYs.

The analysis assumes that 70% of those with breast cancer are node-negative and 30% node positive. Survival projections are from the National Cancer Institute. Adverse events that were statistically significant in the BCPT were included (endometrial cancer, pulmonary emboli, cataracts).

Costs were measured in 1998 US dollars and came from Group Health Cooperative charges for treatment of complications, reductions in hip fractures. Patient borne costs were excluded and a discount rate of 3% was used.

TTO values for preferences regarding the use of chemoprevention, invasive breast cancer and metastatic disease were used. Death was assumed to occur 3 years after the onset of metastatic disease. Utilities from a range of existing studies were used to value adverse events.

The results indicate that Tamoxifen is unlikely to be cost-effective at any age ($76318, $130076, and $143293 at starting ages of 35, 50 and 60 respectively.)

These results are extremely sensitive to the length of time an individual is expected to maintain prophylactic benefit after having stopped taking the drug (the base case assumes no benefit after a 5yr period taking drug). If this benefit is extended to 10yrs and 15 yrs then it becomes cost-effective in younger women.

The result is also sensitive to the QALY values used for Tamoxifen prophylaxis and breast cancer, the price of Tamoxifen and the baseline risk of cancer. It should be noted that the cohort in this study were not chosen to reflect women with a familial history. However, it should be noted that 75% had at least twice the population risk.
Hershman et al. (2002)

This paper is very similar to the Grann et al. (2000) study of Tamoxifen. The same author group are responsible for this paper. It reports a hypothetical cohort of high risk women as in BCPT using Markov model of cost-effectiveness with Monte Carlo simulation and many of the parameter values used are equal.

Results are presented for 5 high-risk subgroups (Gail model relative risk > 1.6, atypical hyperplasia, 5yr Gail model risk > 5%, lobular carcinoma-in-situ, ≥ 2 first degree relatives affected) and for three age-groups (35, 50 and 60yrs at start of prophylaxis). The additional cost per QALY in 1998 dollars was as follows:

<table>
<thead>
<tr>
<th></th>
<th>Age 35</th>
<th>Age 50</th>
<th>Age 60</th>
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<tbody>
<tr>
<td>Gail Model RR&gt;1.6</td>
<td>79,320</td>
<td>122,519</td>
<td>137,753</td>
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<tr>
<td>5-year Gail model risk &gt;5%</td>
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<tr>
<td>35</td>
<td>10,818</td>
<td>27,901</td>
<td>54,884</td>
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<tr>
<td>50</td>
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<td></td>
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<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>9,777</td>
<td>26,990</td>
<td>53,765</td>
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<tr>
<td>35</td>
<td></td>
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<td>50</td>
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<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
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<td></td>
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<tr>
<td>35</td>
<td>16,232</td>
<td>37,351</td>
<td>68,334</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
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<tr>
<td>≥2 1st degree relatives affected</td>
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<tr>
<td>35</td>
<td>40,990</td>
<td>80,869</td>
<td>127,750</td>
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<td>50</td>
<td></td>
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As in the previously described study, cost-effectiveness is particularly sensitive to the duration of benefits after stopping prophylaxis.

7.5.6 Comment

There are documented cases of subsequent breast cancer development after both subcutaneous (nipple-areola sparing) and total mastectomy. It is therefore essential to inform any woman considering such surgery that it will not prevent the development of all breast cancers. Some women are found to have breast cancer at the time of surgery and this possibility should also be raised.

Bilateral risk reducing mastectomy is a major undertaking for any woman. Careful patient selection and pre-operative preparation is required. The decision to opt for surgery should be patient and not clinician led. A woman considering risk reducing surgery should be managed by a specialist
multidisciplinary team with clinical genetic, psychological, and oncplastic surgical input. Verification of familial cancer risk is essential prior to surgery. Pre-operative counselling about the psychosocial / sexual consequences should be undertaken. The risks of surgery should be fully discussed including the potential complications of any planned breast reconstructive surgery.
7.6 Risk reducing oophorectomy

Recommendations

1. Risk-reducing bilateral oophorectomy is appropriate only for a small proportion of women who are from high risk families and should be managed by a multidisciplinary team. (D)

2. Information about bilateral oophorectomy as a potential risk-reducing strategy should be made available to women who are classified as high risk. (D)

3. Family history should be verified where no mutation has been identified before bilateral risk-reducing oophorectomy. (D)

4. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing oophorectomy. (D)

5. Any discussion of bilateral oophorectomy as a risk-reducing strategy should take fully into account factors such as anxiety levels on the part of the woman concerned. (D)

6. Healthcare professionals should be aware that women being offered risk-reducing bilateral oophorectomy may not have been aware of their risks of ovarian cancer as well as breast cancer and should be able to discuss this. (D)

7. The effects of early menopause should be discussed with any woman considering risk-reducing bilateral oophorectomy. (D)

8. Options for management of early menopause should be discussed with any woman considering risk-reducing bilateral oophorectomy, including the advantages, disadvantages and risk impact of HRT. (D)

9. Women considering risk-reducing bilateral oophorectomy should have access to support groups and/or women who have undergone the procedure. (D)

10. Women considering risk-reducing bilateral oophorectomy should be informed of possible psychosocial and sexual consequences of the procedure and have the opportunity to discuss these issues. (D)

11. Women not at high risk who raise the possibility of risk-reducing bilateral oophorectomy should be offered appropriate information, and if seriously considering this option should be offered referral to the team that deals with women at high risk. (D)

12. Women undergoing bilateral risk-reducing oophorectomy should have their fallopian tubes removed as well. (D)
Evidence statement

1. Risk reducing oophorectomy before menopause is effective in reducing breast cancer risk. (III)

2. In the general female population, undergoing a risk reducing oophorectomy at or below 40 years of age reduces the risk of breast cancer by between 50-75%. (III)

3. For women with a family history (including BRCA1, BRCA2 carriers) the relative risk reduction (50-75%) is similar but absolute risk reduction will be greater. (III)

4. The use of HRT following oophorectomy may have an impact (negative) on the level of risk reduction, but there is no good evidence. (IV)

5. There is a lack of prospective studies of psychosexual outcomes in women with a family history of breast cancer.

6. Anxiety may be a significant motivating factor for surgery in women seeking risk reducing oophorectomy. (IV)

7. The evidence with respect to the reduction of cancer worry and of increased general psychological distress following surgery is conflicting (from retrospective studies). (IV)

8. Negative impacts of surgery on sexual functioning and menopausal symptoms have been reported in small, qualitative, retrospective studies. (IV)

9. Unmet needs for information about expected menopausal symptoms and safety in using HRT have been reported. (IV)

7.6.1 Introduction

Risk reducing oophorectomy may be considered as a risk reducing strategy in pre-menopausal women at high risk of developing breast cancer. BRCA1 gene carriers may also consider this option to specifically reduce their ovarian cancer risk.

Women considering risk reducing oophorectomy should be fully informed of the risks and potential complications of surgery and in particular the effects of an early menopause. The subsequent use of HRT post-oophorectomy should also be discussed and its effect on the level of risk reduction.

7.6.2 Research literature evidence

Risk reducing oophorectomy studies (effectiveness)

Studies


In a prospective cohort study, the incidence of, and time to, breast cancer or BRCA-related gynaecological cancers after a mean follow-up of 24 months was studied in 98 women who underwent salpingo-oophorectomy at a mean age of 47.5 years and 72 women who underwent
The classification and care of women at risk of familial breast cancer

The incidence of cancers was less in the oophorectomy group (3 breast and 1 peritoneal cancers) than in the surveillance group (8 breast, 4 ovarian, and 1 peritoneal cancers). The estimated proportion free from breast or BRCA-related gynaecological cancer at 5 years was significantly greater in the oophorectomy group than in the surveillance group (P=0.006). Postoperative complications were reported in 4 out of 80 women who underwent risk reducing oophorectomy without hysterectomy.


This retrospective cohort study compared the incidence of coelomic epithelial and breast cancers in two separate groups of women with BRCA1 or BRCA2 mutations who had, or had not, undergone bilateral risk reducing oophorectomy.

In the first sample of women (coelomic epithelial cancer risk), coelomic epithelial cancer developed in 8 of 259 women who had undergone oophorectomy at a mean age of 42.0 years (mean follow-up of 8 years), compared to 58 of 292 controls (mean follow-up of 9 years). Of the 8 cancers in the oophorectomy group, 6 women received a diagnosis of ovarian cancer at the time of surgery. With the exclusion of these 6 women, bilateral risk reducing oophorectomy was associated with a statistically significant reduction in the risk of coelomic epithelial cancer (hazard ratio, 0.04 (95% CI, 0.01-0.16)).

In the second sample of women (breast cancer risk), breast cancer developed in 21 of 99 women who had undergone oophorectomy at a mean age of 40.1 years (mean follow-up of 11 years) compared to 60 of 142 controls (mean follow-up of 12 years). Bilateral risk reducing oophorectomy was found to significantly reduce the risk of breast cancer (hazard ratio, 0.47 (95% CI, 0.29-0.77)). Postoperative complications are not reported in either sample of women.


The occurrence of primary invasive breast cancer was compared retrospectively in 43 women with BRCA1 mutations who underwent bilateral risk reducing oophorectomy at a mean age of 39.4 years (mean follow-up of 10 years), and a control group of 79 women with BRCA1 mutations who did not undergo surgery (mean follow-up of 8 years).

Ten breast cancers developed in the oophorectomy group compared to 30 breast cancers in the control group, indicating that, in women with BRCA1 mutations, bilateral risk reducing oophorectomy was associated with a statistically significant reduction in absolute risk of developing breast cancer (adjusted hazard ratio = 0.53; 95% confidence interval = 0.33-0.84). This risk reduction was even greater in women who were followed up 5-10 years, or at least 10 years, after surgery. Use of HRT did not negate the reduction in breast cancer risk after surgery. Postoperative complications were not reported.

Other identified studies of relevance

Three studies were identified which used decision analysis to estimate: the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 or BRCA2 mutations (Schrag et al (1997); the effect of risk reducing oophorectomy and mastectomy in terms of survival, quality of life and cost-effectiveness in women with BRCA1 and BRCA2 women (Grann et al (1998); and the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 mutations (van Roosmalen et al (2002). All 3 studies estimate life expectancy gains as a result of both types of risk reducing surgery in BRCA1 and/or BRCA2 women. However, as the
findings of these studies are based on modelling techniques, the cohort studies summarised above will take precedence in terms of providing more robust evidence.

Preliminary analysis of a prospective cohort study by Struewing et al (1995) on the incidence of ovarian and breast cancers after risk reducing oophorectomy found a statistically non-significant reduction in both cancers among women who had undergone surgery compared to those who had not. However, data on the subjects and controls are not provided so the baseline comparability of populations can not be determined.

Data from hospital records on 263 women who underwent risk reducing oophorectomy in 41 hospitals in Ontario, Canada, between 1992-1998 were reviewed to determine indications, patterns of practice and complication rates (Elit et al, 2001). Family history of ovarian cancer was the reason for surgery in 127 of these women, with the remaining 136 having a coexisting gynaecological complaint. Sixteen of the women were recorded as having a BRCA1 or BRCA2 mutation. Overall, 36 (13.7%) of these women experienced complications from surgery, including intra-operative problems, reoperation, haematoma, infection and wound problems, and conversion from laparoscopy to laparotomy was required in 17 women during the operation. The frequency of complications by type of surgery were 17% (7/41) for laparoscopic-assisted vaginal hysterectomy, 23% (36/155) for laparotomy and 12% (5/38) for laparoscopy.

7.6.3 Risk reducing oophorectomy studies (psychosocial outcomes)

Studies

Tiller 2002

Tiller et al (2002) reported a small prospective study in 22 women having oophorectomy. Age was a significant predictor of surgery uptake in 95 women who originally expressed an intention to undergo surgery. 86.4% women were highly satisfied: the majority (12:15) of premenopausal women were taking HRT. Those not using replacement therapy consistently reported a negative impact on sexual functioning. There was a significantly greater reduction in cancer anxiety in women electing to have surgery compared to those who did not. The findings suggested that anxiety reduction potentially compensated for other adverse effects, but the small sample limits generalisation.

Elit 2002

Elit et al (2001) reported a negative impact on quality of life following risk reducing oophorectomy in 40 women with a family history of ovarian cancer (Women had all completed surgery since 1992: 53% underwent a preventive intervention alone whilst 47% had other gynaecological reasons. A comprehensive assessment of psychosocial functioning was completed which showed that menopause quality of life scores were reduced (poorer QoL) compared to women of similar age, despite the fact that 65.7% reported current use of HRT. Only 8% reported menopausal symptoms as leading them to feel regret. Satisfaction with sexual functioning was moderately to extremely compromised in 42%-54% of women. Scores on measures of mental health was comparable to the general population. Further interpretation of Elit et al’s results is difficult without data from a control group and the sample was too small to explore possible predictive factors of adjustment, such as age, type of surgery, use of HRT.

Fry 2001

A retrospective comparison study of 29 women who had had surgery and 28 in a screening control group (30) was carried out using self-report measures. Scores for social and emotional functioning were worse in the surgery group, using the Short-form 36 item Health Status questionnaire (SF-36).
Scores for general psychological distress measured with the General Health Questionnaire, were also significantly higher, although there was only a trend to report more menopausal symptoms in the surgical group. It was concerning that there was no apparent benefit in terms of improved cancer worry scores in the women who had oophorectomy, but methodological limitations mean that results must be considered cautiously.

**Meiser 2000**

In a small qualitative study of 6 premenopausal women (and 8 women who had post-menopausal surgery), all bar one had used HRT, which had mitigated most of their menopausal symptoms and the sexual impact. Most women were satisfied with the procedure and emphasised reduced anxiety about cancer. Premenopausal women reported unmet information needs including the effects of surgical menopause and the link between HRT and breast cancer.

7.6.4 **Summary: risk reducing oophorectomy research**

The findings from 3 observational and 3 decision analysis studies suggest that risk reducing oophorectomy has a beneficial effect in terms of significantly reducing the risk of breast and/or various gynaecological cancers in women with BRCA1 and/or BRCA2 mutations. Postoperative complications were reported in a minority of women in one of the observational studies, and in a review of hospital records in Canada, 14% of women who underwent risk reducing oophorectomy experienced adverse effects from the surgery.

In terms of psychosocial outcomes the impact of risk reducing oophorectomy reported in a small number of smallish studies gave inconsistent findings. Findings about issues such as cancer worry and general satisfaction with the procedure were varied in different studies. These tended to depend upon factors such as age, menopausal status and so on.
7.7 Tamoxifen (tertiary care)

Comment

Tamoxifen is not licensed in the UK for use as chemo prophylaxis in women who do not have a diagnosis of breast cancer.

Ongoing trials (including IBIS) will provide further information in this area.

7.7.1 Research literature evidence

7.7.1.1 Meta-analyses, systematic reviews and re-analyses

Note: the meta-analysis by Cuzick et al was not available when this was first considered by the guideline development group. It was considered by the group when it became available. The studies considered by the group prior to the paper by Cuzick et al are presented in the following section. There is overlap between the studies considered by the group and those included in the paper by Cuzick et al.


The effect of tamoxifen or raloxifene on breast cancer prevention was evaluated by combining data from 6 trials. In terms of breast cancer incidence, synthesis of data from tamoxifen prevention trials showed a reduction in incidence of 38% (95% CI, 28-46; P<0.0001). Taking oestrogen receptor (ER) status of breast cancers into account, no reduction in the incidence of ER-negative breast cancers was observed (hazard ratio 1.22 (95% CI, 0.89-1.67; P=0.21)), however, ER-positive breast cancer incidence was significantly reduced by 48% (95% CI, 36-58; P<0.0001). Rates of endometrial cancer were raised in all tamoxifen prevention trials (consensus RR=2.4 (95% CI, 1.5-4.0; P=0.0005)) and in adjuvant trials (hazard ratio 3.4 (95% CI, 1.8-6.4; P=0.0002)), with most of the excess risk observed in women aged 50 years or older. No similar increase was observed in the raloxifene trial. Venous thromboembolic events were also increased across all tamoxifen prevention studies with a RR of 1.9 (95% CI, 1.4-2.6; P<0.0001), and in the raloxifene trial. The authors conclude that tamoxifen can reduce the risk of ER-positive breast cancer, although it is not recommended as prophylaxis except in women at very high risk of breast cancer who are at low risk of side effects.

7.7.1.2 Studies

IBIS investigators (2002)

The IBIS study aims to evaluate the reduction in incidence of, and mortality from, breast cancer associated with taking 20 mg tamoxifen daily for 5 years. Women were enrolled in this multi-centre, randomised controlled trial if they were aged 45-70 years with a 2-fold elevation of breast cancer risk, aged 40-44 with a 4-fold elevation, or aged 35-39 with a 10-fold elevation. Generally, increased risk was determined from family history, previous LCIS or atypical hyperplasia.
First results for 7139 women with a median follow-up of 50 months show an incidence of 170 breast cancers, with a rate 32% lower in women taking tamoxifen than women taking placebo (69 vs 101, respectively; P=0.01). Age and use of HRT did not significantly affect risk reduction. ER-positive breast cancer developed in 44 women on tamoxifen compared to 63 on placebo, and ER-negative breast cancers in 19 on tamoxifen compared to 19 on placebo. There was a 2-fold excess of endometrial cancers in women taking tamoxifen, although this increase was not statistically significant (P=0.2). However, the rate of thromboembolic events was about 2.5 times higher in the intervention group compared to the placebo group (P=0.004); and the death rate from all causes was significantly higher in the intervention group compared to the placebo group (P=0.028). The authors report that tamoxifen can reduce the risk of breast cancer in healthy women by about a third, although it appears to increase thromboembolic events and the all-cause death rate. They conclude that the overall risk to benefit ratio for tamoxifen in prevention is still unclear.

**Veronesi et al (2002)**

In an update of the Italian Tamoxifen Prevention Study (see Veronesi et al (1998)), the authors report the findings relating to 5408 healthy women aged 35 to 70 years who had undergone hysterectomy for reasons other than cancer, who were randomly assigned to receive either tamoxifen (20 mg daily) or placebo with a median follow up of 81.2 months.

Results showed no significant difference in incidence of breast cancer between women receiving tamoxifen compared to placebo (1.3% vs 1.7% respectively; P=0.215). The frequency of breast cancer was significantly higher in controls compared to women taking tamoxifen who had used HRT at baseline or during the trial (P=0.022), and this difference remained significant when analysis was restricted to the women from both groups who were continuous users of HRT (P=0.048). The authors conclude that tamoxifen has no significant protective effect against breast cancer in women at usual or slightly reduced risk, although they suggest that tamoxifen is effective in women using HRT.

**Fisher et al (1998)**

In the Breast Cancer Prevention Trial (BCPT: P1) study, 13388 women were randomly assigned to receive either tamoxifen (20 mg daily) or placebo for at least 5 years. Women were enrolled in the study if they were at increased risk of breast cancer due to age (60 years or older) or were aged 35-59 years with a 5-year predicted risk for breast cancer of at least 1.66% (according to Gail index); or had a history of lobular carcinoma in situ (LCIS).

In total, 368 breast tumours (264 invasive and 104 non-invasive) were detected after a mean follow-up of 48 months. Tamoxifen reduced the relative risk of invasive breast cancer by 49% (P<0.00001) and non-invasive breast cancer by 50% (P<0.002). It reduced the occurrence of oestrogen receptor (ER)-positive tumours by 69%, although no difference was observed in the occurrence of ER-negative tumours. Tamoxifen was also found to be effective in preventing breast cancer in all subgroups, including all age groups, women with a history of LCIS (56% reduction) or atypical hyperplasia (86% reduction) and in those with any category of predicted 5-year risk of breast cancer. Administration of tamoxifen was found, however, to be associated with a significantly increased risk of endometrial cancer, pulmonary embolism and new cataracts.

**Powles et al (1998)**

This study started as a pilot trial in which women were randomly assigned to receive either tamoxifen (20 mg daily) for 8 years or placebo. The study was later extended to include a total of 2471 women. Eligibility criteria were age between 30-70 years, and at least one first degree relative with breast cancer.
After a median follow-up of 70 months, the number of breast cancer events did not differ significantly between women on tamoxifen or placebo (34 and 36 respectively; P=0.8). There were 4 deaths from breast cancer in the tamoxifen group and 1 in the placebo group. Serious adverse events were low with no significant differences between groups, although there were 4 cases of endometrial cancer in the tamoxifen group, compared with 1 in the placebo group. The authors conclude that they were unable to show a beneficial effect of tamoxifen on breast cancer incidence in healthy women with a family history of breast cancer.

**Veronesi et al (1998)**

A total of 5408 healthy women aged 35 to 70 years who had undergone hysterectomy for reasons other than cancer were randomly assigned to receive either tamoxifen (20 mg daily) or placebo for 5 years in the Italian Tamoxifen Prevention Study.

After a median follow-up period of 46 months, no significant differences in breast cancer incidence were detected between treatment groups; 19 in the tamoxifen group and 22 in the placebo group (P=0.64). Breast cancer incidence in women who were also taking HRT was, however, significantly reduced in the tamoxifen group (1 case) compared to the placebo group (8 cases) (P=0.02). There was no difference in the frequency of ER-positive breast cancer between the tamoxifen group (10 cases) and the placebo group (8 cases). Progesterone-receptor-positive cases were more frequent, although not significantly, in breast cancers occurring in the placebo group (10 cases) than in the tamoxifen group (6 cases).

In 1997 recruitment was stopped early due to concerns about high rates of participant dropout, and side effects (in particular, a significantly increased incidence of hypertriglyceridaemia in women in the tamoxifen group). It is also of note that study participants were generally regarded to be at low risk of breast cancer.

**King et al (2001)**

A genomic analysis of BRCA1 and BRCA2 mutations for 288 women who developed breast cancer after entry into the BCPT-P1 (Fisher et al, above) aimed to evaluate the effect of tamoxifen on incidence of breast cancer. Of the 288 women screened for BRCA1 and BRCA2, 19 (6.6%) carried the mutations. Of 8 women with BRCA1 mutations who developed breast cancer, 5 were in the tamoxifen group and 3 were in the placebo group (RR 1.67; 95% CI, 0.32-10.70). Of 11 women with BRCA2 mutations who developed breast cancer, 3 were in the tamoxifen group and 8 in the placebo group (RR 0.38; 95% CI, 0.06-1.56). When data were combined from several series of BRCA1 and BRCA2 breast cancer patients, 83% of BRCA1 breast tumours were ER-negative, whereas 76% of BRCA2 tumours were ER-positive. They conclude that tamoxifen reduced breast cancer incidence among healthy BRCA2 carriers by 62%, but did not reduce breast cancer incidence among healthy women with BRCA1 mutations.


This matched case-control study was carried out to evaluate whether tamoxifen has a protective effect against contralateral breast cancer in 209 women with bilateral breast cancer who were BRCA1 or BRCA2 mutation carriers (cases) and 384 women with unilateral disease who were BRCA1 or BRCA2 mutation carriers (controls). In women who had ever taken tamoxifen, the likelihood of developing cancer in the contralateral breast was significantly reduced (multivariate OR=0.50; 95% CI, 0.28-0.89). Tamoxifen had a protective effect against contralateral breast cancer for both BRCA1 mutation carriers (OR=0.38; 95% CI, 0.19-0.74) and for BRCA2 mutation carriers (OR=0.63; 95% CI, 0.20-1.50). The protective effect of tamoxifen increased with duration of use of up to 4 years (OR for 2-4 years usage was 0.25; 95% CI, 0.07-0.91). A reduction in risk of contralateral cancer was also associated with oophorectomy (OR=0.42; 95% CI, 0.22-0.83) and with
chemotherapy (OR=0.40; 95% CI, 0.26-0.60). The authors conclude that tamoxifen has a protective effect against contralateral breast cancer in women with BRCA1 or BRCA2 gene mutations, and that this protective effect appears to be independent of a woman’s oophorectomy status.

Gail et al (1999)

This study was undertaken in order to develop tools which may identify women for whom the benefits of tamoxifen outweighed the risks. In terms of methods, information was reviewed on invasive and in-situ breast cancer incidence, as well as on other health outcomes, in women who were not taking tamoxifen, as was data on the effects of tamoxifen on these outcomes. Results suggested that the risks and benefits of tamoxifen depended on age and race, as well as on specific risk factors for breast cancer. Specifically, absolute risks from tamoxifen of endometrial cancer, stroke, pulmonary embolism and deep vein thrombosis increased with age, and differed between white and black women. The authors developed tables and aids to describe risk and benefits of tamoxifen and identify classes of women for whom the benefits outweigh the risks. They conclude that tamoxifen is most beneficial for younger women with an increased breast cancer risk.

7.7.2 Tamoxifen studies: (psychosocial outcomes)

Studies

Fallowfield et al (2001)

As an adjunct to the Royal Marsden and IBIS tamoxifen studies, a prospective cohort study was conducted to compare the psychological and sexual functioning in 488 women at high familial risk of breast cancer who were randomised to tamoxifen (20mg daily) or placebo for at least 5 years.

Results showed a marginally significant effect in women taking tamoxifen in terms of improved psychological morbidity (OR 0.72; 95% CI 0.53-1.00); also differences between women receiving the intervention compared to placebo in terms of anxiety scores favoured tamoxifen, although this effect of treatment was not significant when baseline anxiety levels were taken into account (P=0.09). There was no effect of treatment in terms of sexual activity, adjusting for baseline sexual activity and time on study (OR 1.63; 95% CI 0.86-3.08). The authors conclude that long-term use of tamoxifen is not associated with adverse effects relating to women’s psychosocial and sexual functioning, although women on tamoxifen were more likely to report vasomotor symptoms and vaginal discharge.


An initial report of Health-related quality of life in the NSABP trial is presented, comparing tamoxifen with placebo. The report covers the baseline and first 36 months of follow-up data on 11,064 women recruited over the first 24 months. No differences were found for the proportion of women scoring above a clinically significant level on the depression scale, or for the SF-36 (QL) summary physical and mental health scores. Women in the tamoxifen group reported consistently higher number of symptoms associated with vasometer and gynaecologic symptoms. Significant increases were found in the proportion of women on tamoxifen for sexual problems at a definite or serious level. Overall rates of sexual activity remained similar. Therefore women need to be informed of these effects, though weight gain and depression, often anecdotally reported, were not increased on tamoxifen.
7.7.3 Summary of tamoxifen research

Four RCTs which have evaluated the effect of tamoxifen for breast cancer prevention have produced wide variations in findings. Whereas the largest of the studies (Fisher et al 1998) demonstrated a 49% reduction in invasive breast cancer, the two smaller studies (Powles et al 1998; Veronesi et al 2002, 1998) detected no difference in breast cancer incidence between the tamoxifen and placebo groups. Results of the most recent RCT (IBIS investigators 2002) indicate that tamoxifen reduced breast cancer incidence by 32%, compared to placebo. The 2 larger RCTs (Fisher et al 1998; IBIS investigators 2002), however, both found an increase in endometrial cancers and thromboembolic events in women taking tamoxifen. These overall differences in findings between studies may be due to variations in study population, length of follow-up and statistical power.

A recent meta-analysis synthesised data from 6 studies which assessed the effect of tamoxifen or raloxifene for breast cancer prevention (Cuzick et al 2003). Overall results showed that tamoxifen reduced breast cancer incidence by 38%; ER-positive breast cancer incidence was reduced by 48%, although no reduction in incidence of ER-negative tumours was observed. Preventative tamoxifen, however, significantly increased rates of endometrial cancer and venous thromboembolic events.

One cohort study (Fallowfield et al 2001) found that long-term use of tamoxifen had no adverse effects on psychosocial and sexual functioning, although women on tamoxifen were more likely to report vasomotor symptoms and vaginal discharge.

Risks and benefits of tamoxifen were assessed in one study (Gail et al 1999) and it was suggested that tamoxifen was most beneficial in younger women with an increased breast cancer risk.

Two studies focused on the use of tamoxifen in women who were BRCA1 or BRCA2 mutation carriers. One of the studies (Narod et al 2000) found that tamoxifen had a protective effect against contralateral breast cancer in women with BRCA1 and BRCA2 gene mutations, independent of oophorectomy status. The second study found that tamoxifen reduced breast cancer incidence by 62% in healthy BRCA2 mutation carriers, but not in healthy BRCA1 mutation carriers.
8. Risk factors
8.1 Risk factors

Recommendations

1. Women should be provided with standardised written information about risk, including age as a risk factor. (D)

2. Modifiable risk factors should be discussed on an individual basis with each woman in the relevant care setting. (D)

Comment

Most cancers do not have a single cause, they result from the interaction of multiple factors that range from genetic characteristics to personal lifestyle. The term risk factor refers to anything that is associated with an increased chance of developing a particular type of cancer. Risk factors are a matter of probability. They influence an individual’s odds of developing a disease. That is not the same thing as actually causing a disease to occur. Some people with one or more risk factors for a particular type of cancer never develop it, while other people who have no known risk factors do develop that type of cancer. Most breast cancer cases fall into the second category, because they are not predicted by known risk factors. Nevertheless, identification of risk factors for cancer can be useful for risk modification or to identify individuals who may benefit more from cancer screening. Traditionally, scientists divided the factors that influence an individual’s odds of developing a disease into two groups: modifiable risk factors and non-modifiable risk factors (also called predisposing factors or predispositions). Modifiable risk factors are aspects of an individual’s lifestyle that affect the risk of a disease that can be altered, such as diet or smoking. Health education efforts have usually focused on modifiable risk factors because they can be altered or eliminated. Non-modifiable risk factors (or predisposing factors) are inherent. Conditions, such as age, or aspects of an individual’s genetic program such as sex or specific gene mutations that increase that person’s likelihood of developing a disease. For women as a whole, incidence of breast cancer increases with age. The rate of increase slows after menopause. The risk of breast cancer is higher in middle-aged and elderly women than in young women. Those living in Western countries have a higher relative risk of breast cancer. Other possible risk factors are considered in more detail in this section.

8.2 Risk associated with family history

The risk of breast cancer in women with an affected first degree relative (mother, sister or daughter) is approximately twice the risk to other women. The risk of breast cancer is related to the strength of the family history. The risk increases with the number of affected relatives, and increases as the age of affected relative(s) decrease. Only a minority of this increase in risk is due to the known high risk genes BRCA1 or BRCA2. The chance of carrying a BRCA1 or BRCA2 mutation is related to the strength of the family history not only of breast cancer but also of ovarian cancer and male breast cancer. The risks of breast cancer in carriers of BRCA1 or BRCA2 mutations have been estimated as between 60 and 80% and between 40 and 80% respectively.
• The risk of breast cancer in women with an affected first degree relative (mother, sister or daughter) is approximately twice the risk to other women.

• The risk of breast cancer is related to the strength of the family history. The risk increases with the number of affected relatives, and increases as the age of the affected relative(s) decrease.

• Only a minority of this increase risk is due to the known high risk genes BRCA1 and BRCA2.

• The chance of carrying a BRCA1 or BRCA2 mutation is related to the strength of the family history not only of breast cancer but also of ovarian cancer and male breast cancer.

• The risks of breast cancer in carriers of BRCA1 or BRCA2 mutations have been estimated as between 60 and 80% and between 40 and 80% respectively.

8.3 Note re research literature

We did not set out to present the literature that looked at risk factors for breast cancer for all women (population level). Rather the intention was to see if there was literature that looked specifically at risks for women with a family history, to see if the risks for this group of women were similar or different to the population as a whole.

There was variability in the reporting approach found in many studies. Whilst some reported on the findings in relation to women with a family history others did not.

We started with meta-analysis – although in most instances it was meta-analyses of case control or cohort studies rather than RCTs (because of the nature of the questions being addressed).

8.4 Note re modifiable risk factors

Some risk factors cannot be changed, e.g. age or sex. Some others are often difficult to change as actions or behaviours have already taken place that affect risk, such as the age at which a woman has children. Other risk factors are more amenable to influence and change such as diet and exercise behaviour. Different types of risk factors are discussed to allow an overall profile to be developed for individual women.
8.5 Hormone replacement therapy

Recommendations

1. Women with a family history of breast cancer who are considering taking, or already taking, HRT should be informed of the increase in breast cancer risk with type and duration of HRT. (C)

2. Advice to individual women should vary according to the individual clinical circumstances (such as asymptomatic, age, severity of menopausal symptoms, or osteoporosis). (D)

3. HRT usage in a woman at familial risk should be restricted to as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible. (D)

4. A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk. (D)

5. Alternatives to HRT should be considered for specific symptoms such as osteoporosis or menopausal symptoms. (D)

6. Consideration should be given to the type of HRT if it is being considered for use in conjunction with risk-reducing gynaecological surgery. (D)

Evidence statement

1. The totality of the evidence suggests that HRT is associated with an increase in breast cancer risk. (III)

2. The risk associated with HRT is small for short duration use (up to 2 years) but is in the region of a two fold risk for women taking combined HRT for 10 years or more. (III)

3. The benefits of early menopause on the relative risk of breast cancer are unlikely to be completely removed by taking HRT until about 50 years of age. (IV)

4. The Million Women Study found that the relative risk of breast cancer in current users increased with increasing total duration of use of HRT. (III)

5. The Collaborative Group found that risk appears to be confined to current users and women who have used HRT in the last 5 years. (III)

6. The Million Women Study suggests that there is little or no overall increase in the relative risk of breast cancer in past users of HRT. (III)

7. The Collaborative Group found that risk of HRT use disappears 5 years after stopping. (III)

8. The Collaborative Group has shown that there is 2.3% increase in relative risk for every year used. (III)
9. In women with a positive family history, the relative risk is consistent with findings in the general population. (III)

10. The Million Women Study found that the associated risk was substantially greater for oestrogen-progestagen than for other types of HRT. (III)

8.5.1 Research literature evidence

8.5.1.1 HRT: meta-analyses, systematic reviews and re-analyses

Bush et al (2001)

A systematic review was conducted to assess whether there was evidence to support an association between use of ERT or HRT and risk of breast cancer (note: included studies do not appear to have undergone systematic quality assessment). Forty-five studies were identified which assessed the association between ERT and breast cancer risk; 20 which assessed the association between HRT and breast cancer risk; 5 which assessed the risk of HRT and death from breast cancer; and 6 which assessed the risk of HRT and breast cancer survival (overall total of 55 studies). Data on risk estimates for breast cancer in ever-users of ERT and HRT compared to never-users showed an overall lack of consistency and only modest increases or decreases in risk of breast cancer. A similar lack of consistency was shown in findings from studies which evaluated breast cancer risk by duration of hormone use. However, in studies which assessed the risk of HRT and death from breast cancer, there was consistently a lower risk of death from breast cancer in hormone users compared to non-users. The authors conclude that the evidence does not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more estrogen only.

Collaborative Group on Hormonal Factors in Breast Cancer (1997)

Epidemiological data from 51 studies in 21 countries was combined to evaluate the relationship between breast cancer risk and use of hormone replacement therapy (HRT), involving data on 52,705 women with breast cancer and 108,411 women without breast cancer (note: included studies do not appear to have undergone systematic quality assessment). Main analyses were based on 53,865 postmenopausal women of whom 17,830 (33%) had used HRT at some time. The main findings were that for current/recent users of HRT the relative risk of breast cancer increased by a factor of 1.023 (95% CI; 1.011-1.036; 2p=0.0002) for each year of use; the relative risk for women who had used HRT for 5 years or more was 1.35 (95% CI, 1.21-1.49; 2p=0.00001). However, for past users (5 or more years after cessation of HRT use) there was no significant increase in relative risk, either overall or in relation to duration of use. Of the factors examined which may have affected these results (including family history of breast cancer), only weight and body-mass index had a significant effect among current/recent users who had a duration of HRT usage of 5 years or more. The authors conclude that breast cancer risk is increased in women using HRT and increases with longer duration of use; however, this increased risk is reduced after HRT use ceases and has largely disappeared after about 5 years.

Colditz et al (1993)

Data from 31 published reports (25 case-control and 6 follow-up studies; references not provided) of the effect of oestrogen use on breast cancer risk was combined in a meta-analysis (note: included studies do not appear to have undergone systematic quality assessment). Overall, results indicated that ever-use of hormone replacement therapy is not associated with an increased risk of breast cancer (RR 1.02; 95% CI, 0.93-1.12); however, current use was found to be associated with increased...
risk (RR 1.40; 95% CI, 1.20-1.63). No significant trend was observed between years of oestrogen therapy and risk of breast cancer when data from 17 of the studies was combined, although women with 10 or more years of oestrogen usage had a relative risk of 1.23 (95% CI, 1.08-1.40). Data combined from 4 studies indicated that ever-use of oestrogen therapy plus progestin was not associated with a reduced risk with an overall relative risk of 1.13 (95% CI, 0.78-1.64). There was no evidence to support a differential effect of oestrogen therapy among women with a family history of breast cancer compared to those without, nor among women with a prior history of benign breast disease. The authors conclude that although their results excluded a large effect of oestrogen therapy on breast cancer risk, they were unable to rule out some risk associated with current or long-term use.

Sillero-Arenas et al (1992)

The effect of HRT after menopause on breast cancer risk was evaluated in a meta-analysis of 37 studies (23 case-control, 13 cohort and one clinical trial). Results found that overall, ever-use of HRT had a small but statistically significant effect on risk of breast cancer (RR 1.06; 95% CI, 1.00-1.12). Those women who had experienced a natural menopause seemed to be at increased risk (RR 1.13; 95% CI, 1.04-1.22). A significant weighted relative risk was observed in current HRT users (RR 1.23; 95% CI, 1.12-1.35), especially in those who had a natural menopause (RR 1.63; 95% CI 1.26-2.10). The authors conclude that HRT may increase the risk of breast cancer, especially in women with natural menopause.

Steinberg et al (1991)

In this meta-analysis, 16 case-control studies were identified which evaluated the effect of oestrogen replacement therapy (ERT) on the risk of breast cancer. Study findings were combined to quantify the proportional increase in breast cancer risk for each year of ERT use. Risk of breast cancer did not appear to increase for women who experienced any type of menopause until at least 5 years of oestrogen use, with a significant mean proportional increase in risk of 0.015 (95% CI, 0.004-0.021) per year of use. Findings showed a 30% increase in the risk of breast cancer after 15 years of oestrogen use (relative risk (RR) 1.3; 95% confidence interval (CI), 1.2-1.6). This increase was largely due to results of studies that included premenopausal women or women using estradiol (with or without progestin). Findings from 5 of the studies, 2 of which included premenopausal women, showed that in women with a family history of breast cancer, those who had ever used ERT had a significantly higher breast cancer risk (RR 3.4; 95% CI, 2.0-6.0) than those who did not (RR 1.5; 95% CI, 1.2-1.7).


This study was conducted to evaluate the relationship between ERT and breast cancer; 28 studies were identified (18 case-control, 10 cohort studies) from the literature. The overall relative risk of breast cancer associated with ERT from all studies was 1.07; however, the authors note that relative risks varied widely from this overall estimate and were significantly different from each other (P<0.00005). The authors examined the effects of type, duration and dosage of treatment and make the following conclusions. There is some evidence to suggest that breast cancer risk may increase slightly with duration of treatment, and some studies suggest that a daily dosage of 1.25mg or more of conjugated estrogens may also increase breast cancer risk (RR of 2.0 or less in all studies). There is consistent evidence from multiple studies that a daily dosage of 0.625 mg or less of conjugated estrogens for several years does not appreciably increase the risk of breast cancer (RR 1.08; 95% CI, 0.96-1.2). ERT consisting of 0.625 mg/d of conjugated estrogens is not contraindicated because of breast cancer risk in women with a history of benign breast disease.
Million Women Study (2003)

The Million Women Study was a prospective cohort study. It was set up to investigate the relationships between various patterns of use of HRT and breast cancer incidence and mortality. It recruited 1,084,110 women through 66 centres who provide screening through the NHS Breast Screening Programme, in the period May 1996-March 2001. Data collection was via questionnaires issued to women with their invitation to screening letter. Main analyses were presented for postmenopausal women, with a defined time since menopause (828,923 women). The findings showed that HRT causes a duration-dependent increase in the risk of breast cancer. The associated increased risk in breast cancer begins to decline when HRT use is stopped and by 5 years since cessation, the relative risk reaches the same level as women who have never taken HRT. The relative risk of breast cancer incidence for ever users of HRT compared with never users was 1.43 (1.36-1.50, p<0.0001). Amongst those who had ever used HRT, those who were current users had a relative risk of breast cancer incidence of 1.66 (1.58-1.75, p<0.0001) and past users had a relative risk of 1.01 (0.94-1.09, p<0.0001). (Further details including relative risks associated with different durations of HRT use can be found in Appendix 13).

Ursin et al (2002)

This US case-control study was conducted to determine whether any particular subgroup of women is at particularly high risk of breast cancer if they use postmenopausal combined oestrogen and progestin replacement therapy (EPRT). (The study also aimed to determine whether tumour characteristics in women who develop cancer while using ERT or EPRT are different from those in women not using these therapies.) Data were presented for 1,897 postmenopausal women and 1,637 controls with an age range of 55-72 years, who had not undergone simple hysterectomy. No association between EPRT use and women with a family history of breast cancer was found (first degree relative vs none; P=0.57). No association was also found between EPRT use and other subgroups of women in terms of body mass index, alcohol intake, parity, and history of benign breast disease. The authors conclude that they found no evidence to suggest that particular subgroups of women, including women with a family history of breast cancer, are at higher risk of developing breast cancer if they use EPRT.

Sellers et al (1997)

A study using questionnaire and registry data was conducted to determine whether HRT was associated with increased risks for breast cancer and total mortality in women with a family history of breast cancer. Data were obtained from a random sample of 41,837 postmenopausal US women (age range 55-69 years) who enrolled in an observational study of risk factors for cancer with a follow-up period of 8 years. A family history of breast cancer was reported by 12.2% of the cohort of women at risk. Frequency of reported use of HRT did not differ by family history, with 38.3% of women without a family history and 37.7% with a family history (P>0.2); also duration of use was similar (P>0.2). Among women with a family history of breast cancer, those who were current users of HRT (for at least 5 years’ duration) developed breast cancer at an age-adjusted annual rate of 61 cases per 10,000 person-years (95% CI, 28-94 cases). This rate was not statistically significantly higher than the rate in women who had never used HRT (46 cases per 10,000 person years (CI, 36-55 cases)). Among women with a family history, those who used HRT had a significantly lower risk for total mortality compared to women who had never used HRT (RR 0.67; CI, 0.51-0.89). The authors conclude that in women with a family history of breast cancer, HRT use is not associated with a significantly increased breast cancer incidence but is associated with a significantly reduced total mortality rate.
8.5.2 HRT and effect on breast cancer risk in women with a family history of breast cancer

The Million Women Study looked at the relative risks of incident invasive breast cancer in relation to recency and type of HRT use and examined them separately by age, family history of breast cancer, BMI and ever use of oral contraceptives. The only factor that seemed to modify the relative risk estimates materially was BMI (with relative risks being larger among thinner women, i.e. those who had a BMI ≤ 25 kg/m²).

Two other studies were identified which assessed the role of HRT in breast cancer risk in women with a family history of breast cancer. These studies were reported as being included in the Collaborative Group Reanalysis (1997) (see above).

8.5.3 Oestrogen and oestrogen-progesterone replacement therapy

**Million Women Study (2003)**

The Million Women Study presented findings that showed that different HRT regimens were associated with different relative risks of breast cancer incidence. Preparations used by current users of HRT were as follows: 41% were taking preparations containing oestrogen only, 50% were taking combinations of oestrogen-progestagen, 6% reported taking tibolone, 1% said they were using other preparations and unknown in 2% of participants. As well as increased relative risks for all current use for oestrogen only, tibolone and combination preparations, the relative risks were significantly different between the different types. They found that the relative risk associated with oestrogen-progestagen combinations was substantially higher (RR=2.00, 1.88-2.12, p<0.0001) than found with oestrogen only preparations (RR=1.30, 1.21-1.40, p<0.0001) and tibolone (RR=1.45, 1.25-1.68, p<0.0001).


This recent study was a follow-up of participants in the Breast Cancer Demonstration Project, using data from 1980-1995. It was population based not confined to those with a family history. After exclusions, 46,355 subjects were available for analysis. It was confined to women who were menopausal before the start of follow-up period or who became menopausal during the course of the study (those who did not have a menstrual period for at least 3 months due to natural menopause or bilateral oophorectomy). The mean duration of follow-up was 10.2 years with a median of 12.3 years with a maximum follow up of 16 years and minimum of less than 1 year. The average age at start of follow-up was 58 years. Relative risks were given, after adjustment for attained age, age at menopause, education, BMI and mammographic surveillance. Adjustment for race, period of follow-up, age at first live birth, family history of breast cancer, history of benign breast disease and clinical breast examination did not alter estimates.

They report increases in risk associated with use of oestrogen only and oestrogen-progesterone. These increases were largely restricted to recent use (defined as current use and past use occurring within previous 4 years). The relative risks were 1.2 (95% CI, 1.0-1.4) for oestrogen only and 1.4 (95% CI, 1.1-1.8) for oestrogen-progesterone. The relative risk of breast cancer increased by 0.01 (95% CI, 0.002-0.03) for each year of oestrogen only use (P=0.01 for trend) and 0.08 (01 (95% CI, 0.02-0.16) for oestrogen-progesterone only use (P=0.01 for trend).

Associations with duration of oestrogen only use among recent users varied according to BMI (P=0.002 for score test), with increases in risk evident only in women with a BMI of 24.4 kg/m² or less. In this group, the relative risks increased by 0.03 (95% CI, 0.01-0.06) for each year of oestrogen only use.
They concluded that their results suggest that the combined oestrogen-progesterone regimen is associated with greater increases in breast cancer risk than oestrogen alone. Oestrogen alone was associated with increased risk in lean but not heavy (24.4 kg/m²) women.

8.5.4 Summary of HRT and breast cancer risk evidence

The above evidence regarding the use of HRT and its impact on breast cancer risk is of varying quality, relating to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in Appendix 13. The 4 meta-analyses (Dupont et al 1991; Steinberg et al 1991; Sillero-Arenas et al 1992; Colditz et al 1993) combine evidence from approximately the same time periods and databases, with some form of quality assessment of included studies undertaken in 3 of the syntheses. The re-analysis (Collaborative Group 1997) includes more recent studies, although quality assessment of included studies does not appear to have been systematically undertaken. Included studies in the qualitative review (Bush et al 2001), which has the most comprehensive coverage of all the syntheses, have also not undergone quality assessment.

The Million Women Study presented results from over a million women in the UK, of whom 50% were ever users of HRT. The main analyses were concerned with bearing in mind these differences between studies, some trends, however, have been identified from the main findings of these meta-analyses/reviews.

8.5.4.1 Ever-use of HRT

Ever-use of HRT in postmenopausal women was associated with a statistically significant increase in relative risk of breast cancer of 1.43 in the Million Women Study and 1.06 and 1.14 in two of the other studies (Sillero-Arenas et al 1992; Collaborative Group 1997, respectively). However, in a third study (Colditz et al 1993), ever-use of HRT in postmenopausal women was not associated with an increase in breast cancer risk.

8.5.4.2 Duration of HRT use

The Million Women Study found that for current users of each type of HRT, breast cancer increased with total duration of use. Three studies found that breast cancer risk in postmenopausal women increased in relation to increasing duration of HRT use, by 30% after 15 years (Steinberg et al 1991), 63% after 12 years (Sillero-Arenas et al 1992) and 35% after 5 or more years (Collaborative Group 1997). A further study (Colditz et al 1993) found that breast cancer risk increased by 20% after more than 10 years of HRT use, and by 30% after more than 15 years of use, although some studies included premenopausal women. The 2 remaining identified studies (Dupont et al 1991; Bush et al 2001) both found inconsistencies in study results and were thus unable to confirm an association between duration of HRT use and breast cancer risk.

8.5.4.3 Cessation of HRT use

The Million Women Study found that the increased risk of breast cancer associated with HRT use begins to decline when HRT is stopped and reaches the same level as women who have never taken HRT after about 5 years. One study (Collaborative Group 1997) found that the increased risk of breast cancer associated with HRT use reduces after HRT is stopped and has disappeared after about 5 years’ cessation of use.
8.5.4.4 HRT use and breast cancer mortality

The Million Women Study found that the relative risk of death from breast cancer was raised in women who were current users of HRT (RR=1.22), but not in past users (RR=1.05) compared with never users of HRT. One study (Bush et al 2001) found a significant association between HRT use and a reduction in death from breast cancer, with risk estimates of less than 1.0.

8.5.4.5 HRT use in women with a family history of breast cancer

The Million Women Study examined some of their results in a way to see what if any impact some factors, including family history, had. Family history did not have an impact on the relative risks examined (only BMI had a modifying impact on the relative risks examined). Other identified studies which assessed breast cancer risk of HRT use in relation to women with a family history of breast cancer (Steinberg et al 1991; Colditz et al 1993; Collaborative Group 1997), findings were inconsistent. In one study (Collaborative Group 1997), patterns of increased breast cancer risk associated with ever-use, current/recent use and long-term use of HRT were found for women with a family history of breast cancer which matched the study’s findings for postmenopausal women in general; and in a second study (Steinberg et al 1991), ever-use of ERT was associated with increased breast cancer risk in all women with a family history of breast cancer compared to women with no history (RR=3.4 compared to RR=1.5). However, in the third study (Colditz et al 1993), no significant association was found between breast cancer risk and HRT use in women with a family history of breast cancer.

8.5.5 Comment

Factors that influence the amount of estrogen produced by a woman’s body over her lifetime (such as the ages at the onset of menstruation and at menopause) are known to influence breast cancer risk. Possible effects on breast cancer risk are only one of the many factors that need to be considered by a woman and her physician when making decisions about ERT/HRT.
8.6 Hormonal contraceptives

Recommendation

1. Advice to women up to age 35 years with a family history of breast cancer should be in keeping with general health advice on the use of the oral contraceptive pill. (C)

2. Women aged over 35 years with a family history of breast cancer should be informed of an increased risk of breast cancer associated with taking the oral contraceptive pill, given that their absolute risk increases with age. (C)

3. For women with BRCA1 mutations, the conflicting effects of a potential increased risk of breast cancer under the age of 40 years and the lifetime protection against ovarian cancer risk from taking the oral contraceptive pill should be discussed. (C)

4. Women should not be prescribed the oral contraceptive pill purely for prevention of cancer, although in some situations reduction in ovarian cancer risk may outweigh any increase in risk of breast cancer. (D)

5. If a woman has a BRCA1 mutation and is considering a risk-reducing oophorectomy before the age of 40 years, the oral contraceptive pill should not be prescribed purely for the reduction in ovarian cancer risk. (D)

Evidence statements

1. Use of oral contraceptives slightly increases the risk of breast cancer. (III)

2. This increase in risk appears to be confined to current and recent use (within 5-10 years, relative risk 1.24 for current users). (III)

3. In women with a positive family history, the relative risk is consistent with findings in the general population. (III)

4. One study has shown an increased risk for BRCA1 mutation carriers (odds ratio 1.20, relative risk under 40 = 1.40). (III)

5. There is no evidence regarding the progesterone only contraceptives and risk associated with family history.

8.6.1 Research literature evidence

Five meta-analyses, one collaborative re-analysis and 3 recent case-control studies which evaluate the impact of oral contraceptive (OC) use on breast cancer risk have been identified from the literature.
8.6.1.1 Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (1996)

This re-analysis combined the findings of 54 published and unpublished case-control and cohort studies, reported to represent about 90% of the epidemiological evidence on breast cancer risk and OC use (included studies did not undergo quality assessment). The relative risk of breast cancer in women who had ever used OCs compared to women who had never used them was statistically significant (RR=1.07 (SD 0.02), 2p=0.00005). In terms of duration of OC use, there was a weak indication of a trend of increasing risk with increasing duration (P=0.05). For each age group at 1st OC use between less than 20 years to 35 years and over, relative risks were slightly greater than 1.0, with the largest increase in women who started use as teenagers. Similarly, relative risks were slightly above 1.0 in each 5-year period of time since 1st OC use, with a trend of decreasing risk with increasing time since 1st use (P=0.002). There was also evidence of an increased risk of breast cancer being diagnosed in current users (RR=1.24 (SD 0.04), 2p<0.00001), in recent users (RR=1.16 (SD 0.04), 2p=0.00001), and 5-9 years after stopping use (RR=1.07 (SD 0.03), 2p=0.009). For women who stopped use 10 or more years previously, the relative risk of breast cancer did not differ significantly from 1.0, and there was a strong trend of decreasing risk with time since last use (P=0.00001). There was no significant difference in the association between time since last use of OCs and breast cancer risk between women with and without a family history of breast cancer. The authors conclude that there is a small increase in breast cancer risk in women using OCs and in the 10 years after they stop, although this increased risk does not persist beyond 10 or more years.

Schlesselman (1995)

Seventy-nine epidemiological studies published between 1980 and 1994 were combined in this meta-analysis to evaluate the net effect of duration of OC use and risk of breast, cervical, endometrial, ovarian and liver cancer (included studies did not undergo quality assessment). Pooled findings for 25 studies relating to breast cancer risk and OC use in older women (>45 years to <60 years) suggest a non-significant trend (P=0.35) of slightly increasing risk with increasing duration of OC use, with relative risks of 1.062, 1.068 and 1.072 for 4, 8 and 12 years of OC use, respectively. These findings indicate no adverse effect of OC use on breast cancer risk in this age group of women.

Hawley et al (1993)

A synthesis of the findings of 38 case-control studies carried out between 1966-1990 was performed, with individual studies assigned a quality rating score. Analyses found no statistically significant association between breast cancer risk and ever-use of OCs for all studies pooled (RR=1.08; 95% CI, 0.55-1.61), nor when ‘higher quality’ studies were combined (RR=1.07; 95% CI, 0.78-1.36). Long-term duration (up to 14 years) of OC use also did not increase breast cancer risk (P=0.386 for all studies combined, and 0.189 for ‘higher quality’ studies combined). A significant association was observed, however, between risk and OC use before 1st full-term pregnancy (P<0.001 for all studies combined, and 0.011 for ‘higher quality’ studies combined). The data suggest that there is no increased breast cancer risk in women who have ever used OCs, or who have used them for long durations, although OC use before a 1st full-term pregnancy appears to increase a woman’s risk. The authors state, however, that the findings may be confounded by inclusion of lower quality studies in the synthesis.

Rushton et al (1992)

This meta-analysis combined the findings of 21 case-control and 6 cohort studies published between 1980 and 1989 (included studies did not undergo quality assessment). Breast cancer risk increased significantly by 16% in women aged less than 45 years (RR=1.16; 95% CI, 1.07-1.25), although not...
in women aged 45 years or more. Risk was greatest in women in the 30-34 years age group (RR=1.25; 95% CI, 1.04-1.50). No significant association was observed between OC use and breast cancer risk in parous women, although risk almost reached significance in nulliparous women (RR=1.21; 95% CI, 0.99-1.47). Findings also suggested a steady increase in breast cancer risk with duration of OC use, with a RR of 1.04 (95% CI, 0.94-1.16) for durations of less than 2 years to 1.27 (95% CI, 1.12-1.44) for more than 8 years of OC use. The authors conclude that risk of breast cancer from OC use may be increased by about 20% in younger, nulliparous women and in long-use duration subgroups. They note, however, that there was substantial heterogeneity between study findings.


A synthesis of 26 case-control and 6 cohort studies published between 1966 and 1990 was carried out in this meta-analysis. Ever-use of OCs was significantly associated with breast cancer risk in case-control studies (RR=1.07; 95% CI, 1.03-1.12), but not in cohort studies. An increased risk with ever-use was also observed in premenopausal women when all studies were pooled (RR=1.14; 95% CI, 1.05-1.24), although not in postmenopausal women. Additionally, OC use increased breast cancer risk in women with cancer diagnosed before age 45 (RR=1.15; 95% CI, 1.08-1.23), and in women who used OC before their 1st full-term pregnancy (RR=1.17; 95% CI, 1.06-1.30). No significant association between breast cancer risk and OC use was observed in women with a family history of breast cancer. In conclusion, these findings suggest an increased risk of premenopausal breast cancer in early OC users.

Romieu et al (1990)

The results of 27 case-control and 5 cohort studies published between 1966 and 1989 were pooled according to study type in this meta-analysis (included studies did not undergo quality assessment). For the case-control studies, there was no association between increased breast cancer risk and ever-use of OC (RR=1.06; 95% CI, 0.98-1.14), duration of 10 or more years’ use of OC (RR=1.14; 95% CI, 0.90-1.42), nor when analyses were restricted to studies published after 1980, when lower dose OCs were introduced (RR=1.22; 95% CI, 0.91-1.63). Ever-use of OCs in women with a family history of breast cancer was also not associated with increased breast cancer risk. There was, however, a statistically significant 46% increase in risk for 10 years of OC use when data were limited to premenopausal women (P=0.001). Furthermore, 4 or more years of OC use before 1st full-term pregnancy in women aged less than 46 years was associated with a significantly increased breast cancer risk (RR=1.72; 95% CI, 1.36-2.19). Pooled data for the cohort studies showed no adverse effect of breast cancer risk for ever-use and duration of OC use. The authors conclude that there was no increase in breast cancer risk for women, including those with a family history of breast cancer, who ever used OCs, even after long duration of use. There was, however, an increased risk of premenopausal breast cancer in women with long duration of OC use, especially in women who used OCs before their 1st full-term pregnancy.

8.6.1.2 Studies


Women aged 35-64 years took part in a US case-control study, with OC use in 4,575 women (cases) who developed invasive breast cancer compared to OC use in 4,682 women who had not developed the disease. Similar numbers of cases and controls had used some type of OC (77% vs 79%, respectively), although there were significant differences between the two arms on a number of variables, including the number of term pregnancies and the presence or absence of a family history of breast cancer. There was little evidence that OCs increase breast cancer risk in any of the categories of OC usage. For current OC users, the odds ratio was 1.0 (95% CI, 0.8-1.3) and for
previous users was 0.9 (95% CI, 0.8-1.0). Breast cancer risk did not increase with longer durations of use, with higher doses of estrogen, or among women who had begun using OCs at a young age. Former use was associated with a small but significant reduction in RR among the older women. There was a non-significant RR of 1.5 among the older women who were currently using low dose estrogen, compared with older women who had never used OCs. No association between ever-use and current use of OCs and family history of breast cancer was observed. The authors conclude that current or former OC use is not associated with increased breast cancer risk, nor is starting OC use at a young age.


Breast cancer risk associated with OC use in women with a mutation in the BRCA1 or BRCA2 gene was evaluated in this matched case-control study carried out at 52 centres in 11 countries worldwide. Cases (n=1,311) and controls (n=1,311) were aged 46-47 years, and were mainly US (45.8%) or Canadian (22.8%) residents. Most cases and controls were white (about 60%) or Jewish (about 30%), with almost 75% of women in each group carrying the BRCA1 mutation. After adjusting for parity and ethnicity, the odds ratio (OR) indicated an increased breast cancer risk for ever users of OCs who were BRCA1 mutation carriers relative to never users (OR=1.20; 95% CI, 1.02-1.40), although BRCA2 mutation carriers were not at increased risk (OR=0.94; 95% CI, 0.72-1.24). Analyses were subsequently confined to BRCA1 mutation carriers only. Compared to never users of OCs, results showed that for those who used OCs for 5 or more years, the adjusted OR was 1.33 (95% CI, 1.11-1.60). Breast cancer risk was also increased in women who ever used OCs before the age of 30 (OR=1.29; 95% CI, 1.09-1.52), in women who had ever used OCs who were diagnosed with breast cancer before the age of 40 (OR=1.38; 95% CI, 1.11-1.72), and in women who first used OCs before 1975 (OR=1.42; 95% CI, 1.17-1.75). The authors conclude that OC use is associated with increased breast cancer risk in BRCA1 mutation carriers, but not in BRCA2 mutation carriers, although it is acknowledged that data were limited in this subset of women.


This paper reports on material from a historical cohort of 426 families of breast cancer probands, diagnosed between 1944 and 1952, with follow-up data on families collected by telephone between 1991 and 1996. A total of 394 sisters and daughters of the probands, 3002 granddaughters and nieces and 2754 women who married into the families made up the participants. Limitations of the data meant that the relationship between oral contraceptive use and risk could be more robustly investigated into use of earlier (pre 1975) preparations of the oral contraceptive pill. Their findings suggested that in women with a strong family history of breast cancer, breast cancer risk may be raised by use of oral contraceptives. Their analysis suggests that after accounting for age and birth cohort, ever use of oral contraceptives was associated with a significantly increased risk of breast cancer among sisters and daughters of the probands (RR, 3.3; 95% confidence interval (CI), 1.6-6.7). An increase in risk was not found amongst granddaughters and nieces of the probands (RR, 1.2; 95% CI, 0.8-2.0). They argued that these findings were essentially unchanged after adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education. Their results showed the most evident increase in risk amongst those who had used pre 1975 formulations of the oral contraceptive pill and they had insufficient cases of breast cancer to provide a robust analysis of post 1975 preparations.

Van Hoften et al (2000)

In a Dutch case-control study carried out between 1982 and 1984, OC use in 309 pre- and postmenopausal women who developed breast cancer (cases) was compared to that of 610 pre- and postmenopausal women (controls) who had not developed the disease. Women aged <55 years and >55 years were defined as premenopausal and postmenopausal, respectively, as data on menopausal
status was not available. Although women who had ever used OCs had a slightly increased risk of breast cancer, especially those aged over 55 years, this association was not statistically significant, either for the total group of women or for the 2 subgroups of age. A small, non-significant increased breast cancer risk for between 1-10 years’ duration of OC use was observed, although there was a significant doubling in risk in women aged over 55 years who had used OCs for more than 10 years (odds ratio=2.05; 95% CI, 1.07-3.95). The data suggest, therefore, that OC use for over 10 years is associated with a twofold increased risk of breast cancer in women aged over 55 years, but not in younger women.

8.6.2 Summary of oral contraceptive use and breast cancer risk evidence

The above evidence regarding the use of oral contraceptives and their impact on breast cancer risk is of varying quality, covers different time periods, and relates to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in Appendix 14. Of the meta-analyses/re-analysis, four (Romieu et al 1990, Delgado-Rodriguez et al 1991, Hawley et al 1995, Collaborative Group 1996) combine evidence from approximately the same time periods, with some form of quality assessment of included studies undertaken in two of the syntheses. Of the remaining two meta-analyses (Rushton et al 1992, Schlesselman 1995), both combine evidence published after 1980, with no quality assessment of included studies in either synthesis.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

8.6.2.1 Ever-use of oral contraceptives

Findings of 2 meta-analyses and the 2 recent case-control studies suggest that ever-use of OCs in all women is not associated with an increased risk of breast cancer (Romieu et al 1990, Hawley et al 1995, van Hoften et al 2000, Marchbanks et al 2002). The re-analysis found, however, that ever-use of OCs in all women was associated with a statistically significant 7% increase in breast cancer risk (Collaborative Group 1996). A further meta-analysis similarly found a 7% increase in risk of breast cancer when case-control studies where combined, but no association when cohort studies were combined (Delgado-Rodriguez et al 1991).

In 3 meta-analyses and one case-control study, no association between ever-use of OCs in postmenopausal women and increased breast cancer risk was observed (Romieu et al 1990, Delgado-Rodriguez et al 1991, Rushton et al 1992, van Hoften et al 2000).

Findings relating to ever-use of OCs in premenopausal women, however, were inconsistent, with no association with increased risk of breast cancer observed in one of the case-control studies (van Hoften et al 2000), but a 14% and 16% increased risk observed in 2 meta-analyses (Delgado-Rodriguez et al 1991, Rushton et al 1992, respectively).

8.6.2.2 Current use of oral contraceptives

Two studies which assessed the impact of current use of OCs on risk of breast cancer in all women produced different findings, with a statistically significant 24% increase in breast cancer risk observed in the re-analysis (Collaborative Group 1996), but no increase observed in one of the case-control studies (van Hoften et al 2000).

8.6.2.3 Duration of oral contraceptives

Increasing duration of OC use in all women was not found to be associated with an increased risk of breast cancer in 2 meta-analyses (Romieu et al 1990, Hawley et al 1995) and the 2 case-control
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studies (van Hoften et al 2000, Marchbanks et al 2002). In a further meta-analysis, however, increasing duration of OC use in all women was found to be associated with increased risk, with a 27% increase observed for more than 8 years of OC use (Rushton et al 1992).

Findings relating to increasing duration of OC use and risk of breast cancer in premenopausal and postmenopausal women were also inconsistent between studies. A 46% increased risk of breast cancer after 10 years of OC use in premenopausal women was observed in one meta-analysis (Romieu et al 1990), whereas duration of OC use of more than 10 years in premenopausal women was not found to be associated with increased risk in a case-control study (van Hoften et al 2000). Similarly, increasing duration of OC use in postmenopausal women was not found to be associated with increased risk in one meta-analysis (Schlesselman 1995), although duration of OC use of more than 10 years was associated with a statistically significant doubling in breast cancer risk in a case-control study (van Hoften et al 2000).

8.6.2.4 Cessation of oral contraceptive use

In the re-analysis which assessed breast cancer risk in all women after stopping OC use, a 16% increased risk was observed between 1-4 years after stopping OC use, and a 7% increase between 5-9 years after stopping use (Collaborative Group 1996). In the same study, no increased risk of breast cancer in all women was observed 10 or more years after they stopped OC use. In a case-control study, however, no increase in risk of breast cancer was observed in all women relating to time since they stopped OC use (Marchbanks et al 2002).

8.6.2.5 Oral contraceptive use before 1st full-term pregnancy

Statistically significant increases in risk of breast cancer in women who used OCs before their 1st full-term pregnancy was observed in 3 meta-analyses (Romieu et al 1990, Delgado-Rodriguez et al 1991, Hawley et al 1995). In one of the meta-analyses (Romieu et al 1990), a 72% increased risk for 4 or more years’ OC use was found in this subgroup of women.

8.6.2.6 Oral contraceptive use in women with a family history of breast cancer

There was consistent evidence that the effects of OC use on breast cancer risk was similar in women with and without a family history (Romieu et al 1990, Delgado-Rodriguez et al 1991, Collaborative Group 1996, Marchbanks et al 2002).

8.6.2.7 Oral contraceptive use in women with a mutation in the BRCA1 or BRCA2 gene

There is evidence from one case-control study that ever use of OCs was associated with a 20% increase in breast cancer risk in women who were BRCA1 mutation carriers, although BRCA2 mutation carriers were not found to be at increased risk (Narod et al 2002).

8.6.3 Comment

Numerous scientific studies have investigated the relationship between the use of oral contraceptives (birth control pills) and the risk of breast cancer. In considering any increase in breast cancer risk, one has to recognize the addition of exogenous oestrogen but it may be that at least part of the effect is due to the fact that the oral contraceptive pill does prevent women from becoming pregnant, thereby reducing the breast cancer protection of an early pregnancy.
8.7 Breastfeeding

Recommendation

1. Women should be advised to breast feed if possible because this is likely to reduce their risk of breast cancer, and is in accordance with general health advice. (C)

Evidence statement

1. Breastfeeding confers a protective effect on breast cancer risk. (III)
2. The protective effect of breast feeding is in addition to the protective effect of pregnancy alone. (III)
3. The reduction in breast cancer risk is related to total duration of breast feeding. (III)
4. The Collaborative Group found that each twelve months of breastfeeding confers a reduction of about 4%. (III)
5. The relative risk reduction is similar in women with a family history. (III)

8.7.1 Research literature evidence

One systematic review, 1 meta-analysis and 1 collaborative re-analysis have been identified from the literature which evaluates the association between breastfeeding and breast cancer risk in the female population in general. No studies have been identified which evaluate a relationship between breastfeeding and breast cancer risk in women with a family history of breast cancer, although reference to this subgroup of women is made in one of the above-identified studies.

8.7.1.1 Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (2002a)

Eighty percent of the world-wide epidemiological evidence, consisting of 47 case-control and cohort studies from 30 countries was combined in this collaborative re-analysis of 50,302 women with invasive breast cancer and 96,973 women without the disease. Comparison of cases and controls found that cases had fewer births than controls, were more likely to be nulliparous, were less likely to have breastfed and had shorter lifetime duration of breastfeeding. In terms of effect of breastfeeding on breast cancer risk, after stratifying for parity, lifetime duration of breastfeeding, age factors and menopausal status, the RR of breast cancer was significantly reduced by 4.3% for each year of breastfeeding (CI, 2.9-5.8; P<0.0001). This decrease was in addition to a reduction in RR of breast cancer of 7% observed for each birth (P<0.0001). Adjustment for factors such as whether women were from developed or developing countries, or whether women had a family history of breast cancer did not alter the size of these associations. Public health implications of the lack of, or short duration of, breastfeeding and the high incidence of breast cancer in developed countries are discussed.
Lipworth et al (2000)

In this systematic review, 28 epidemiological studies published between 1966 and 1998 were assessed (note: included studies do not appear to have undergone systematic quality assessment) to evaluate whether a history of breastfeeding decreases breast cancer risk. In terms of ever breastfeeding and breast cancer risk, evidence of an inverse association was limited and inconclusive, with findings either suggestive of no association, or a definite but small protective effect. In studies which found a protective effect, RRs for parous women who had ever breast fed ranged from 0.54 to just less than 1.0, compared to women who had never breast fed. Evidence for an association between breast cancer risk and number of children breast fed was inconsistent, with studies either showing significant reductions in risk or no trend of decreasing risk with increasing number of children breast fed. In terms of duration of breastfeeding, reductions in ORs for premenopausal women who breast fed for at least 12 months were observed in some studies, although other studies found no reduction in risk. Overall, there appeared to be evidence of a protective effect on risk among women in non-Western countries with long durations of breastfeeding. In most studies, any protective effect of breastfeeding appeared to be strongest, or confined to, premenopausal women. The authors conclude that breastfeeding confers a relatively weak protective effect on breast cancer risk, limited to premenopausal women, although they note that potential confounding factors make comparison of study findings difficult.


Twenty-three case-control studies published between 1980 and 1998 which evaluated the relation between breastfeeding and breast cancer were combined in a meta-analysis. Using a random effect model, the combined OR for ever versus never breastfeeding was 0.84 (95% CI, 0.78-0.91), suggesting a slight but significant protective effect. For ever versus never breastfeeding mothers, a significant decrease in breast cancer risk for women who were non-menopausal at the time of breast cancer diagnosis was also observed (OR=0.81; 95% CI, 0.72-0.91). For women who breastfed for at least 12 months, a significant decrease in combined OR was observed, relative to women who had never breastfed (OR=0.72; 95% CI, 0.65-0.80). Across categories of duration, a trend towards decreasing risk with increasing duration of breastfeeding was observed (P<0.0005). Findings are suggestive of a slight but significant reduction in breast cancer risk in women who had ever breastfed. This decrease appeared to be related to duration of breastfeeding, and was noted in women who were not menopausal at the time of breast cancer diagnosis.

8.7.2 Summary of breastfeeding and breast cancer risk evidence

Results of one systematic review, 1 meta-analysis and 1 collaborative re-analysis conclusively found a significant protective effect of breastfeeding on breast cancer risk. For the systematic review, the evidence was suggestive of a slight decrease in risk limited to premenopausal women, especially women from non-Western countries with long durations of breastfeeding. The meta-analysis found a significant reduction of 16% in breast cancer risk associated with ever breastfeeding compared to never breastfeeding, which was more marked in women who were non-menopausal at the time of breast cancer diagnosis. A significant trend towards decreasing risk with increasing duration of breastfeeding was also observed, with a 28% reduction in breast cancer risk in women who breastfed for at least 12 months. In the collaborative re-analysis, similarly, breast cancer risk was significantly reduced by 4.3% for each year of breastfeeding, in addition to a reduction in risk associated with each birth. For women with a family history of breast cancer, similar risk reductions were observed.

8.7.3 Comment

If breast-feeding does protect against breast cancer, it may do so by delaying the resumption of ovulation (with its accompanying high estrogen levels) after pregnancy. The benefits of breast-feeding for the infant are well established, and all authorities agree that breast-feeding is the preferred method of infant feeding unless it is contraindicated for a specific medical reason.
8.8 Other reproductive/fertility issues

8.8.1 Induced abortion

*Comment*

There is little evidence regarding history of induced abortion as a potential modifying factor for the development of breast cancer in the general female population, and no evidence relating to women with a family history of breast cancer.

8.8.1.2 Research literature evidence

One meta-analysis has been identified from the literature which evaluates the association between induced abortion and breast cancer risk in the female population in general. No studies have been identified which evaluate a relationship between induced abortion and breast cancer risk in women with a family history of breast cancer.

Brind et al (1996)

Twenty-eight observational studies describing 23 independent studies which published data between 1966 and 1996 on the effect of history of induced abortion on breast cancer risk were combined in a meta-analysis (note: included studies do not appear to have undergone systematic quality assessment). Breast cancer risk was significantly increased with any history of induced abortion (reported by 21 of the studies), with an overall odds ratio (OR) of 1.3 (95% CI, 1.2-1.4). When parity was taken into account, breast cancer risk was observed to be significantly increased in nulliparous women (OR=1.3; 95% CI, 1.0-1.6); in parous women who underwent induced abortion before their 1st-term pregnancy (OR=1.5; 95% CI, 1.2-1.8); and in women who underwent induced abortion after their 1st-term pregnancy (OR=1.3; 95% CI, 1.1-1.5). The authors conclude that induced abortion increases a woman’s risk of breast cancer regardless of parity or timing of abortion relative to 1st-term pregnancy. Furthermore, the authors state that the consistently positive associations found amongst included studies in terms of induced abortion and breast cancer incidence rule out the possibility that the association results from bias or any other confounding variable.

8.8.1.3 Comment

The guideline development group thought that the limited studies available are inconclusive.
8.8.2 Sub-fertility and induced ovulation

Comment

Studies of sub-fertility and induced ovulation in relation to breast cancer risk show inconsistent results.

8.8.2.1 Research literature evidence

One systematic review looked at the issue of sub-fertility and induced ovulation (by use of fertility drugs). One study looked at incidence of cancer following fertility treatment in a UK clinic.

8.8.2.1.1 Meta-analyses, systematic reviews and re-analyses


This systematic review looked at the potential long term effects of fertility drugs, as well as the indications for fertility drug use on the risk of cancers of the ovary, breast and endometrium. As the reason for fertility drug use was of concern (i.e. might it confound any association between fertility drug use and cancer risk) they only included studies that specifically examined the cause of infertility. They examined data from cohort studies and case control studies. Different studies looked at different causes of sub-fertility and cancer risk and others looked at the use of fertility drugs and cancer risk (including breast cancer) whilst some studies looked only at breast cancer risk. Data from seven cohort studies that presented standardised incidence rates for breast, ovary and endometrium cancer, did not show that the risk of breast cancer was significantly different from that in the general population. The authors also argued that studies of sub-fertility in relation to breast cancer risk show inconsistent results. There are methodological difficulties with many of the studies and they argued that even some of the larger studies had inadequate power to reliably assess breast cancer risk in relation to sub-fertility diagnosis. They found only a few studies which assessed breast cancer risk in relation to fertility drug use. These studies had inconsistent results and were based on short follow-up. Overall they concluded that the association between fertility drug use and cancer risk has been examined in a few studies with inconsistent results.

8.8.2.1.2 Studies

Doyle et al (2002)

This study aimed to investigate the incidence of cancer in a cohort of women attending a large infertility clinic in the UK. Women (UK residents, over the age of 20 at time of treatment, received at least one cycle of infertility treatment) were identified between January 1975 and December 1989, followed up and cancer incidence rates calculated. The study cohort comprised 5556 women, 75% of whom had received ovarian stimulation drug treatment at the clinic. On average the group who received ovarian stimulation were slightly older and had a higher proportion of nulliparous women after the last treatment cycle than the group who did not receive ovarian drug stimulation treatment. A total of 118 cancers were incident in the cohort from the beginning of 1990 until the end of 1997, including 55 breast, 4 uterine and 6 ovarian. There was no significant difference between stimulated and unstimulated groups (p=0.89, 0.07, 0.53 for breast, uterus and ovary respectively). Compared with the general population the numbers of cancer of the breast and uterus were higher than expected in both stimulated and unstimulated group but not significantly so (all p>0.38). The authors concluded therefore that overall the incidence of breast, uterine and ovarian cancers was no greater than expected on national rates over the period of follow-up, and that they found no evidence for a link between ovarian stimulation treatment and increased cancer incidence.
8.9 Alcohol consumption

Recommendation

1. Women with a family history should be informed that alcohol may increase their risk of breast cancer slightly. However, this should be considered in conjunction with any potential benefit of moderate alcohol intake on other conditions (such as heart disease) and adverse effects associated with excessive alcohol intake. (C)

Evidence statement

1. Risk of breast cancer increases with alcohol consumption. (III)
2. The Collaborative Group reported an increase of 7.1% in relative risk for each additional 10g per day intake of alcohol. (III)
3. There is no good evidence that the relative risk associated with increasing alcohol consumption is different for women with a family history compared to women as a whole. (III)

8.9.1 Research literature evidence

Five meta-analyses/systematic reviews which evaluate the impact of alcohol consumption on breast cancer risk for women in general have been identified from the literature. One cohort study which assesses the effect of alcohol consumption on breast cancer risk in women with a family history of breast cancer has been identified.

8.9.1.1 Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (2002b)

This study reanalysed 80% of worldwide data on the relationship between breast cancer and consumption of alcohol and/or tobacco, involving 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. The relative risk of breast cancer increased significantly with increasing intake of alcohol, increasing by 7.1% for each additional 10 g per day of alcohol (P<0.00001) in both ever-smokers and never-smokers. Adjustments for 11 potential confounding factors (including family history of breast cancer, use of hormonal preparations and menopausal status) did not alter the magnitude of this increase in relative risk. However, the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. Analysis of data for 22,255 cases and 40,832 controls who reported no alcohol intake found that breast cancer risk in ever smokers did not differ significantly from that of never smokers (RR=1.03, SE 0.023, NS). The authors note that among women who drank alcohol, the findings for an association between smoking and breast cancer were difficult to extricate from the effects of alcohol itself. They conclude that smoking has little or no independent effect on breast cancer risk, and the increase in breast cancer risk attributed to alcohol needs to be interpreted in the context of the beneficial effects of a moderate intake.
Ellison et al (2001)

This meta-analysis combined the findings of 42 cohort and case-control studies (the authors note that the quality of included studies varied widely, although details of quality assessment are not reported) on breast cancer incidence, and 2 studies on breast cancer mortality, in order to assess breast cancer risk and breast cancer mortality according to alcohol intake. In comparison to non-drinkers, women who consumed 6 g (about one-half drink) per day had a 4.9% increased breast cancer risk (95% CI, 1.03-1.07); those who drank 12 g (about 1 drink) and 24 g (about 2 drinks) per day had 10% (95% CI, 1.06-1.14) and 21% (95% CI, 1.13-1.30) increased risks, respectively. Results of the 2 studies which evaluated breast cancer mortality and alcohol consumption gave a risk estimate of slightly below 1.0 for up to 6 g per day. In conclusion, the authors suggest a modest relation of alcohol consumption to breast cancer risk.


The results of 6 prospective studies (included studies do not appear to have been systematically quality assessed) with a total sample of 322,647 women, including 4,335 women with invasive breast cancer, were combined to assess breast cancer risk by type and intake of alcohol, and the impact of potential risk modifiers (including family history of breast cancer). Alcohol consumption was positively associated with risk of invasive breast cancer, with an intake of 30-60 g (about 2-5 drinks) per day giving a RR of 1.41 (95% CI, 1.18-1.69) compared to non-drinkers. However, the association was not statistically significant for women who consumed 60 g or more per day (RR=1.31; 95% CI, 0.86-1.98) compared to non-drinkers. A significant linear increase in risk was also observed for alcohol intakes of less than 60 g per day (RR=1.09; 95% CI, 1.04-1.13) for an increment of 10 g (about 0.75-1 drink) per day. There were no statistically significant interactions between breast cancer risk and alcohol intake when other breast cancer risk factors (for example, menopausal status, family history of breast cancer, HRT use and body mass index) were taken into account. The authors conclude that alcohol intake is associated with a linear increase in invasive breast cancer risk, and that this association is not modified by other factors.

Longnecker (1994)

A meta-analysis and qualitative review was carried out to evaluate the association between alcohol intake and risk of breast cancer from the results of 10 cohort and 28 case-control studies. Synthesis of risk estimates found significantly increased breast cancer risks associated with an intake of 1, 2 or 3 drinks per day, with relative risks of 1.11 (95% CI 1.07-1.16), 1.24 (95% CI, 1.15-1.34) and 1.38 (95% CI, 1.23-1.55), respectively. There was no evidence of variation in size of association by study design (cohort compared to case-control). A qualitative review of studies found no evidence of effect modification on these results, apart from limited data on an association with estrogen replacement therapy. The authors conclude that there is strong evidence of a dose-response relation between alcohol consumption and breast cancer risk.

Steinberg et al (1991)

The association between alcohol consumption and breast cancer risk in women was assessed by systematic review of 6 cohort and 20 case-control studies. Study findings were inconsistent across both types of study designs. Only one of the 3 cohort studies which assessed overall breast cancer risk in drinkers compared to non-drinkers observed a significant association with a relative risk among drinkers of 1.5 (95% CI, 1.1-2.2). However, 5 of the cohort studies found breast cancer risk to be significantly increased in women with ‘high’ levels of alcohol intake, with the highest risk estimate of 3.18 (95% CI, 1.14-8.85) in women with an intake of more than 6 drinks per day. Of the 11 case-control studies which compared breast cancer risk in drinkers versus non-drinkers, 5 found significant positive associations (RRs varied from 1.2-2.5). A significant dose-response gradient with increasing alcohol intake was also observed in 8 case-control studies. In 4 studies where no
significant association was found between alcohol and breast cancer risk, a significant increase in risk was observed in women who drank more than a specified amount daily. There was some evidence from 2 studies of a decrease in risk associated with increased alcohol consumption. In conclusion, the authors found insufficient evidence to support a causal relationship between alcohol intake and breast cancer risk.

Longnecker et al (1988)

In this meta-analysis of 12 case-control and 4 cohort studies, breast cancer risk in women by intake and ever-consumption of alcohol was evaluated. For both the case-control and cohort studies a statistically significant dose-response relation between alcohol consumption and breast cancer risk was observed (P=0.01 and <0.05, respectively). Risk estimates associated with an alcohol intake of 24 g of alcohol (about 2 drinks) per day relative to non-drinkers were 1.4 (95% CI, 1.0-1.8) for case-control studies, and 1.7 (95% CI, 1.4-2.2) for cohort studies. At lower levels of alcohol consumption, there were weak to modest associations for both study designs. A synthesis of 6 case-control studies found an overall risk estimate for ever-consumption of alcohol compared with never-use of 1.1 (95% CI, 1.0-1.2). The authors conclude that their findings were strongly supportive of an association between alcohol intake and breast cancer risk.

8.9.1.2 Studies

Vachon et al (2001)

This cohort study investigated the association between alcohol intake and breast cancer risk in 5,042 women from 426 families with a history of breast cancer compared to 3,990 women who married into these families. Data were included from 2,974 surrogates (usually 1st-degree relatives) where relatives were deceased or unable to provide data. Ever-use of alcohol in all study participants compared to non-drinkers was associated with a 22% increased risk (95% CI, 0.99-1.50). Among 1st-degree relatives of women with breast cancer, daily drinkers had a significantly increased risk compared with non-drinkers (RR=2.45; 95% CI, 1.20-5.02). This increase was less evident among 2nd-degree relatives (RR=1.27; 95% CI, 0.73-2.22). In comparison, there was no significantly increased breast cancer risk in those women who married-in and reported daily alcohol intake. Similar findings were observed when analyses where restricted to families at particularly high risk of breast cancer (i.e. families that had 3 or more breast and/or ovarian cancers). The authors conclude that alcohol-associated breast cancer risks may be modified by genetic susceptibility. They acknowledge, however, that their findings should be interpreted cautiously due to factors such as recall bias, potentially poor data quality and lack of generalisability.

8.9.2 Summary of alcohol consumption and breast cancer risk evidence

Results of 4 meta-analyses identified from the literature, which evaluate the impact of alcohol consumption on breast cancer risk in women, consistently show statistically significant increases in relative risks. Associations vary slightly between studies in terms of specific intake of alcohol and increase in breast cancer risk, with definitions of an alcoholic drink in relation to equivalent gram weight showing slight differences between studies. One study (Longnecker et al, 1988) observed significant increases in risk with an alcohol intake of 24 g (defined as about 2 drinks) per day, although only weak or modest associations at lower levels of alcohol consumption. A subsequent study by Longnecker (1994), however, found significantly increased relative risks of breast cancer associated with an intake of 1, 2 or 3 drinks per day (1 drink defined as 13 g of alcohol), showing strong evidence of a dose-response relationship. The third identified meta-analysis (Smith-Warner et al, 1998) found significantly increased breast cancer risks in women who drank 30-60 g (defined as about 2-5 drinks) per day, although no increased risks were observed in women who drank 60 g or more per day compared with non-drinkers. Other breast cancer risk factors, including family history
of breast cancer, did not influence these results. The fourth and most recent meta-analysis (Ellison et al, 2001) found a significant linear increase in breast cancer risk with increasing intake of alcohol of 6, 12 and 24 g (defined as about one-half, 1 and 2 drinks, respectively) per day.

Results of a systematic review (Steinberg et al, 1991) found inconsistencies in results across studies, with the authors unable to support a causal association between alcohol intake and breast cancer risk.

Results of the collaborative reanalysis of worldwide data (Collaborative Group, 2002) found that the lifetime risk of breast cancer is estimated to increase by about 0.7 per 100 women for each extra unit of alcohol consumed daily, although this increase should be considered in the context of the beneficial effects of a moderate intake of alcohol. Smoking has little or no independent effect on breast cancer risk.

A cohort study (Vachon et al, 2001) which evaluated the association between alcohol consumption and breast cancer risk in women with a family history of breast cancer compared to those who married into these families found significantly increased risks in 1st-degree relatives of breast cancer patients who drank daily compared to non-drinkers, but non-significant increases for 2nd-degree relatives. For women who married into these families and reported daily intake of alcohol, no significantly increased breast cancer risks were observed. The authors, however, advise caution in interpreting these findings due to methodological limitations.

8.9.3 Comment

Women who drink moderate amounts of alcohol have been found to have a slightly higher risk of breast cancer than do those who abstain. It is uncertain, however, whether this association reflects a cause-and-effect relationship. The weaker an association is, the more difficult it is to tell whether that association is due to a true cause-and-effect relationship or to something else. It is extremely difficult to determine whether any effect reflects a true cause-and-effect relationship or is due to other factors—such as difficulties in measurement or differences between the lifestyles of drinkers and abstainers. The use of alcohol may vary among women who differ with regard to other factors that are known to influence breast cancer risk—such as age, obesity, and reproductive history.
8.10 Smoking

Recommendation

1. Women should be advised not to smoke, in line with current health advice. (D)

Evidence statement

1. There is no good evidence for an association between smoking and breast cancer. (IV)

2. In the Collaborative reanalysis, for women who reported they did not drink, compared to women who never smoked the relative risk of breast cancer was close to 1 in current or past smokers. (III)

3. A recent large meta analysis concluded that cigarette smoking increases breast cancer risk, with a higher risk in premenopausal women and in those who started smoking at an earlier age. (III)

8.10.1 Research literature evidence

One meta-analysis and, one systematic review and one re-analysis have been identified from the literature which evaluate the association between smoking and breast cancer risk in the female population in general. Two recent observational studies (1 cohort and 1 case-control) have been identified which evaluate the relationship between smoking and breast cancer risk in a similar population. A further recent cohort study has been identified which assesses the association between smoking and breast cancer risk in families at high-risk of breast and/or ovarian cancer.

8.10.1.1 Meta-analyses, systematic reviews and reanalyses

Khuder et al (2001)

The relationship between smoking and breast cancer was evaluated in this meta-analysis of 31 case-control and 9 cohort studies published between 1984 and 2001 (note: included studies do not appear to have been quality assessed). Breast cancer risk was significantly increased in women who ever smoked (RR=1.10; 95% CI, 1.02-1.18), in current smokers (RR=1.11; 95% CI, 1.01-1.22), and in former smokers (RR=1.10; 95% CI, 1.00-1.21). Although risk was significantly raised in postmenopausal women, premenopausal women who were ever smokers or former smokers were at higher risk (RR=1.21; 95% CI, 1.08-1.36 and RR=1.30; 95% CI, 1.19-1.51, respectively). A significant dose-response trend was observed (P<0.01) for breast cancer risk according to the number of cigarettes smoked per day, with a RR of 1.03 (95% CI, 1.01-1.06) in women who smoked 1-10 cigarettes per day, increasing to 1.30 (95% CI, 1.05-1.61) in women who smoked 40 or more cigarettes per day. A significant dose-response trend was also observed (P<0.01) for breast cancer risk and duration of smoking, with a combined RR of 1.03 (95% CI, 1.02-1.04) associated with smoking for 1-19 years, increasing to 1.12 (95% CI, 1.07-1.17) with 30 or more years of smoking. Initiation of smoking at a younger age (mean 14 years) was associated with a significant increase in risk (RR=1.14; 95% CI, 1.06-1.23). The authors conclude that cigarette smoking increases breast cancer risk.
cancer risk, with a higher risk in premenopausal women and in those who started smoking at an earlier age.

**Palmer et al (1993)**

Fourteen case-control and 5 cohort studies published up to 1992 were reviewed to evaluate a causal relationship between cigarette smoking and breast cancer risk (included studies did not undergo quality assessment). Review of the evidence found that cigarette smoking did not appear to reduce breast cancer risk, and there was also little evidence to suggest that smoking increases risk. Most studies found either no association or very small positive associations for ever smoking, current smoking or heavy smoking. There was inconsistent evidence about whether women who initiate smoking in their early teens are at increased breast cancer risk. Adjusting for risk factors such as parity, family history of breast cancer and body mass index did not influence risk estimates. The authors discuss the possibility of bias and confounding amongst studies.

**Collaborative Group on Hormonal Factors in Breast Cancer (2002)**

This study reanalysed 80% of worldwide data on the relationship between breast cancer and consumption of alcohol and/or tobacco, involving 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. The relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. Analysis of data for 22,255 cases and 40,832 controls who reported no alcohol intake found that breast cancer risk in ever smokers did not differ significantly from that of never smokers (RR=1.03, SE 0.023, NS). The authors note that among women who drank alcohol, the findings for an association between smoking and breast cancer were difficult to extricate from the effects of alcohol itself. They conclude that smoking has little or no independent effect on breast cancer risk, and the increase in breast cancer risk attributed to alcohol needs to be interpreted in the context of the beneficial effects of a moderate intake.

**8.10.1.2. Studies**

**Terry et al (2002)**

Breast cancer risk and the effect of ever, former and never cigarette smoking was evaluated in a prospective cohort study of 89,807 women recruited between 1980 and 1985 in Canada. A significant increase in breast cancer risk was observed for women who had ever smoked, with an age-adjusted RR of 1.15 (95% CI, 1.05-1.27), compared to women who had never smoked. Women who were former smokers, however, were not at increased risk (RR=1.00; 95% CI, 0.91-1.10), compared to never-smokers. In terms of duration of smoking, women who had smoked for 40 years or longer had about a 60% increased breast cancer risk compared to never-smokers (RR=1.61; 95% CI, 1.19-2.19). Intensity of smoking also increased risk, with women who smoked 30-39 and 40 or more cigarettes a day having RRs of 1.21 (95% CI, 1.04-1.42) and 1.37 (95% CI, 1.15-1.62), respectively. Women with at least 40 pack-years of cigarette consumption over 40 years or more were at particularly high risk (RR=1.83; 95% CI, 1.29-2.61). In terms of breast cancer risk and age at initiation of smoking, and years since stopping smoking, there were no clear associations. Adjusting for multiple variables, including family history of breast cancer, did not affect any of the associations found across smoking measures. Overall findings suggest that smoking of very long duration and high intensity is associated with increased breast cancer risk.

**Band et al (2002)**

In a Canadian case-control study, 318 premenopausal and 700 postmenopausal women listed on the British Columbia cancer registry were compared to 340 premenopausal and 685 postmenopausal population-based controls in terms of effect of cigarette smoking on breast cancer risk. Study
findings showed that the effect of smoking on breast cancer risk differed between pre- and postmenopausal women. In premenopausal women, risk was raised in women who smoked before a 1st pregnancy, but only when smoking was initiated within 5 years of onset of menarche (OR=1.69; 95% CI, 1.13-2.51). In nulliparous premenopausal women, risk was also significantly increased in women who smoked 20 or more cigarettes per day (OR=7.08; 95% CI, 1.63-30.8) and for 20 or more pack-years (OR=7.48; 95% CI, 1.59-35.2). Findings for postmenopausal women, however, showed no associations between smoking and breast cancer risk, except a reduced risk observed in women who started to smoke after a 1st full-term pregnancy (OR=0.64; 95% CI, 0.42-0.98) and whose body mass index increased since early adulthood (OR=0.49; 95% CI, 0.27-0.89).

Couch et al (2001)

The association between cigarette smoking and breast cancer risk in 132 high-risk US families (defined as families with 3 or more members affected with breast and/or ovarian cancer) was evaluated in a historical cohort study involving 1,891 women who had ever smoked and 2,246 women who had never smoked. Among sisters and daughters of breast cancer patients, those who ever smoked had a 2.4-fold increase in breast cancer risk (95% CI, 1.2-5.1) compared to never-smokers. No association was observed in nieces, granddaughters or women who married into the families. When analyses were restricted to 35 families at highest-risk (defined as having 5 or more members with breast and/or ovarian cancer), sisters and daughters who had ever smoked were at 5.8-fold increased breast cancer risk (95% CI, 1.4-23.9), compared with never smokers. Again, no increased risk was observed in nieces and granddaughters. The authors conclude that smoking may significantly increase breast cancer risk in sisters and daughters from families at high risk of breast and/or ovarian cancer.

8.10.2 Summary of smoking and breast cancer risk evidence

Results from a systematic review and a meta-analysis which assessed the association between smoking and breast cancer risk reached different conclusions, with the systematic review (Palmer et al) finding either no, or very small positive, associations and the meta-analysis (Khuder et al) finding significant increases in risk in ever, former and current smokers, with particularly high risks observed for premenopausal women and those who initiated smoking at an earlier age. The Collaborative group concluded that smoking has little or no independent effect on breast cancer risk.

Two North American observational studies both found that smoking significantly increased breast cancer risk. In the cohort study (Terry et al), ever smoking (although not former smoking) increased risk; also smoking of very long duration and high intensity was associated with particularly high risk, with, for example, an 83% increase in breast cancer risk in women who smoked 20 or more cigarettes per day over 40 years or more, relative to never-smokers. In the case-control study (Band et al), results suggested increases in risk in premenopausal women who smoked before a 1st pregnancy (but only when smoking was initiated within 5 years of onset of menarche) and in nulliparous premenopausal women. Postmenopausal women, however, were not at increased breast cancer risk, with some subsets of women showing a reduction in risk associated with smoking.

A third North American observational study found a significant 2.4-fold increase in breast cancer risk of smoking in sisters and daughters from families at high risk of breast and/or ovarian cancer.

8.10.3 Comment

There is some evidence that cigarette smoking may be associated with a small increase in breast cancer risk. However, because the results of scientific studies have not been consistent, this relationship is currently regarded as merely speculative.
8.11 Weight and physical activity

Recommendation

1. Women should be advised on the probable increased postmenopausal risk of breast cancer from being overweight. (C)

2. Women should be advised about the potential benefits of physical exercise on breast cancer risk. (C)

Evidence statement

1. No specific evidence was found between the relationship between diet and exercise and familial breast cancer risk.

2. Moderate physical exercise is associated with a decrease risk in breast cancer in the general population. (III)

3. A high BMI is associated with a significant increase in postmenopausal breast cancer risk in the general population. (III)

8.11.1 Research literature evidence

An IARC report (2002b) reported findings from many cohort and case–control studies, which looked at reproductive and lifestyle factors. These were for general populations rather than those with a family history. A systematic review by Harvie et al (2003) looked at the effect of central obesity on breast cancer risk.

8.11.1.1 Weight

8.11.1.1.1 Premenopausal women:

A recent IARC report reported that for premenopausal women, in populations with a high incidence of breast cancer, those with high BMIs (over 28kg/m²) were found to have a slightly reduced breast cancer risk. It also reported that despite this reduced breast cancer incidence risk, the breast cancer mortality rate is not lower among heavier premenopausal women (IARC 2002b: 237).

Harvie et al (2003) found that waist measurement or waist to hip ration had little, if any effect, on risk of breast cancer. However they did find that using adjusted data (adjusted for BMI) showed a relative reduction (42%) in women with the smallest waist to hip ratio and that there was a relationship between central obesity and increased risk.

8.11.1.2 Postmenopausal women:

A recent IARC report reported that more than 100 studies over nearly 30 years in populations in many countries have established that increased body weight increases breast cancer risk among postmenopausal women. It went on to say that almost all of these studies have shown that this association is largely independent of a wide variety of reproductive and lifestyle risk factors, also that
recent studies have indicated that it is independent of the effect of physical activity. The association between being overweight and breast cancer appears to increase in a stepwise fashion with advancing age after the menopause (IARC 2002b: 237).

Harvie et al (2003) found that women with the smallest waists (quintile) had a lower relative risk of breast cancer than those in the highest waist measurement quintile (39%, using unadjusted but pooled data) and similar findings for waist to hip measurement (34%, using unadjusted but pooled data). This relationship was attenuated when adjustment for BMI was made.

8.11.1.2. Physical activity

Most of the more than 30 epidemiological studies, conducted in Asia, Europe and North America, demonstrated lower breast cancer risk among the most physically active women. In 8 of the 14 cohort studies and in 14 of the 19 case-control studies, lower breast cancer risk was seen among women who were most active. The decrease in risk of breast cancer was, on average, about 20-40%. (IARC 2002b: 238)

8.11.2  Comment

In scientific studies, obesity has been consistently associated with an increased risk of breast cancer among postmenopausal women. As is the case with reproductive risk factors, this relationship may be mediated by oestrogen production. Fat cells produce some and obese postmenopausal women, therefore, tend to have higher blood oestrogen levels than non-obese women do. Obesity does not seem to be a risk factor for breast cancer in premenopausal women. In these younger women, the ovaries are the main producers of oestrogen. The much smaller amount of oestrogen produced by the fat cells doesn’t appear to have any significant impact on breast cancer risk. Scientific studies have consistently shown that the risk of breast cancer is lower among physically active premenopausal women than among sedentary women. The effect of physical activity on breast cancer risk may be due at least in part to effects of exercise on the female hormones. Although the effects of obesity and physical inactivity on breast cancer risk are not as strong as the effects of previous breast disease or family history of breast cancer, they are important risk factors because they are modifiable. Exercise and weight control currently represent the most effective lifestyle changes that a woman can make to reduce her risk of breast cancer. Lack of physical activity is an established risk factor for premenopausal breast cancer and represents part of a complete approach to weight management. In addition, women who stay active can also reduce their risk of other diseases, such as coronary heart disease and colon cancer, and they can increase their quality of life.
8.12 Menstrual/reproductive factors

Recommendation

1. Healthcare professionals should be able to provide information on the effects of hormonal and reproductive factors on breast cancer risk. (D)

Evidence statement

1. Older age at 1st live birth, or at 1st birth, is associated with significant increases in breast cancer risk. (III)

2. Increased parity has been found to be associated with a decrease in breast cancer risk;
   • 38% decrease in risk in women who reported 5 or more live births
   • 32% decrease in risk in women who reported 3 or more births compared to women who reported 1 birth (III)

3. Earlier menarche is associated with an increase in risk of breast cancer. (III)

4. For women with a family history, the relative risk of menstrual and reproductive factors is consistent with the population. (III)

8.12.1 Research literature evidence

Two meta-analyses and a collaborative group re-analysis were identified from the literature which evaluated the association between menstrual/reproductive factors and breast cancer risk in the female population in general. The Collaborative group also looked at issues relating to women with first degree relatives with breast cancer.

Collaborative Group on Hormonal Factors in Breast Cancer (2001)

The Collaborative group looked at the relevance of breast cancer in first degree relatives on a range of other risk factors for breast cancer. The relationships between risk factors for women with a family history were similar to those for women without a family history. They argued that reproductive factors that reduce the risk ration for breast cancer, such as high parity, early childbearing and early menopause, should lead to a greater reduction in the absolute incidence of breast cancer in women with a family history of the disease than in women without such a history, just because the relevant risk ratios are similar in both groups.


Results of 7 published and 1 unpublished epidemiological studies identified between 1966 and 1995 which evaluated the effect of menstrual and reproductive factors on breast cancer incidence among Japanese women were combined in this meta-analysis. Synthesis of results found a significantly lower odds ratio (OR) for women with onset of menstruation after age 16 (OR=0.68; 95% CI, 0.59-0.77), relative to women with aged less than 14 at menarche. In terms of breast cancer risk and age at 1st birth, significantly higher ORs were observed for women in any age group for 1st birth after age
25, and for nulliparous women, compared to women with 1st birth before age 25. Women aged 25-29 years had an OR of 1.32 (95% CI, 1.14-1.53), aged 30-34, an OR of 1.71 (95% CI, 1.41-2.09) aged 35 years or more, an OR of 2.26 (95% CI, 1.85-2.77), and nulliparous women, an OR of 1.56 (95% CI, 1.27-1.91). A significant protective effect of higher parity (3 or more children) on breast cancer risk was noted (OR=0.68; 95% CI, 0.54-0.86), relative to women who had 1 child. Also menopausal status influenced breast cancer risk, with premenopausal women at significantly higher risk (OR=2.21; 95% CI, 1.53-3.20) compared to women with menopause before age 50; an increased OR was not noted, however, for women with menopause after age 50. Findings suggest that early age at menarche, late age at 1st birth and premenopausal status were significantly associated with increased breast cancer risk among a population of Japanese women.


In this meta-analysis of 3 Italian case-control studies published between 1986 and 1987 (a systematic quality assessment of included papers was not performed), the impact of menstrual and reproductive factors on breast cancer risk was assessed in 4,072 women with, and 4,099 women without, breast cancer. Combined results showed that women with younger ages at onset of menstruation (aged 12-14 years and less than 12 years) were at significantly increased risk of developing breast cancer (RR=1.32; 95% CI, 1.15-1.52 and RR=1.19; 95% CI, 1.00-1.42, respectively) relative to women who were aged 15 years or over at menarche. In terms of menopausal status, there was a significant trend towards decreasing breast cancer risk with earlier menopause, with women aged 45-49 years and less than 45 years at menopause at lower risk of breast cancer (RR=0.77; 95% CI, 0.67-0.90 and RR=0.73; 95% CI, 0.61-0.88, respectively), relative to women aged 50 years or more at menopause. High parity (5 live births or more) was associated with a significantly decreased breast cancer risk (RR=0.62; 95% CI, 0.50-0.76). Women whose age at their 1st live birth was between 22-24 years, 25-27 years and 28 years or more had a 22% (95% CI, 1.06-1.43), 40% (1.20-1.63) and 75% (1.50-2.04) increased risk of breast cancer, respectively, relative to women aged less than 22 years at 1st live birth. Results also indicated a 2-fold increase in breast cancer risk in women with a history of breast cancer in 1st degree relatives compared to women with no family history. The authors conclude that menstrual and reproductive factors have a strong influence on breast cancer risk.

8.12.2 Summary of menstrual/reproductive factors and breast cancer risk evidence

The above meta-analysis evidence regarding the effect of menstrual and reproductive factors on breast cancer risk is of varying quality, covers different time periods, and relates to specific populations of women, namely from the Italian and Japanese populations.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

8.12.2.1 Age at menarche

Both studies observed an increased breast cancer risk associated with younger age at onset of menstruation. Significant increases of 32% and 19% in women aged 12-14 years and less than 12 years at menarche, respectively, compared to women aged 15 year or over at menarche were found in the earlier study (Negri et al 1988). Conversely, in the second study (Nagata et al 1995), onset of menstruation at age 16 or over was found to be significantly associated with a 32% decrease in breast cancer risk, relative to women aged less than 14 years at menarche.
8.12.2.2 Age at 1st (live) birth

Older age at 1st live birth (Negri et al) or at 1st birth (Nagata et al 1995) was associated with significant increases in breast cancer risk in both studies. In the first of the studies, women aged between 22-24 years, 25-27 years and 28 years or over had increases in risk of 22%, 40% and 75%, respectively, relative to women aged less than 22 years (Negri et al 1988). In the second study, women aged between 25-29 years, 30-34 years and 35 years or more had odds ratios of 1.32, 1.71 and 2.26, relative to women aged under 24 years and younger years (Nagata et al 1995).

8.12.2.3 Parity

In both studies increased parity was found to be associated with a decrease in breast cancer risk, with significant decreases in risk of 38% in women who reported 5 or more live births (Negri et al 1988), and 32% in women who reported 3 or more births (Nagata et al 1995), compared to women who reported one birth.

8.12.2.4 Menopausal status

In the first of the studies (Negri et al 1988), women who experienced an earlier menopause (aged between 45-49 and less than 45 years) had a 23% and a 27% decrease, respectively, in breast cancer risk, relative to women who were aged 50 years or over at menopause. In the second study (Nagata et al 1995), no increased breast cancer risk was observed in women aged 50 or more at menopause compared to women aged under 50 years. However, premenopausal women were found to have a 2-fold increase in breast cancer risk relative to women aged under 50 years at menopause.

8.12.2.5 Women with a family history

The Collaborative reanalysis found that the relationships between risk factors for women with a family history were similar to those for women without a family history.

8.12.3 Comment

Women who reach menarche (the first menstrual period) at a relatively early age (12 or younger) and those who reach menopause at a relatively late age (55 or older) are more likely than other women to develop breast cancer. Nulliparity and late age at first birth both increase lifetime incidence of breast cancer. These relationships are believed to be mediated through estrogen produced within the woman’s body. During the reproductive years, a woman’s body produces high levels of estrogen. Women who start to menstruate at an early age and/or reach menopause at a late age are exposed to high levels of estrogen for more years than are women who have a late menarche or early menopause. Another aspect of reproductive history that is associated with breast cancer risk is age at first pregnancy. Women who have their first full-term pregnancy at a relatively early age have a lower risk of breast cancer than those who never have children or those who have their first child relatively late in life. Pregnancy may lead to lasting changes in the sensitivity of breast tissue to cancer-causing agents, as well as in the maturation of breast tissue. In addition, several hormonal changes occur after a full-term pregnancy and may persist for years.
9. Audit criteria

The measures that could be used as a basis for audit are in the table overleaf.
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Standard</th>
<th>Exception</th>
<th>Definition of terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard written information should be developed for use in primary,</td>
<td>100% of centres to provide this information</td>
<td>Nil</td>
<td>Written information that will provide consistent advice to women, including risk</td>
</tr>
<tr>
<td>secondary and tertiary care</td>
<td></td>
<td></td>
<td>and breast awareness information, lifestyle advice etc.</td>
</tr>
<tr>
<td>Local protocols should be developed with clear referral mechanisms</td>
<td>100% of organisations should have local protocols</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>between primary, secondary and tertiary care and with appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>facilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological services available in secondary care</td>
<td>100% of secondary care have a named individual providing psychological</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information should be provided about the potential advantages and</td>
<td>100% of women who are offered mammographic surveillance</td>
<td>Nil</td>
<td>Information includes written information and discussion on</td>
</tr>
<tr>
<td>disadvantages of mammographic surveillance</td>
<td></td>
<td></td>
<td>▪ Reduced sensitivity in younger breasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Radiation risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Possible psychological impact of recall visit</td>
</tr>
<tr>
<td>Risk-reducing surgery should be managed by a multidisciplinary team</td>
<td>100% women who have risk reducing surgery</td>
<td></td>
<td>Risk-reducing surgery refers to bilateral mastectomy and oophorectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A multidisciplinary team should include:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ facilities to verify family history and clinical genetic risk assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ mammography before surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ psychological assessment and counselling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ information about support groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>oncoplastic/breast reconstructive skills</td>
</tr>
</tbody>
</table>
Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

\[
\text{Number of patients whose care is consistent with the criterion plus number of patients who meet any exception listed} \times 100
\]

\[
\frac{\text{Number of patients to whom the measure applies}}{100}
\]

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.
10. Research issues

This subject would benefit from further research in most areas. The guideline development group identified the following areas which they felt would help improve the evidence base for future versions of this guideline.

1. Validation of risk assessment models is urgently needed.
2. Different risk communication strategies should be evaluated.
3. Prospective studies are needed of the short and long terms psychosocial and sexual impact of risk reducing surgery in women with a family history of breast cancer.
4. Costs and benefits of surveillance in the 30-40 years age groups should be assessed by national pooling of all UK data.
5. The effectiveness of MRI as a surveillance technique, especially in high risk women / gene carriers.
6. The effectiveness of surveillance, in particular mammography, in those aged 40-49 years.
7. Endocrine prevention studies (tamoxifen, aromatase inhibitors) would be valuable.
8. Relative effectiveness of different methods of gene mutation testing.
9. The role and usefulness of computer packages in risk assessment, audit and other aspects of care would be useful.
11. Selected glossary

This glossary was developed for accompanying Information for the Public.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age-specific risk</strong></td>
<td>The estimated risk of developing the disease in the next year based on a specific age. This is usually calculated over the five or ten year intervals.</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td>Both sides, in this case referring to both breasts or ovaries.</td>
</tr>
<tr>
<td><strong>Breast Cancer Genes</strong></td>
<td>To date, three genes have been found that, if faulty, can result in the individual having an increased risk of breast cancer. These are called BRCA1, BRCA2 and TP53. There are probably other genes as yet undiscovered that affect the risk of breast cancer. There may also be interactions between genes and with the environment.</td>
</tr>
<tr>
<td><strong>Breast Reconstruction</strong></td>
<td>An operation carried out following a mastectomy to recreate the breast mound. This may be carried out at the same time as the mastectomy (immediate reconstruction) or at a later date (delayed reconstruction). Breast reconstruction can involve more than one operation. These are different methods of reconstruction. Some use the woman’s own tissue either from her back or her abdomen. Others require the insertion of implants usually made of silicone. Operations can also be carried out to recreate the nipple and the surrounding areola.</td>
</tr>
<tr>
<td><strong>Cancer centre</strong></td>
<td>Cancer services are based in cancer centres. Such centres provide the entire spectrum of cancer care – both on-site and to associated cancer units.</td>
</tr>
<tr>
<td><strong>Care plan</strong></td>
<td>A document which details the care and treatment that a patient/user receives and identifies who delivers the care and treatment.</td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>An individual who has a blood relative with the disease or condition. In this case it refers to having a blood relative who has developed breast cancer. It does not necessarily mean and increased risk compared to women in the general population.</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>A gene is like a book with many words. A fault can be the result of ▪ a ‘spelling’ mistake which alters the message, this is called a mutation. ▪ a missing ‘word’ or ‘phrase’, this is called a deletion.</td>
</tr>
<tr>
<td><strong>GP</strong></td>
<td>General Practitioner.</td>
</tr>
<tr>
<td><strong>Hormone Replacement Therapy</strong></td>
<td>Female hormones administered as tablets or patches and replacing the normal female hormones (oestrogen and progesterone) after a natural menopause (the stopping of periods) or induced menopause (removal of the ovaries often at the time of a hysterectomy).</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>The production of images of organs or tissues using radiological procedures, e.g. x-rays, ultrasound and MRI scans.</td>
</tr>
<tr>
<td><strong>Investigation</strong></td>
<td>A medical procedure to assist diagnosis.</td>
</tr>
<tr>
<td><strong>Lifetime risk</strong></td>
<td>The estimated risk of an individual woman developing the disease during her lifetime assuming she lives to the age of 80.</td>
</tr>
<tr>
<td><strong>Mammogram</strong></td>
<td>An x-ray which can detect changes in the breast often at an early stage.</td>
</tr>
</tbody>
</table>
before a lump (which may be a breast cancer) can be felt.

**Mastectomy**

An operation aiming to remove all of the breast tissue. When the operation is performed on both breasts it is bilateral. There are two different types of mastectomy:

Simple Mastectomy aims to remove all of the breast. This includes the breast tissue and the nipple and surrounding areola.

Subcutaneous Mastectomy removes the majority of the breast tissue but leaves the nipple and areola and some underlying breast tissue.

**Magnetic resonance imaging (MRI)**

A special imaging technique used to visualise internal structures of the body. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then monitors the summation of the spinning energies within living cells. Images are very clear and are particularly good for soft tissue.

**NHS Breast Screening Programme (NHSBP)**

A service that provides free breast screening every three years for all women in the UK aged 50 and over. Women aged between 50 and 64 are routinely invited for breast screening every three years; and work is being carried out to extend the programme to women up to and including the age of 70 by 2004. Once women reach the upper age limit for routine invitations for breast screening, they are encouraged to make their own appointment.

**Oophorectomy**

The surgical removal of an ovary. When both ovaries are removed, it is bilateral. The operation may often be carried out using laproscopic (“keyhole”) surgery. If a hysterectomy (removal of the uterus or womb) is being carried out at the same time then it will be an open operation rather than laproscopic surgery (leaving an abdominal scar).

**Osteoporosis**

A reduction in bone mass which can lead to bones breaking easily.

**Primary tumour**

Original site of the cancer; the first.

**Prophylaxis**

The prevention of disease; preventive treatment. Interventions to prevent an unwanted outcome.

**Protocol**

A policy or strategy which defines appropriate action. Also covers the adoption, by all staff, of national or local guidelines to meet local requirements in a specified way, resulting in what are known as local protocols.

**Recurrence**

Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.

**Relatives - First degree relatives**

These are the closest blood relatives (relatives by marriage do not count). These include father, mother, son, daughter, brother, sister. They are on both the mother and father’s side of the family.

**Relatives – Second degree relatives**

These are blood related grandparents, grandchildren, uncle, aunt, first cousin, nephew and niece. They are on both the mother and father’s side of the family.

**Relatives - Third degree relatives**

These are blood related great grandparents, great grandchildren, great uncle, great aunt, children of great uncle or great aunt, second first cousin, children of first cousin, grand nephew and grand niece. They are on both the mother and father’s side of the family.

**Risk**

Being at risk of breast cancer means that there is a possibility that the...
person will develop the disease, but doesn’t necessarily mean that it will happen.

**Risk factor**

A clearly defined occurrence or characteristic that, in research studies of similar people, has been associated with the increased rate of a subsequently occurring disease or health problem. Risk factors include aspects of personal behaviour, lifestyle, environmental exposure, or inborn or inherited characteristics, which are known to be associated with the disease.

**Risk - Average risk**

Women who do not have a family history have a 1 in 11 chance of developing breast cancer by the age of 80 – this is a frequency of 9% in the population. This is average risk.

**Risk - High Risk**

Risk is estimated based on family history. High risk of developing breast cancer is defined as an estimated risk of:
- greater than 8% between age 40 and 50 years
- or a lifetime risk of 30% or greater

High risk also includes a 20% or greater chance of a faulty **BRCA1, BRCA2** or **TP53** gene in the family. (If, however, a person has a genetic test and is found not to be carrying the identified faulty gene, their risk is then, in most cases, average.)

Less than 1% of women will have are at high risk of developing breast cancer.

**Risk - Moderate risk**

When the frequency of breast cancer within a family suggests that there may be a faulty gene or combinations of genes that are passed down through generations and may contribute to the development of breast cancer. Moderate family history is more common than strong family history and accounts for an estimated 20% of all breast cancers. However, relatively little is currently understood about this form of familial breast cancer and it cannot currently be identified through genetic testing.

Moderate risk of developing breast cancer is defined as a risk of:
- 3–8% between age 40 and 50 years
- or a lifetime risk of 17% or greater but less than 30%.

**Specialist**

Person who is an expert in the subject.

**Trial or Clinical Trial**

Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease.

**X-ray**

An imaging technique that uses energy beams of very short wavelengths that can penetrate most substances except heavy metals. This is the most common form of imaging technique used in clinical practice everywhere in the world, with the image captured on photographic film.
12. References


The classification and care of women at risk of familial breast cancer


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