National Institute for Health and Care Excellence

Final

Addendum to Clinical Guideline 164, Familial breast cancer

Clinical Guideline Addendum 164.1

Methods, evidence and recommendations

March 2017

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the NICE surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the committee are joined by up to 6 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the committee' is referred to, this means the entire committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in appendix A. The committee members' declarations of interest can be found via appendix B.

1 Summary section

1.1 Update information

The NICE guideline on familial breast cancer (NICE clinical guideline CG164) was reviewed in November 2015 as part of NICE's routine surveillance programme to decide whether it required updating. New evidence on chemoprevention was found that may have an impact on current recommendations. The aim of this update was to review new evidence in this area.

The review question that the committee considered was:

1) What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

The original guideline can be found here.

The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.21 Recommendations

1. Healthcare professionals within secondary care or specialist genetic clinics should discuss the absolute benefits and risks of options for chemoprevention with women at high or moderate risk of breast cancer. Discussion, using a decision aid, should include the following to promote shared decision-making and informed preferences:

- the reduced risk of invasive breast cancer
- the lack of effect on mortality
- the side effects of the different options
- alternative approaches, such as surveillance alone and, for women at high risk, risk-reducing surgery.

Women should also be given information in an accessible format. [2013, amended 2017]

<u>Recommendations about chemoprevention for women at high risk of breast cancer</u>

2. **Offer tamoxifen[a] for 5 years to premenopausal women at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [2017]**

3. **Offer anastrozole[b] for 5 years to postmenopausal women at high risk of breast cancer unless they have severe[c,d] osteoporosis. [2017]**

4. **For postmenopausal women at high risk of breast cancer who have severe[c] osteoporosis or do not wish to take anastrozole:**
   - offer tamoxifen[a] for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, or
   - consider raloxifene[e] for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. [2017]

5. **Do not offer chemoprevention to women who were at high risk of breast cancer but have had bilateral risk-reducing mastectomy. [2013, amended 2017]**

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a At the time of publication (March 2017), tamoxifen did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. Licensing arrangements remained unchanged when the guideline was updated (November 2016).

b At the time of publication (March 2017, anastrozole did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

c In this guideline severe osteoporosis is defined as having a T-score of at least –2.5 SD as measured by DEXA (dual-energy X-ray absorptiometry).This definition is in line with that used by the WHO and in the NICE technology appraisal guidance on the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160), which is 'T-score equal to or less than –2.5 SD, in the presence of one or more documented fragility fractures'. The T-score is a measure of how far a person's bone mineral density is below the mean value of young adults.

d The summary of product characteristics for anastrozole indicates that women with osteoporosis or at risk of osteoporosis should have their bone mineral density assessed when starting treatment and then at regular intervals. Treatment or prophylaxis for osteoporosis should be started when needed and carefully monitored.

e At the time of publication (March 2017), raloxifene did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Recommendations about chemoprevention for women at moderate risk of breast cancer

6. **Consider tamoxifen[a] for 5 years for premenopausal women at moderate risk of breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [2017]**

7. **Consider anastrozole[b] for 5 years for postmenopausal women at moderate risk of breast cancer unless they have severe[c,d] osteoporosis. [2017]**

8. **For postmenopausal women at moderate risk of breast cancer who have severe[c] osteoporosis or do not wish to take anastrozole:**
   - consider tamoxifen[a] for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, or
   - consider raloxifene[e] for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. [2017]

Recommendations for all women taking drugs for chemoprevention

9. **Do not continue chemoprevention beyond 5 years in women with no personal history of breast cancer. [2013, amended 2017]**

1.3 Patient-centred care

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.4 Methods

This update was developed based on the process and methods described in Developing NICE guidelines: the manual.

2 Evidence review and recommendations

2.1 Introduction

The NICE guideline on familial breast cancer was reviewed in 2015 by the surveillance team and new evidence (2 RCTs) on chemoprevention was identified that mandated an updated review of this topic. The review question was covered in two protocols (appendix C) as follows:

- Protocol 1a focused on the efficacy and is RCT based
- Protocol 1b focused on the adverse effects and is based on both long-term RCT's and observational studies to ensure the whole evidence base for adverse events is reviewed

The protocols were separated out for transparency purposes for searching and sifting and the findings from both parts of the review were presented and interpreted together with a single LETR table and a single set of recommendations.

2.2 Review question

What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

2.3 Clinical evidence review

An update search was conducted (see appendix D) which identified 2177 articles. The titles and abstracts were screened and 64 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 60 were excluded as they did not meet the criteria. An additional 8 studies from the original guideline were also excluded for not meeting the update inclusion criteria, bringing the total number of excluded studies to 68. Four new studies from the update search met the criteria and were included with an additional 8 studies from the original guideline (total included therefore = 12 studies).

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.3.1 Methods

For a summary of the review protocol and methods, please refer to appendix C.

The committee noted published MIDs were not identified in the literature or original guideline and the topic experts were not aware of any published thresholds. The GRADE defaults were not thought to be appropriate to use given one topic expert highlighted that the minimally important difference ought to be an absolute risk not a relative risk as this is deemed more clinically useful. The topic experts further highlighted the perception of risk is very subjective and varies among individuals. In this circumstance, the committee selected the line of no effect as the MID on which imprecision was assessed.

Overall summary of evidence

The 12 included studies covered the following comparisons:

- Tamoxifen versus placebo : 4 studies in 8 publications

- Tamoxifen versus raloxifene : 1 study in 2 publications Anastrozole versus placebo : 2 studies in 4 publications

Some studies covered more than one comparison and so appear more than once both above and in the summary of included studies (table 1 below) - for the full evidence tables please see appendix G and for full GRADE profiles please see appendix H.

For studies where there were more than one publication of the same cohort, only the most updated analysis has been included in the meta-analyses (to avoid double counting of data) unless the study reported on additional outcomes not covered by the updated analysis.

Overall, the quality of the evidence ranged from very low to high. Typical reasons for downgrading included randomisation or blinding not described in detail, adverse events data collected by self report and imprecision in the effect estimates.

1 **Table 1: Summary of included studies**

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Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
Tamoxifen versus placebo studies				
Cuzick 2015 (reported in 4 papers) RCT	7,154 pre- and postmenopausal women from the IBIS-1 trial aged between 35-70 who were at high risk of breast cancer based on family history	Tamoxifen 20mg vs placebo for 5 years	• Development of invasive cancer • Development of ductal carcinoma in situ • Non-adherence to chemoprevention • Overall survival • Adverse events	• 97% had family history of breast or related cancers.
Fisher 2005 (reported in 2 papers) RCT	13,207 women aged between 35-69 who were at a high risk of breast cancer. Menopausal status not reported.	Tamoxifen 20mg vs placebo for 5 years	• Development of invasive breast cancer • Development of DCIS • Non-adherence to chemoprevention • Overall survival • Adverse events	• Roughly 75% from each arm of the study had a family history of breast or related cancers. • For the outcome 'development of invasive breast cancer' this study reported data specifically for the subgroup with family history of breast or related cancers; the data for this particular outcome therefore appears within the direct evidence GRADE tables (table H.1) and has not been downgraded for indirectness.
Powles 1998 RCT	2471 postmenopausal women aged between 30 and	Tamoxifen 20mg vs placebo for 8 years	• Development of invasive breast cancer,	-

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
	70 with an increased risk of breast cancer because of family history		• development of ductal carcinoma in situ • Non-adherence to chemoprevention • Overall survival • Adverse events	
Fallowfield 2001 Prospective cohort study	488 pre- and postmenopausal women who were recruited into 2 RCTs investigating Tamoxifen compared to placebo for those where at high risk of breast cancer based on family history	Tamoxifen 20mg vs placebo for at least 5 years	• Non adherence to chemoprevention • Adverse events	Prospective cohort study of participants recruited into 2 trials (the TAMOPLAC and IBIS trials)
Anastrozole versus placebo studies				
Cuzick 2014 (reported in 3 papers) RCT	3,864 postmenopausal women from the IBIS-2 trial at increased risk of breast cancer based on family history.	Anastrozole 1mg/day versus placebo for 5 years	• Adverse events • Non-adherence to chemoprevention	-
Sestak 2012 Secondary analysis of RCT	1,145 postmenopausal women from IBIS-2 trial at increased risk of	Anastrozole 1mg/day versus placebo for 5 years.	• Adverse events	-

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
	breast cancer based on family history			
Tamoxifen versus raloxifene studies				
Vogel 2010 (reported in 2 papers) RCT	19,471 women aged ≥35 years and postmenopausal who were at a high risk of breast cancer	Tamoxifen 20mg daily versus Raloxifene 60mg daily vs for 5 years maximum.	• Development of invasive breast cancer • Development of ductal carcinoma in situ • Non-adherence to chemoprevention • Overall survival • Adverse events	• 71% from each arm of the study had family history of breast or related cancers. • For the outcome 'development of invasive breast cancer' this study reported data specifically for the subgroup with family history of breast or related cancers; the data for this particular outcome therefore appears within the direct evidence GRADE tables (table H.3) and has not been downgraded for indirectness.

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2.41 Health economic evidence review

2.4.12 Methods

3 Evidence of cost effectiveness

4 The Committee is required to make decisions based on the best available evidence of both
5 clinical and cost effectiveness. Guideline recommendations should be based on the expected
6 costs of the different options in relation to their expected health benefits rather than the total
7 implementation cost.

8 Evidence on cost effectiveness related to the key clinical issues being addressed in the
9 guideline update was sought. The health economist undertook a systematic review of the
10 published economic literature.

11 Economic literature search

12 A systematic literature search was undertaken to identify health economic evidence within
13 published literature relevant to the review questions. The evidence was identified by
14 conducting a broad search relating to chemoprevention for familial breast cancer in the NHS
15 Economic Evaluation Database (NHS EED) and the Health Technology Assessment
16 database (HTA). The search also included Medline and Embase databases using an
17 economic filter. Studies published in languages other than English were not reviewed. The
18 search was conducted on 17th May 2016. The health economic search strategies are detailed
19 in appendix K.

20 The health economist also sought out relevant studies identified by the surveillance review or
21 Committee members.

22 Economic literature review

23 The health economist:

24 • Identified potentially relevant studies for each review question from the economic search
25 results by reviewing titles and abstracts. Full papers were then obtained.
26 • Reviewed full papers against pre-specified inclusion and exclusion criteria to identify
27 relevant studies.
28 • Extracted key information about the studies' methods and results into full economic
29 evidence tables (appendix N).
30 • Generated summaries of the evidence in economic evidence profiles.

31 Inclusion and Exclusion criteria

32 Full economic evaluations (studies comparing costs and health consequences of alternative
33 courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence
34 analyses) and comparative costing studies that address the review question in the relevant
35 population were considered potentially includable as economic evidence.

36 Studies that only reported burden of disease or cost of illness were excluded. Literature
37 reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and
38 studies not in English were excluded.

39 Remaining studies were prioritised for inclusion based on their relative applicability to the
40 development of this guideline and the study limitations. For example, if a high quality, directly
41 applicable UK analysis was available, then other less relevant studies may not have been

included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix M).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

Table 2 explains the information contained in the economic evidence profile.

Table 2: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.

Item	Description
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, new economic analysis was undertaken by the health economist.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- As the cost effectiveness of chemoprevention has been demonstrated by previous economic analyses, the new economic evaluation consisted of a simplified cost consequences model. Wherever possible, methods were consistent with the NICE reference case.
- The Committee was involved in the design of the model, selection of inputs and interpretation of results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, Committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was quality assured by another health economist within NICE's Centre for Clinical Practice.

Full methods for the cost-effectiveness analysis conducted for this guideline are described in appendix O.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the

'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*. As the evaluation in this analysis was a cost consequences analysis rather than a cost utility analysis, outputs were reported in terms of incremental cost per breast cancer case prevented, rather than the incremental cost per QALY. Therefore, results were not directly comparable to a £20,000 per QALY threshold. However, the analysis did present results in terms of the QALY gain required per breast cancer case averted in order for each intervention to be cost effective at a £20,000 threshold. This allowed committee members to assess the likely cost effectiveness of interventions according to their experience of the disease area.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.2 Results of the economic literature review

The search returned 487 articles. 479 of these were excluded based on title and abstract. Full papers were obtained for 8 articles. 7 of these studies were subsequently excluded, with 1 article included in the health economic evidence review. Additionally, a relevant economic model produced for the 2013 familial breast cancer update was identified. Table 3 contains the economic evidence profile for this review question summarising the results of the studies included in the systematic review and modelling conducted for the previous guideline. Full economic evidence tables are contained in appendix N.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix L. Appendix M contains a list of excluded studies and the reason for their exclusion.

2.4.3 Economic modelling

2.4.3.1 Introduction

Novel economic modelling was undertaken for this review question. The full report of the economic model developed for this update is provided in appendix O.

The objective of the model was to investigate the cost effectiveness of aromatase inhibitors compared to no chemoprevention, and compared to anastrozole and raloxifene in high- and moderate-risk patients eligible for any of these treatments. The economic analysis was based on the model developed for the 2013 update to this guideline.

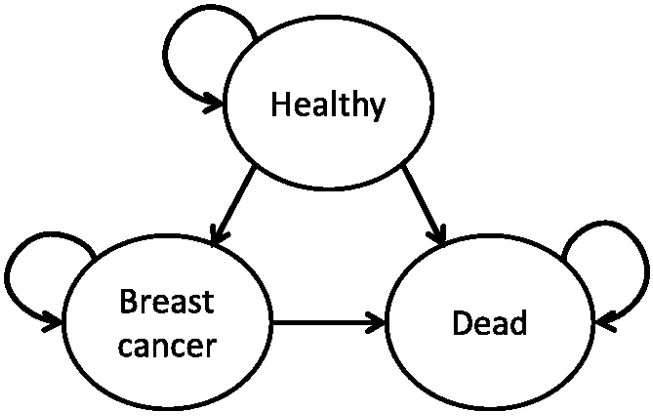
2.4.3.2 Methods

The model considered treatment of postmenopausal women of age 50 and above with 20mg tamoxifen, 60mg raloxifene, or 1mg anastrozole administered once-daily over a five year period, with no chemoprevention as the comparator. A lifetime time horizon was used in order to estimate all costs and health outcomes associated with treatment.

The model used a Markov structure with a cycle length of one year in order to estimate the incidence of breast cancer and mortality over patients' lifetimes, as shown in Figure 1. The

model also considered the annual incidence of adverse events associated with chemoprevention: endometrial cancer, venous thromboembolism, and fractures.

Figure 1: Model structure



For the no treatment arm of the model, age-specific incidence rates of breast cancer and baseline mortality were used to inform progression probabilities. Baseline rates from the clinical review were used to inform the annual probability of adverse events. For the treatment arms of the model (tamoxifen, raloxifene, and anastrozole) relative risks derived from the results of the clinical literature review were applied to baseline rates of breast cancer and adverse events in order to derive treatment-specific rates.

The assumption was made that 50% of patients receiving chemoprevention discontinued treatment after one year. It was assumed that these patients did not receive any of the benefits or risks associated with treatment – i.e. incidence of breast cancer and adverse events were the same as for patients receiving no treatment.

It was assumed that the benefits of chemoprevention (in terms of breast cancer risk reduction) persisted for the remainder of patients' lives (as clinical evidence shows that chemoprevention reduces the long-term incidence of breast cancer), but that relative risks for endometrial cancer and thromboembolic events returned to baseline levels after the end of treatment, and relative risks for fractures returned to baseline five years after the end of treatment.

The following costs were included in the model:

- Chemoprevention drugs
- Chemoprevention monitoring – assumed to comprise two GP consultations per year for the duration of treatment
- Breast cancer treatment (including radiotherapy, chemotherapy, and drug costs)
- Endometrial cancer treatment
- Thromboembolic event treatment
- Fracture treatment (consisting of common osteoporotic fracture categories: hip fracture, wrist fracture, vertebral fracture, and other fractures)
- DEXA scans – it is assumed that all patients treated with anastrozole receive a DEXA scan at the outset of treatment, due to concerns of bone mineral density reduction associated with aromatase inhibitor treatment

As well as reporting results deterministically, one-way and probabilistic sensitivity analyses were carried out in order to characterise uncertainty in the results.

2.4.3.31 Results

Incremental results compared to no chemoprevention per 1,000 patients are presented in Table 3 for high-risk patients and Table 4 for moderate-risk patients. Results show that, for both high- and moderate-risk patient populations, anastrozole results in considerably fewer breast cancer cases and lower costs than tamoxifen and raloxifene. For the high risk population, anastrozole results in a negative incremental cost per breast cancer case prevented compared to no treatment of -£984, compared to values of £4,621 and £25,387 for tamoxifen and raloxifene respectively. For the moderate risk population, anaztrozole has an incremental cost per breast cancer case prevented of £2,314, compared to values of £9,606 and £36,566 for tamoxifen and raloxifene. The relative cost effectiveness of anastrozole occurs because the cost of breast cancer treatment comprises the majority of total costs for each intervention, and therefore treatments which produce greater reductions in the incidence of breast cancer also produce greater cost savings.

For the high-risk cohort of patients, anastrozole produces cost savings compared to no chemoprevention. This is not the case for the cohort of moderate-risk patients, where the lower baseline risk of breast cancer results in fewer prevented breast cancer cases, and therefore smaller cost savings. However, in absolute terms, incremental costs per breast cancer case prevented are low for anastrozole in the moderate-risk cohort, indicating that these treatments are likely to be cost effective.

Incremental adverse events were identical between high- and moderate-risk patient cohorts. Results showed that numbers of endometrial cancer cases and thromboembolic events were similar between all chemopreventive agents, although tamoxifen was associated with 2 more thromboembolic events per 1,000 patients than raloxifene and anastrozole. Anastrozole was associated with an increase in the number of hip fractures compared to no treatment, whereas tamoxifen and raloxifene both showed a reduction in fractures. However, the increase in fractures associated with anastrozole was relatively small in absolute terms (4 additional fractures per 1,000 patients compared to no treatment).

One-way sensitivity analyses (results of which are displayed in Table 5 and Table 6) showed for both patient cohorts that results are sensitive to parameters which affect the baseline incidence, relative risk, or cost of breast cancer. Results were also sensitive to changes in assumed patient adherence. Results were relatively insensitive to parameters which affect adverse events, including extending the persistence of relative risks associated with adverse events to 20 years after the end of treatment. Removing costs of chemotherapy for breast cancer from the model (in order to reflect the fact that ER-positive breast cancer – the type of cancer prevented by chemoprevention – is typically less responsive to chemotherapy, and is therefore less likely to be used in treatment) caused a moderate increase in ICERs of all treatments, although not of a degree likely to affect decision making. Replacing model inputs on the relative incidence of breast cancer and adverse events for raloxifene with data from the RUTH trial (comparing raloxifene to placebo) resulted in raloxifene being considerably more cost effective. This sensitivity analysis was included as the committee felt that the data comparing raloxifene to tamoxifen may not fully reflect the effectiveness of raloxifene, given that outcomes for trials comparing raloxifene with placebo are typically more favourable than those comparing raloxifene to tamoxifen.

Mean results of 1,000 probabilistic iterations for high- and moderate-risk patients are displayed in Table 7 and Table 8. These results generally show that mean probabilistic results are consistent with deterministic results. The spread of the probabilistic iterations shows that results are generally robust. For high-risk patients, anastrozole has the highest probability of being the most cost effective treatment at any cost per breast cancer case prevented threshold. Anastrozole is also associated with a 59% probability of being cost-saving compared to no treatment. Results for moderate-risk patients showed a similar pattern, although with a trend for fewer incremental breast cancer cases prevented and higher incremental costs. Anastrozole was associated with a lower probability of being cost

saving compared to no treatment (18%). However, there was a high degree of certainty around the effectiveness of anastrozole, with 100% of iterations resulting in fewer breast cancer cases than no treatment.

2.4.3.44 Conclusion

The results of this cost consequences analysis show that anastrozole is likely to be cost effective in preventing breast cancer in both high- and moderate-risk postmenopausal women. For both populations, anastrozole resulted in both fewer breast cancer cases and lower total costs than tamoxifen and raloxifene.

Compared to no treatment, tamoxifen is also likely to be a cost effective strategy for both high- and moderate-risk patient groups. In the base case analysis, the cost effectiveness of raloxifene is less clear, due to relatively high incremental costs per breast cancer case prevented. However, using data from the RUTH trial in the sensitivity analysis results in a considerable increase in cost effectiveness, indicating a high degree of uncertainty around the results for raloxifene.

Although aromatase inhibitors are associated with a higher incidence of fractures than both no treatment and the other chemopreventive agents included in the analysis, this number is small in absolute terms, and any harm is likely to be offset considerably by the benefit of prevented breast cancer cases.

Results have shown that all chemopreventive agents are more cost effective in high-risk patients. However, the incremental cost per breast cancer case prevented for anastrozole is sufficiently low for moderate-risk patients (£2,314) treatment is likely to be cost effective for this population as well.

Table 3: Deterministic results for high-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Costs and effects per 1,000 patients			
Total incremental cost	£97,346	£237,865	-£34,539
Breast cancer cases prevented	21	9	35
Incremental cost per breast cancer case prevented	£4,621	£25,387	-£984
QALYs required per breast cancer case to be cost effective at £20,000/QALY threshold	0.23	1.27	dominant
Adverse events per 1,000 patients			
Incremental endometrial cancer cases	1	0	0
Incremental thromboembolic events	3	1	1
Incremental fractures	-4	-7	4

Table 4: Deterministic results for moderate-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Costs and effects per 1,000 patients			
Total incremental cost	£154,647	£263,180	£61,743
Breast cancer cases prevented	16	7	27
Incremental cost per breast cancer case prevented	£9,606	£36,566	£2,314
QALYs required per breast cancer case to be cost effective at £20,000/QALY threshold	0.48	1.83	0.12
Adverse events per 1,000 patients			
Incremental endometrial cancer cases	1	0	0
Incremental thromboembolic events	3	1	1
Incremental fractures	-4	-7	4

Table 5: One-way sensitivity analysis results – incremental cost per breast cancer case prevented for high-risk post-menopausal patients

Scenario	Tamoxifen	Raloxifene	Anastrozole
Incidence of BC reduced by 50%	£17,316	£54,990	£7,116
Incidence of BC increased by 100%	-£1,916	£10,676	-£5,266
Treatment relative risks for breast cancer incidence set to lower 95% CI	£1,104	£54,056	-£3,542
Treatment relative risks for breast cancer incidence set to upper 95% CI	£12,268	£14,820	£9,919
Adherence set to 100%	£1,948	£18,773	-£3,168
Adherence set to 25%	£9,967	£38,615	£3,385
Incidence of adverse events reduced by 50%	£4,622	£25,948	-£1,090
Incidence of adverse events increased by 100%	£4,607	£24,206	-£759
Treatment relative risks of adverse events set to lower 95% CI	£4,048	£26,395	-£1,490
Treatment relative risks of adverse events set to upper 95% CI	£5,359	£24,642	-£192
Costs of treatment reduced by 50%	£2,178	£18,213	-£1,609
Costs of treatment increased by 100%	£9,508	£39,736	£268
Costs of adverse events reduced by 50%	£4,620	£25,939	-£1,089
Costs of adverse events increased by 100%	£4,624	£24,284	-£773
Costs of breast cancer reduced by 50%	£9,744	£30,531	£4,114
Costs of breast cancer increased by 100%	-£5,624	£15,099	-£11,179
Relative risks of adverse events persist for 20 years after end of treatment	£5,034	£24,788	-£848
Breast cancer treatment is associated with no chemotherapy costs	£7,291	£28,068	£1,674
Relative risks for raloxifene taken from the RUTH trial	-	£668	-

Table 6: One-way sensitivity analysis results – cost per breast cancer case prevented per 1,000 moderate-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Incidence of BC reduced by 50%	£26,959	£77,256	£13,338
Incidence of BC increased by 100%	£797	£16,271	-£3,358

	Tamoxifen	Raloxifene	Anastrozole
Treatment relative risks for breast cancer incidence set to lower 95% CI	£5,031	£73,744	-£1,032
Treatment relative risks for breast cancer incidence set to upper 95% CI	£19,536	£22,858	£16,492
Adherence set to 100%	£6,109	£27,956	-£561
Adherence set to 25%	£16,601	£53,787	£8,064
Incidence of adverse events reduced by 50%	£9,607	£37,296	£2,174
Incidence of adverse events increased by 100%	£9,588	£35,028	£2,610
Treatment relative risks of adverse events set to lower 95% CI	£8,856	£37,878	£1,648
Treatment relative risks of adverse events set to upper 95% CI	£10,572	£35,597	£3,356
Costs of treatment reduced by 50%	£6,409	£27,227	£1,490
Costs of treatment increased by 100%	£16,001	£55,246	£3,962
Costs of adverse events reduced by 50%	£9,604	£37,284	£2,176
Costs of adverse events increased by 100%	£9,609	£35,130	£2,591
Costs of breast cancer reduced by 50%	£14,529	£41,504	£7,220
Costs of breast cancer increased by 100%	-£240	£26,691	-£7,497
Relative risks of adverse events persist for 20 years after end of treatment	£10,146	£35,786	£2,493
Breast cancer treatment is associated with no chemotherapy costs	£10,146	£35,786	£2,493
Relative risks for raloxifene taken from the RUTH trial	-	£4,473	-

1

2 **Table 7: Mean PSA results for high-risk post-menopausal patients**

	Tamoxifen	Raloxifene	Anastrozole
Incremental cost (versus no chemoprevention)	£100,699.78	£249,453.45	-£32,489.16
Breast cancer cases prevented	21	9	35
Cost/BC case prevented	£4,758.28	£28,367.96	-£919.36
QALYs required per BC case averted to be CE	0.24	1.42	Dominant

3

Table 8: Mean PSA results for moderate-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Incremental cost (versus no chemoprevention)	£155,098	£266,093	£67,762
Breast cancer cases prevented	16	7	26
Cost/BC case prevented	£9,488	£36,912	£2,569
QALYs required per BC case averted to be CE	0.47	1.85	0.13

Table 9: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Noah-Vanhoucke et al. (2011) Chemoprevention with tamoxifen versus no chemoprevention USA	Partially applicable*	Minor limitations*	Based on the Archimedes Breast Cancer Model (detailed, continuous-time model of breast cancer incidence, tumour growth, detection and spread). Considers patients stratified by risk group (five year incidence of breast cancer).	By risk group: ≥0% = $333.81 ≥0.8% = $255.63 ≥1% = $196.07 ≥1.25% = $98.27 ≥1.66% = -$47.58 ≥2% = -$158.48 ≥3% = -$485.00 ≥4% = -$613.55	QALYs by risk group (per 1,000 treated women): ≥0% = 29.0 ≥0.8% = 38.7 ≥1% = 44.1 ≥1.25% = 57.7 ≥1.66% = 84.8 ≥2% = 112.3 ≥3% = 119.3 ≥4% = 199.8	By risk group: ≥0% = $11,528.05 ≥0.8% = $6,603.31 ≥1% = $4,450.38 ≥1.25% = $1,702 ≥1.66% = Dominates ≥2% = Dominates ≥3% = Dominates ≥4% = Dominates	One-way sensitivity analysis revealed that results are robust to changes to discount rate and costs, whereas ICERs are sensitive to hazard ratios of side effects (particularly endometrial cancer and stroke).
NICE cost consequence analysis (2013 update) Chemoprevention (tamoxifen or raloxifene versus no chemoprevention) UK	Partially applicable†	Minor limitations†	The model assumes that all premenopausal women receiving chemoprevention are treated with tamoxifen, whereas postmenopausal women receive an even split of tamoxifen and raloxifene.	Cost per breast cancer case prevented = £3,010.	N/A	N/A	One-way sensitivity analysis demonstrated that cost per breast cancer case prevented was most sensitive to total cost of breast cancer and relative risk reduction of chemoprevention.

Acronyms:
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

**Study was deemed partially applicable as it was conducted in a non-UK healthcare setting. The analysis was determined to have only minor limitations as the model considered all relevant health outcomes and costs, and used a lifetime time horizon*

†Study was deemed partially applicable as it does not consider all of the relevant comparators, and only considers chemoprevention as an overall strategy, rather than examining the cost effectiveness of individual chemopreventive agents. The analysis was determined to have only minor limitations as the model considered all relevant health outcomes and costs, and used a lifetime time horizon.

2.5 Evidence statements

2.5.1 Clinical evidence statement

Tamoxifen versus placebo (GRADE tables H.1 and H.2)

Four studies (3 RCTs and one prospective cohort study) compared tamoxifen with placebo (n = 488 to 13,207) in women aged 30 to 70. Treatment duration ranged from 5 to 8 years. Low quality evidence from a meta-analysis of the 3 RCTs (n= 19687) indicated tamoxifen is associated with a lower incidence of invasive breast cancer when compared to placebo [RR (95%CI): 0.70 (0.61 to 0.80)]. Moderate quality evidence from a meta-analysis of the 3 RCTs indicated tamoxifen was associated with a lower incidence of ductal carcinoma in situ compared to placebo RR 0.59 (0.44 to 0.78) and also headaches.

High to very low quality evidence from 3 studies found that tamoxifen was associated with a higher rate of different adverse events including hot flushes, vaginal discharge, endometrial cancer and thromboembolic events compared to placebo.

No difference was found for any of the other outcomes and no evidence was identified for the outcome health related quality of life.

Tamoxifen versus raloxifene (GRADE tables H.3 and H.4)

One RCT (n=19,471) included women, aged 35 years of age or older, with or without a family history of breast or related cancers and in women aged 35 years or older compared tamoxifen with raloxifene. Treatment duration was 5 years. Moderate quality evidence indicated that for those with a family history of breast or related cancer (n=13,861) tamoxifen is associated with a lower incidence of invasive breast cancer [RR (95%CI): 0.81 (0.66 to 0.99)].

Moderate quality evidence from the same study also found that tamoxifen showed a higher incidence of thromboembolic events, uterine invasive cancer, cataracts and non-adherence to chemoprevention in those receiving tamoxifen compared to raloxifene however these outcomes related to the whole study population; data for the subgroup with family history was not reported.

No difference was found for any of the other outcomes and no evidence was identified for the outcome health related quality of life.

Anastrozole versus placebo (GRADE table H.5)

One RCT (n=3864) in women aged 45-60 years compared anastrozole with placebo. Treatment duration was 5 years. Moderate quality evidence from this study indicated anastrozole is associated with a lower incidence of invasive breast cancer [RR (95%CI): 0.51 (0.33 to 0.77), ductal carcinoma in situ RR 0.30 (0.12 to 0.75) and improved adherence to chemoprevention at 5 years when compared to placebo.

The same study found a higher incidence of hypertension, musculoskeletal and vasomotor symptoms but a lower incidence of all other cancers (composite outcome) associated with anastrozole compared to placebo.

No significant difference was found for any of the other outcomes and no evidence was identified for the outcome health related quality of life.

2.5.2 Health economic evidence statements

A 2010 cost utility analysis found that treating all postmenopausal patients <55 with tamoxifen produces an ICER of $11,530 (USD) compared to no chemoprevention, and

treating higher risk patients (five-year risk ≥1.66%) results in cost savings as well as additional health benefits. This analysis was considered partially applicable (due to being based on the US healthcare system) and with minor limitations.

A cost consequences analysis undertaken for the 2013 guideline update found that offering tamoxifen to high risk premenopausal patients and tamoxifen or raloxifene to high risk postmenopausal patients results in a cost of £3,010 per breast cancer case prevented. Therefore, chemoprevention is highly likely to be cost effective in this setting. This analysis was considered partially applicable (due to considering chemoprevention treatments jointly, rather than individually) and with minor limitations.

A cost consequences analysis undertaken for this update found that offering high- or moderate-risk postmenopausal patients anastrozole results in fewer breast cancer cases and lower overall costs than tamoxifen or raloxifene. Model base case results indicated that treatment with anastrozole potentially results in a higher number of fractures (4 additional fractures per 1,000 patients compared to no treatment). However, the harm of these adverse events is likely to be more than offset by the benefit gained from the prevention of breast cancer cases, particularly given that the clinical review did not find that anastrozole results in significantly more fractures than no chemoprevention. It should be noted that the number of additional fractures associated with anastrozole produced by the economic analysis differs slightly from the value in the clinical review. This is due to two factors: the economic model estimates the number of fractures over patients' entire lifetime, rather than over the duration of the trial, and the model uses a different baseline fracture rate from that observed in the RCT of anastrosole versus placebo.

2.63 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The aim of this question was to review new evidence on the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer. The committee therefore prioritised the following outcomes for comparing the effectiveness and side effect profile of tamoxifen, raloxifene and aromatase inhibitors with each other, placebo or no treatment: • Development of invasive Breast Cancer • Overall Survival • Development of Ductal carcinoma in situ (DCIS) • Adverse events including but not limited to the following: - Development of cancer at any site - Development of osteoporosis - Incidence of fractures - Incidence of venous thromboembolism - Non-adherence - Mortality (non-cancer + non—breast cancer) - Menopause related symptoms • Health Related Quality of life • Non-adherence to chemoprevention The committee identified development of invasive breast cancer, adverse events and overall survival as critical outcomes for review. It was highlighted that in practice, the 2 most important factors of concern from the patient perspective would be the chances of developing invasive breast cancer and the side effect profile hence why these outcomes were prioritised. Overall survival was selected as an additional critical outcome as

	Committee discussions
	the committee considered it as a counterbalancing outcome that summed up all composite outcomes. The committee however noted that overall survival is a complex outcome that is somewhat difficult to study in trials given the short follow up. The committee also discussed the importance of DCIS in some detail given the idea that picking up cases of high grade DCIS which has a greater chance of becoming invasive breast cancer potentially prevents the need for chemotherapy in the future.
Quality of evidence	Evidence was available for the majority of outcomes identified in the review protocol. No evidence was available for health related quality of life or for the direct comparisons tamoxifen versus anastrozole and raloxifene and anastrozole. The quality of the evidence ranged from high to very low, with most studies categorised as either moderate or high quality. The main reasons for downgrading evidence were concerns of risk of bias in the studies (including randomisation and blinding not described for one study) and serious imprecision. The committee considered that studies in which only a proportion of subjects had family history did not need to be downgraded for indirectness given the majority (generally 70% or more) met the family history criteria. It was hence not expected that the incidence of outcomes chosen for review would differ between those studies in which all had a family history versus those studies in which the majority had a family history. A threshold for proportion with family history was not pre-specified to decide which studies should be included/excluded however all studies in which the number with family history was not reported/not an inclusion criterion were excluded. The committee further felt the adverse events data needed to be interpreted with general caution given the method of data collection (e.g. self-reported questionnaires) and the fact that some studies did not report how such data was collected. Whilst the committee felt the need to review adverse events, they did not think the data relating to headaches informed decision making as headaches were not considered a serious adverse event. Also in studies which looked at a very wide range of adverse events such as cancers at various sites, the committee noted that chance alone would expect to see a significant difference for 1 in 20 outcomes.
Trade-off between benefits and harms	The committee interpreted the evidence from the starting point that the original guideline recommendations relating to chemoprevention split women into various risk categories of high, moderate and low (see appendix R for original risk categories) and menopausal status. Recommendations for pre- and post-menopausal subgroups were not directly informed by the evidence but on the basis of the original guideline recommendations instead which was carried forward in this update based on clinical input from the topic experts. Topic expert advice indicated that tamoxifen is the currently the only drug used in premenopausal women and raloxifene the only drug offered to postmenopausal women with a uterus. The committee noted that providing appropriate written and verbal information on risks and benefits using a patient decision aid would allow women the opportunity to make an informed choice. The committee agreed with the original guideline development group's idea to include specific examples of these risks and benefits within the recommendations to assist in these discussions, including the need to discuss: 1) the reduced risk of invasive breast cancer,

	Committee discussions
	2) evidence of no effect on mortality 3) side effects of different options 4) and approaches such as surveillance and risk reducing surgery. The committee however wished to highlight that risk reducing surgery was specifically for high risk women only – this was not explicit in the original guideline recommendation and has caused some confusion for women at moderate risk who are not eligible for surgery. The committee further emphasised that women would also have the opportunity to discuss their treatment choice, absolute risk and benefits with healthcare professionals within secondary care and/or specialist genetic clinics. <u>Premenopausal women at high risk of breast cancer</u> Moderate to high quality evidence from 2 studies led the committee to agree with the original guideline development group's conclusion that tamoxifen should be offered to premenopausal women at high risk of breast cancer. The committee noted the evidence showed that tamoxifen was effective in reducing the incidence of invasive breast cancer in this group and agreed that this drug could be offered to those at high risk unless they had a past history/increased risk of thromboembolic disease or endometrial cancer. Topic expert input further indicated that this is currently the only drug given to premenopausal women. <u>Postmenopausal women at high risk of breast cancer</u> Moderate to high quality evidence from one new RCT led to the committee offering anastrozole to postmenopausal women at high risk of breast cancer unless there were signs of severe osteoporosis (defined as T score <4 on DEXA scan). Although the RCT on anastrozole versus placebo found no difference in the incidence of fractures, the committee decided to interpret this finding with caution given the study excluded those with a T score <-4. Aromatase inhibitors are known to increase the risk of osteoporosis (see section 3.4 of TA112), bone fractures and musculoskeletal side effects and so the committee did not think the use of this drug was suitable for high risk postmenopausal women with osteoporosis. Instead the committee concluded that for this group or those who do not wish to take anastrazole, tamoxifen could be offered as high quality evidence found it to be more effective than raloxifene and also found that it reduced the incidence of invasive breast cancer when compared to placebo.In line with the original guideline development group's conclusions, whilst tamoxifen was shown to be more effective than raloxifene, the risk of uterine cancer was significantly higher for women taking tamoxifen compared to raloxifene. Therefore, for post-menopausal women at high risk of breast cancer with a uterus, the committee felt that it was appropriate to consider raloxifene as an option unless they have a past history/increased risk of thromboembolic disease or endometrial cancer. Given the overall quality of the evidence for women at high risk of breast cancer and the fact that tamoxifen, raloxifene or anastrozole would do more good than harm to these individuals, the committee agreed to use offer rather than consider for all recommendations except that relating to raloxifene where the action was to consider raloxifene in patients with contraindications for tamoxifen or anastrozole. , The committee further felt the original guideline's recommendation to not offer tamoxifen/raloxifene to women at high risk of breast cancer with a

	Committee discussions
	bilateral mastectomy should be retained. They however felt the need to broaden this recommendation to all chemopreventive agents including anastrozole to reflect the new evidence identified in this update. The committee further wished to highlight the use of a decision aid in recommendation 1.7.20 to promote shared decision making and informed preferences. Pre and post-menopausal women at moderate risk of breast cancer For pre and post-menopausal women at moderate risk of breast cancer, in line with the original guideline development group's conclusions, the committee were less certain of the balance between benefits and harms. They noted the benefits of taking these agents may be less as the risk of getting breast cancer is smaller in this risk group. The committee agreed that it would not be appropriate to prevent women at moderate risk of breast cancer from accessing these drugs, provided they were aware of the risks and benefits. Therefore, the committee agreed that all 3 agents could be 'considered' for women at moderate risk after taking into account the various contraindications. The recommendations for those at moderate risk hence mirrored the recommendations for those at high risk, outlining the same contraindications. Finally, the committee also agreed to retain the original guideline recommendation to not offer chemoprevention beyond 5 years in those with no personal history of breast cancer; this recommendation still stands as all except one of the included studies did not consider chemoprevention beyond 5 years.
Trade-off between net health benefits and resource use	The committee was presented with evidence from two previous economic studies: one cost effectiveness analysis of chemoprevention with tamoxifen in a US population of postmenopausal women aged <55 years, and one cost consequence analysis of chemoprevention with tamoxifen and raloxifene in a high-risk UK population of both pre- and postmenopausal women. Both of these studies indicated that it is likely that chemoprevention is overall a highly cost effective treatment. The former study reported that chemoprevention produces a cost saving over no treatment in high risk women, and the latter study reported a cost of £3,010 per breast cancer case prevented. High- and moderate-risk postmenopausal women The committee considered results of the novel cost consequences analysis developed for this guideline. The evidence indicated that, for high- and moderate-risk postmenopausal women, anastrozole results in fewer breast cancer cases and lower total costs compared to tamoxifen and raloxifene. Anastrozole was also associated with a moderate increase in the number of fractures. Based on this evidence, the committee concluded that postmenopausal women with a high risk of breast cancer without osteoporosis should be offered anastrozole as a first line option, and that anastrozole should be considered as an option for postmenopausal women with a moderate risk of breast cancer without osteoporosis. The novel economic analysis indicated that tamoxifen is likely to be cost effective compared to no treatment (incremental cost per breast cancer case prevented of £4,621 and £9,606 for high- and moderate-risk patients, respectively). As it is also associated with a reduction in the incidence of fractures, the committee concluded that tamoxifen should be offered to postmenopausal women at high or moderate risk of breast cancer with severe osteoposis and without a uterus. In the base case analysis, incremental cost effectiveness results for raloxifene compared to no

	Committee discussions
	treatment were relatively high (incremental cost per breast cancer case prevented of £25,387 and £36,566 for high- and moderate-risk patients respectively), indicating some uncertainty as to whether treatment is cost effective at a threshold of £20,000 per QALY. However, using alternative data inputs from the RUTH trial comparing raloxifene to placebo produced much lower estimates of incremental cost effectiveness ratios. Taking into account this evidence, and the clinical evidence that raloxifene prevents fractures and is associated with a lower risk of endometrial cancer than tamoxifen, the committee concluded that raloxifene should be considered for high- and moderate-risk postmenopausal women with severe osteoporosis and with a uterus.
Other considerations	Although menopausal status was not prioritised by the topic experts for consideration at the review protocol stage, the committee noted that the original recommendations include menopausal status and so this subgroup was subsequently added to the review protocol for consideration. It was however not possible to conduct extra analyses by menopausal status given the small number of studies available for each comparison (please see appendix P). Instead, the commmitte relied on topic expert input to inform such recommendations.The committee did however note that the lack of subgroup analysis by menopausal status in the original studies in turn limited the opportunity to assess premenopausal side effects separately especially given the case that tamoxifen is the only drug recommended for this group. The committee agreed that where possible, the data on other cancers including melanoma ought to be extracted as a composite outcome rather than the numbers for individual cancers themselves. This was because some studies examined a range of other cancers which given the long list of outcomes, increased the probability of avoiding false positives Endometrial cancer however was to be kept as a separate outcome given the pro-oestrogen effect of tamoxifen on the uterus compared to raloxifene. Non-melanoma skin cancer was also excluded from the composite outcome and not reported separately either due to the committee's concern that the data is often skewed as this cancer is very common but poorly reported. The topic experts queried the exclusion of the MAP3 study (Maunsell et al, 2014) and questioned whether all studies that look at risk should be included regardless of family history. Though the use of Gail risk score which incorporates family history was an additional eligibility criterion, it is unclear for how many subjects this data was available as it was optional inclusion criterion and no subgroup analysis for those with family history was performed. The technical team however highlighted that the guideline is defined by familial risk of breast cancer and does not include non-familial factors that increase the risk of breast cancer. Studies which haven't defined risk based on family history/positive genetic tests are therefore outside the inclusion criteria of this update and excluded. The committee were further aware of some indirect evidence from the CORE trial indicating that for women with osteoporosis, raloxifene reduces the incidence of breast cancer examined as secondary outcome by 65%. These trials were not picked up by the update search as the population was those with osteoporosis as opposed to those at risk of breast cancer based on family history. Nevertheless, the topic experts felt the need to highlight this evidence exists as supporting information for the original guideline recommendation on raloxifene.

	Committee discussions
	Although none of the drugs are licensed for chemoprevention in women who do not have diagnosis of breast cancer, the committee felt that evidence of benefit was sufficiently strong to recommend their use for women at high risk of breast cancer. The prescriber should however note that the use of the drugs for chemoprevention would be off-label and follow relevant professional guidance and the General Medical Council's guidance on good practice in prescribing and managing medicines. The committee noted that evidence on other aromatase inhibitors such as exemestane was lacking in those with a family history. The committee decided it was not appropriate to make a broad recommendation to include exemestane as although exemestane and anastrozole are third generation aromatase inhibitors, they are not from an identical class and may therefore have different modes of action. The committee further noted that family history clinics are closing so access to treatment is not straightforward. <u>Equality considerations</u> 1) Those with intellectual disabilities: assessing the mental state/capacity of an individual with intellectual disabilities can be a complex process due to the difficulties associated with determining medical history. Understanding a woman's development and learning disability will therefore affect the assessment and what conclusions can be drawn from it. In light of this, the Committee thought that for those with intellectual disabilities, appropriate assistance such as interpreters/carers should be present when needed to make decision making easier for the individual. Those with intellectual disabilities were thought less likely to seek advice when needed and should hence be encouraged by family members/carers to attend clinics, etc. 2) Pregnancy: the Committee questioned the safety of chemopreventative drugs during pregnancy and noted that it is not advisable to take these drugs during pregnancy or when trying to conceive. An existing recommendation from the original guideline (1.7.29) informs women that they should stop tamoxifen at least 2 months before trying to conceive. This recommendation however does not apply to anastrazole as it is not licensed or routinely used for pre-menopausal women. 3) English not first language: individuals who do not speak English as a first language may not be able to fully describe their medical history in English. Consequently the committee highlighted it may be difficult to accurately establish clinical characteristics and symptom history which could lead to misclassification. This also has implications for discussing and understanding the different treatment options and benefits and harm associated with them. Interpreters where possible should hence be available to assist. 4) Age: Although the inclusion criteria of chemoprevention trials included in the evidence review restricted entry to women aged

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	roughly 30 years and older, the committee agreed not to set a minimum age limit for accessing chemopreventive drugs. The committee did not want to restrict young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. In addition, young age does not reduce the effectiveness of these treatments. Therefore for women of all ages, a full and detailed discussion about the risks and benefits of chemoprevention should be carried out. 5) Written information: The committee noted that providing appropriate written and verbal information on risks and benefits would give women the opportunity to make an informed choice. The committee agreed this could be assisted by a patient decision aid to include specific examples of these risks and benefits. The recommendations also include some specific examples of risks to assist in these discussions, including the need to discuss alternative approaches to chemoprevention such as risk reducing surgery. Facilities to assist those with low literacy/first language not English should be available throughout the process. 6) Religion/culture – the committee noted that in some religions and cultures, cancer is not openly talked about which prevents family members from seeking further help early on. 7) Sex/gender reassignment: the committee noted that although the evidence related specifically to women, breast cancer can also affect men however is much rarer in this group. The committee also discussed gender reassignment as an equality issue given the role chemopreventative drugs could play in reversing gender reassignment for men taking female hormones. 8) Refugees and asylum seekers: the committee also noted that these groups may have limited knowledge of their family history.

2.71 Recommendations

1. Healthcare professionals within secondary care or specialist genetic clinics should discuss the absolute benefits and risks of options for chemoprevention with women at high or moderate risk of breast cancer. Discussion, using a decision aid, should include the following to promote shared decision-making and informed preferences:

- the reduced risk of invasive breast cancer
- the lack of effect on mortality
- the side effects of the different options
- alternative approaches, such as surveillance alone and, for women at high risk, risk-reducing surgery.

Women should also be given information in an accessible format. [2013, amended 2017]

Recommendations about chemoprevention for women at high risk of breast cancer

2. Offer tamoxifen[d] for 5 years to premenopausal women at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [2017]

3. Offer anastrozole[e] for 5 years to postmenopausal women at high risk of breast cancer unless they have severe[f,h] osteoporosis. [2017]

4. For postmenopausal women at high risk of breast cancer who have severe[g] osteoporosis or do not wish to take anastrozole:

- offer tamoxifen[e] for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, or
- consider raloxifene[i] for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. [2017]

5. Do not offer chemoprevention to women who were at high risk of breast cancer but have had bilateral risk-reducing mastectomy. [2013, amended 2017]

Recommendations about chemoprevention for women at moderate risk of breast cancer

6. Consider tamoxifen[e] for 5 years for premenopausal women at moderate risk of breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [2017]

7. Consider anastrozole[f] for 5 years for postmenopausal women at moderate risk of breast cancer unless they have severe[g] osteoporosis. [2017]

8. For postmenopausal women at moderate risk of breast cancer who have severe[g] osteoporosis or do not wish to take anastrozole:

- consider tamoxifen[e] for 5 years if they have no history or increased risk of thromboembolic disease or endometrial cancer, or
- consider raloxifene[i] for 5 years for women with a uterus if they have no history or increased risk of thromboembolic disease and do not wish to take tamoxifen. [2017]

d At the time of publication (March 2017), tamoxifen did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. Licensing arrangements remained unchanged when the guideline was updated (November 2016).

e At the time of consultation (March 2017), anastrozole did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

f In this guideline severe osteoporosis is defined as having a T-score of at least –2.5 SD as measured by DEXA (dual-energy X-ray absorptiometry).This definition is in line with that used by the WHO and in the NICE technology appraisal guidance on the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160), which is 'T-score equal to or less than –2.5 SD, in the presence of one or more documented fragility fractures'. The T-score is a measure of how far a person's bone mineral density is below the mean value of young adults.

h The summary of product characteristics for anastrozole indicates that women with osteoporosis or at risk of osteoporosis should have their bone mineral density assessed when starting treatment and then at regular intervals. Treatment or prophylaxis for osteoporosis should be started when needed and carefully monitored.

Recommendations for all women taking drugs for chemoprevention

9. Do not continue chemoprevention beyond 5 years in women with no personal history of breast cancer. [2013, amended 2017]

2.84 Research recommendations

1. What is the clinical and cost effectiveness of aromatase inhibitors (particularly exemestane and letrozole) compared with tamoxifen and raloxifene for reducing the incidence of breast cancer in women with a family history of breast or ovarian cancer? [2017]

Why is this important?

One randomised controlled trial (RCT) showed anastrozole to be effective for the primary prevention of breast cancer compared with placebo. However, there has been no RCT of other third-generation aromatase inhibitors, such as exemestane and letrozole. Exemstane is not strictly from the same class as anastrozole (and may therefore have different modes of action). More information on the efficacy of these other aromatase inhibitors may offer more options for chemoprevention for women at risk of breast cancer.

Table 10: Criteria for selecting high-priority research recommendations

PICO	**Population:** Women at increased risk of breast cancer based on: • a family history of breast, ovarian or related (prostate/pancreatic) cancer but no personal history of breast cancer • results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53) **Intervention:** Chemoprevention (any dosage/regimen): • Aromatase Inhibitors including exemestane and letrozole **Comparison:** • Tamoxifen, raloxifene, no chemoprevention and placebo **Outcomes:** • Development of invasive Breast Cancer • Development of Ductal carcinoma in situ (DCIS) • Non-adherence to chemoprevention • Health Related Quality of life • Overall Survival
Current evidence base	No evidence comparing exemestane or letrozole with tamoxifen, raloxifene, no chemoprevention or placebo
Study design	RCTs
Other comments	None

31 References

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3 Cancer Intervention Study (IBIS-I): a randomised prevention trial Lancet (London, and
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22 cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study.
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31 Results from the International Breast Cancer Intervention Study II Prevention Trial. Journal of
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33 Vogel VG, Costantino JP, Wickerham DL, et al. (2006). Effects of tamoxifen vs raloxifene on
34 the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study
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36 Vogel VG, Costantino JP, Wickerham DL, et al. (2010). Update of the National Surgical
37 Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial:
38 Preventing breast cancer. Cancer prevention research (Philadelphia, and Pa.), 3(6), 696-
39 706.

41 Glossary

Please refer to the NICE glossary.

Additional terms used in this document are listed below:

Aromatase inhibitor

Aromatase is the enzyme that synthesizes estrogen. As breast and ovarian cancers require oestrogen to grow, aromatase inhibitors are taken to either block the production of oestrogen or block the action of oestrogen on receptors.

Breast cancer risk category

	Breast cancer risk category		
	Near population risk	**Moderate risk**	**High risk[1]**
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%
[1]This group includes known *BRCA1*, *BRCA2* and *TP53* mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (*STK11*), Cowden (*PTEN*) and familial diffuse gastric cancer (E-Cadherin).			

First-degree relatives

Mother, father, daughter, son, sister, brother.

Second-degree relatives

Grandparent, grandchild, aunt, uncle, niece, nephew, half-sister, half-brother.

Severe osteoporosis

In this guideline severe osteoporosis is defined as having a T-score of at least –2.5 SD as measured by DEXA (dual-energy X-ray absorptiometry). This definition is in line with that used by the WHO and in the NICE technology appraisal guidance on the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160), which is 'T-score equal to or less than –2.5 SD, in the presence of one or more documented fragility fractures'. The T-score is a measure of how far a person's bone mineral density is below the mean value of young adults.

Third-degree relatives

Great grandparent, great aunt, great uncle, first cousin, great grandchild, grand nephew, grand niece.

Triple negative breast cancer

Oestrogen receptor, progesterone receptor, HER2 negative breast cancer.

1 Appendices

2 Appendix A: Standing Committee 3 members and NICE teams

A.1 4 Core members

Name	Role
Susan Bewley	Chair
Gita Bhutani	Associate Director for Psychological Professions
Simon Corbett	Cardiologist
Rachel Churchill	Professor of Evidence Synthesis
Gail Fortes Mayer	Commissioner
John Graham	Consultant Oncologist (Vice Chair)
Nathan Griffiths	Consultant Nurse - Paediatric Emergency and Ambulatory Medicine
Manoj Mistry	Lay member
Mark Rodgers	Research Fellow – Methodologist
Sietse Wieringa	General Practitioner

A.2 5 Topic expert Committee members

Name	Role
Gareth Evans	Professor of Medical Genetics and Cancer Epidemiology
Sacha Howell	Medical Oncologist
Paul Pharoah	Professor of Cancer Epidemiology
Judith Reeves	Lead Breast Care Nurse
Amy Taylor	Genetic counsellor
Ursula van Mann	Lay member

A.3 6 NICE project team

Name	Role
Thomas Feist	Senior Guideline Co-ordinator
Jessica Fielding	Public Involvement Adviser
Rupert Franklin	Guideline Commissioning Manager
Andy Hutchinson	Medicines Education Technical Adviser
Bhash Naidoo	Technical Lead (Health Economics)
Louise Picton	Senior medicines adviser
Sharon Summers-Ma	Guideline Lead
Nichole Taske	Technical Lead
Jeremy Wight	Clinical Adviser
Trudie Willingham	Senior Guideline Co-ordinator

7

A.41 Clinical guidelines update team

Name	Role
Martin Allaby	Clinical Adviser
Emma Banks	Co-ordinator
Elizabeth Barrett	Information Specialist
Nicole Elliott	Associate Director (from July 2016)
Ben Johnson	Health Economist
Hugh McGuire	Technical Adviser
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Nitara Prasannan	Technical Analyst
Lorraine Taylor	Associate Director (Until July 2016)

2

Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available in a separate document.

1 Appendix C: Review protocols

C.1 2 Review question 1a

3

	Details
Review question 1a	What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?
Background/ objectives	The NICE guideline on familial breast cancer was reviewed in 2015 by the surveillance team and new evidence (2 RCTs) on chemoprevention was identified; the guideline should therefore be updated to reflect new evidence in this area. Given there seems to be no indication in the use of chempreventative agents including tamoxifen, raloxifene and aromatase inhibitors in men, this update will be restricted to women. The review question will be covered in two protocols as follows: • This protocol (1a) is focussed on the efficacy and is RCT based • The following protocol (1b) is focussed on the adverse effects and is based on both long-term RCT's and observational studies to ensure the whole evidence base for adverse events is reviewed The protocols have been separated out for transparency purposes for searching and sifting and the findings from both parts of the review will be presented and interpreted together with a single LETR table and a single set of recommendations.
Type of review question	Intervention
Types of study to be included	• Randomised controlled trials (RCT) • Systematic review of RCTs
Language	English language only
Status	Published papers (full text only) – searches to be run from July 2012 to present. All studies included in the original guideline will also be considered.
Population	Women at increased risk of breast cancer based on: • a family history of breast, ovarian or related (prostate/pancreatic) cancer but no personal history of breast cancer • results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53)
Intervention	Chemoprevention (any dosage/regimen): • Tamoxifen • Raloxifene • Aromatase Inhibitors
Comparator	• Each Other • No chemoprevention • Placebo
Outcomes	• Development of invasive Breast Cancer • Development of Ductal carcinoma in situ (DCIS)

	Details
	• Non-adherence to chemoprevention • Health Related Quality of life • Overall Survival
Any other information or criteria for inclusion/exclusion	• The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out. • We will exclude studies including women with a personal history of breast cancer.
Analysis of subgroups or subsets	• Menopausal status was added as a post-hoc subgroup
Data extraction and quality assessment	<u>Sifting</u> Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (typical intervention question). However in cases of uncertainty the following mechanisms will be in place: - technical analyst will discuss with a support technical analyst - comparison with included studies of other systematic reviews - recourse to members of the committee ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). However in cases of uncertainty the same mechanisms stated in i) above will be followed. <u>Data extraction</u> Information from included studies will be extracted into standardised evidence tables. <u>Critical appraisal</u> The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual for intervention/observational studies identified: • NICE RCT checklist • NICE systematic reviews and meta-analyses checklist <u>Quality assessment</u> GRADE methodology will be used to assess the quality of evidence on an outcome basis: • Risk of bias will be assessed using critical appraisal checklistsInconsistency will be assessed using I^2. The following arbitrary I^2 thresholds were used to assess inconsistency:

	Details
	- I^2 value <40% or if no events were reported for that outcome = no serious inconsistency - I^2 value 40% to 60% = serious inconsistency - I^2 value >60% = very serious inconsistency • Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population; • Imprecision will be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available Topic experts will be asked to provide MID's. *Reliability of quality assessment:* A full double-scoring quality assessment will not be conducted due to the nature of the review question (typical intervention review) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: • Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. • The Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	• If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. A random effects model will be used if this assumption is not correct. • A narrative evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
Searches	<u>Sources to be searched</u> • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. • Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. <u>Supplementary search techniques</u> • None identified <u>Limits</u> • Studies reported in English • Study design RCT, SR and Observational filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • The search will be run from July 2012 to the present
Key papers	<u>Studies identified by surveillance process</u>

	Details
	• Cuzick J, Sestak I, Cawthorn S et al. (2015) Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncology 16:67-75. • Cuzick J, Sestak I, Forbes JF et al. (2014) Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383:1041-1048. <u>Studies in progress</u> • Professor Cuzick has confirmed further outputs from the IBIS-1 and IBIS-2 trials are expected: IBIS-1 will be analysed stratified by NICE approved risk categories. An analysis of metastatic cancers in IBIS-2 will be made in the next 12 months.

C.21 Review question 1b

2

Components	Details
Review question 1b	What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?
Background/ objectives	To identify the adverse effects of chemoprevention. The review question will be covered in two protocols as follows The previous protocol (1a) is focussed on the efficacy and is RCT based This protocol (1b) is focussed on the adverse effects and is based on both long-term RCT's and observational studies to ensure the whole evidence base for adverse events is reviewed. The protocols have been separated out for transparency purposes for searching and sifting and the findings from both parts of the review will be presented and interpreted together with a single LETR table and a single set of recommendations.
Type of review question	Intervention
Types of study to be included	• Randomised controlled trials (RCT) • Prospective observational studies
Language	English language only
Status	Published papers (full text only) – searches to be run from July 2012 to present. All studies included in the original guideline will also be considered.
Population	Women at increased risk of breast cancer based on: • a family history of breast, ovarian or related (prostate/pancreatic) cancer but no personal history of breast cancer • results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53)
Intervention	Chemoprevention (any dosage/regimen): • Tamoxifen • Raloxifene • Aromatase Inhibitors
Comparator	NA (as we are only interested in rates of adverse events)
Outcomes	Adverse events including but not limited to:

	• Development of cancer at any site • Development of osteoporosis • Incidence of fractures • Incidence of venous thromboembolism • Non-adherence • Mortality (non-cancer + non—breast cancer) • Menopause related symptoms
Any other information or criteria for inclusion/exclusion	• The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out. • We will exclude studies including women with a personal history of breast cancer.
Analysis of subgroups or subsets	-
Data extraction and quality assessment	<u>Sifting</u> Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (typical intervention question). However in cases of uncertainty the following mechanisms will be in place: • technical analyst will discuss with a support technical analyst. • comparison with included studies of other systematic reviews • recourse to members of the committee ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). However in cases of uncertainty the same mechanisms stated in i) above will be followed. <u>Data extraction</u> Data from relevant RCT arms and observational studies will be used to extract adverse event rates. Information from included studies will be extracted into standardised evidence tables. <u>Critical appraisal</u> The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual for intervention/observational studies identified: • NICE RCT checklist • NICE systematic reviews and meta-analyses checklist • NICE observational studies checklist (case-control, cohort checklists)

	Quality assessment GRADE methodology will be used to assess the quality of evidence on an outcome basis: • Risk of bias will be assessed using critical appraisal checklist • Inconsistency will be assessed using I2 • Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population; • Imprecision will be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available Topic experts will be asked to provide MID's. Reliability of quality assessment: A full double-scoring quality assessment will not be conducted due to the nature of the review question (typical intervention review) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: • Internal QA by CGUT technical adviser (10%) on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. • The Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	• If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. A random effects model will be used if this assumption is not correct. • For non-comparative data, i.e. rates of adverse events, a range of incidences as reported in the studies will be provided. • An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
Searches	Sources to be searched • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. • Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques • None identified Limits • Studies reported in English • Study design RCT, SR and Observational filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results

	• The search will be run from July 2012 to the present
Key papers	Studies identified by surveillance process • Cuzick J, Sestak I, Cawthorn S et al. (2015) Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncology 16:67-75. • Cuzick J, Sestak I, Forbes JF et al. (2014) Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383:1041-1048. Studies in progress • Professor Cuzick has confirmed further outputs from the IBIS-1 and IBIS-2 trials are expected: IBIS-1 will be analysed stratified by NICE approved risk categories. An analysis of metastatic cancers in IBIS-2 will be made in the next 12 months.

1 Appendix D: Search strategy

2 Databases that were searched, together with the number of articles retrieved from each
3 database are shown in table 9. The Medline search strategy is shown in table 10. The same
4 strategy was translated for the other databases listed.

D.1 5 Review question 1a/1b

6 **Table 11: Clinical search summary**

Databases	Date searched	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	13/05/2016	646
Cochrane Database of Systematic Reviews (CDSR)	13/05/2016	19
Database of Abstracts of Reviews of Effect (DARE)	13/05/2016	6
Embase (Ovid)	13/05/2016	1254
MEDLINE (Ovid)	13/05/2016	439
MEDLINE In-Process (Ovid)	13/05/2016	54
PubMed	13/05/2016	132

7

8 **Table 12: Clinical search terms (Medline)**

9

Database: Medline
Strategy used:

Database: Medline

Database: Ovid MEDLINE(R) <1946 to April Week 4 2016>
Search Strategy:
---

1 exp Breast Neoplasms/ (242234)
2 (paget* adj1 disease).tw. (6443)
3 (intraductal adj1 papilloma*).tw. (403)
4 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (31989)
5 ((breast or mammary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw. (250277)
6 ((duct* or intraductal or lobular or medullary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (35877)
7 or/1-6 (332444)
8 exp ovarian neoplasms/ (71956)
9 (ovar$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (65905)
10 (granulosa adj4 cell*).tw. (12256)
11 (hboc adj1 syndrome*).tw. (44)
12 (luteoma* or luteinoma*).tw. (191)
13 (meig* adj1 syndrome).tw. (748)
14 (androblastoma* or arrhenoblastoma*).tw. (326)
15 (sertoli* adj1 leydig).tw. (516)
16 (thecoma* or (theca adj1 cell)).tw. (869)
17 or/8-16 (97690)
18 exp Prostatic Neoplasms/ (104251)
19 (prostat$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (102664)
20 18 or 19 (121727)
21 exp Pancreatic Neoplasms/ (61708)
22 (pancrea$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (51822)
23 (adenoma or nesidioblastoma).tw. (37627)
24 ((island or islet) adj1 cell).tw. (7727)
25 or/21-24 (114293)
26 7 or 17 or 20 or 25 (619537)
27 (familial or (family adj histor$)).tw. (126212)
28 (heredit$ or inherit$ or predispos$).tw. (227130)
29 exp Genetics/ (199772)
30 (genetic adj (counsel* or test* or screening)).tw. (26899)
31 (mutation$ adj1 risk*).tw. (178)
32 mutation.tw. (264357)
33 lifetime breast cancer risk*.tw. (58)
34 (inherited adj mutation*).tw. (1035)
35 (mutation adj carrier*).tw. (5027)
36 exp Genetic Testing/ (29519)
37 exp Genetic Predisposition to Disease/ (105017)
38 exp Neoplastic Syndromes, Hereditary/ (46095)
39 Genetic Counseling/ (12430)
40 exp Genetic Techniques/ (1531900)
41 (BRCA1 or BRCA2 or TP53).tw. (17175)
42 Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/ (20468)
43 ((high adj risk) or (increas$ adj risk)).tw. (319935)

Database: Medline

44 exp Mutation/ (650431)
45 or/27-44 (2603450)
46 26 and 45 (120298)
47 7 and 46 (70639)
48 exp Chemoprevention/ (16021)
49 (chemoprevent$ or chemoprophyla$).tw. (21656)
50 exp Tamoxifen/ (19217)
51 (tamoxifen* or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or kessar or tamoplac or tamoxasta).tw. (18442)
52 (raloxifene or evista or keoxifene or bonmax or loxar or loxifen or optruma or raxeto).tw. (2730)
53 (toremifene or estrimex or fareston).tw. (612)
54 exp Aromatase Inhibitors/ (6443)
55 aromatase inhibitor$.tw. (5228)
56 (reduction adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (11553)
57 (exemestane$ or aromasin$).tw. (868)
58 anastr?zol$.tw. (1412)
59 letrozol$.tw. (1748)
60 (aminoglutethimide or amino glutethimide or cytadren or orimeten* or elipt?n or rodazol).tw. (1404)
61 (fadrozole or afema or arensin).tw. (327)
62 or/48-61 (76361)
63 47 and 62 (4393)
64 Randomized Controlled Trial.pt. (414789)
65 Controlled Clinical Trial.pt. (90619)
66 Clinical Trial.pt. (499457)
67 exp Clinical Trials as Topic/ (291886)
68 Placebos/ (33260)
69 Random Allocation/ (86604)
70 Double-Blind Method/ (135160)
71 Single-Blind Method/ (21774)
72 Cross-Over Studies/ (38034)
73 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (820182)
74 (random$ adj3 allocat$).tw. (22907)
75 placebo$.tw. (163223)
76 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (132212)
77 (crossover$ or (cross adj over$)).tw. (60865)
78 or/64-77 (1498016)
79 animals/ not humans/ (4203766)
80 78 not 79 (1394969)
81 Observational Studies as Topic/ (1356)
82 Observational Study/ (20791)
83 Epidemiologic Studies/ (7110)
84 exp Case-Control Studies/ (776974)
85 exp Cohort Studies/ (1529568)
86 Cross-Sectional Studies/ (214156)
87 Controlled Before-After Studies/ (129)
88 Historically Controlled Study/ (51)
89 Interrupted Time Series Analysis/ (141)
90 Comparative Study.pt. (1738534)
91 case control$.tw. (86426)

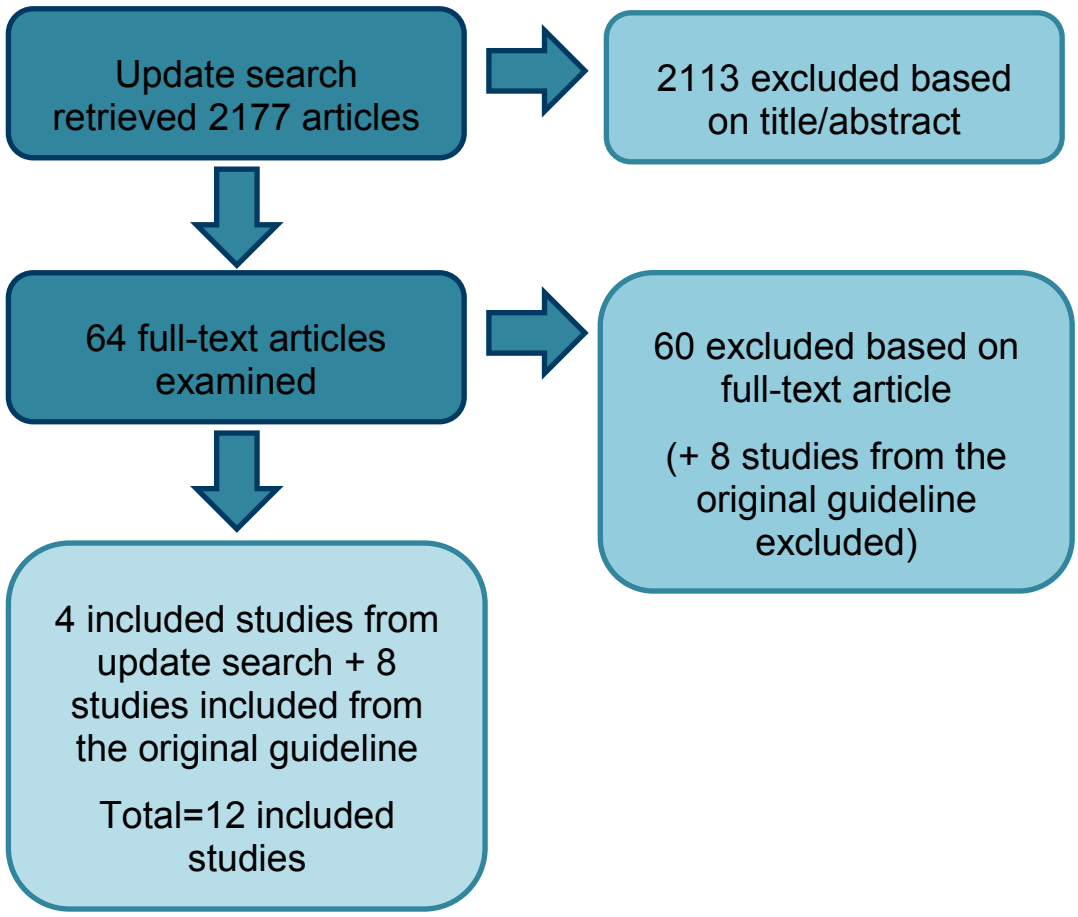
Database: Medline

92 case series.tw. (39227)
93 (cohort adj (study or studies)).tw. (100533)
94 cohort analy$.tw. (4219)
95 (follow up adj (study or studies)).tw. (38607)
96 (observational adj (study or studies)).tw. (51124)
97 longitudinal.tw. (148598)
98 prospective.tw. (375014)
99 retrospective.tw. (299639)
100 cross sectional.tw. (184301)
101 or/81-100 (3573840)
102 Meta-Analysis.pt. (65072)
103 Meta-Analysis as Topic/ (14831)
104 Review.pt. (2043551)
105 exp Review Literature as Topic/ (8569)
106 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (76894)
107 (review$ or overview$).ti. (302452)
108 (systematic$ adj5 (review$ or overview$)).tw. (72361)
109 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (5171)
110 ((studies or trial$) adj2 (review$ or overview$)).tw. (28210)
111 (integrat$ adj3 (research or review$ or literature)).tw. (6369)
112 (pool$ adj2 (analy$ or data)).tw. (16814)
113 (handsearch$ or (hand adj3 search$)).tw. (6059)
114 (manual$ adj3 search$).tw. (3601)
115 or/102-114 (2221194)
116 animals/ not humans/ (4203766)
117 115 not 116 (2080386)
118 80 or 101 or 117 (6073660)
119 63 and 118 (2426)
120 201207*.ed. (66674)
121 201208*.ed. (69855)
122 201209*.ed. (63995)
123 201210*.ed. (63975)
124 201211*.ed. (56185)
125 201212*.ed. (51255)
126 2013*.ed. (741890)
127 2014*.ed. (816925)
128 2015*.ed. (876854)
129 2016*.ed. (307268)
130 or/120-129 (3114876)
131 119 and 130 (442)
132 limit 131 to english language (435)

1

Appendix E: Review flowchart

E.1 Review question 1a/1b



1 Appendix F:Excluded studies

2

Reference	Reason for exclusion
Amir E (2011) Toxicity of adjuvant endocrine therapy in post menopausal breast cancer patients: A systematic review and meta-analysis Journal of the National Cancer Institute 103;17:1299-1309 [included in 2013 update]	Population not met – all have a personal history of breast cancer.
Anonymous . (2014). Anastrozole may aid breast cancer prevention. Cancer Discovery, 4(2), pp.OF4.	Commentary
Behan L A, Amir E, and Casper R F. (2015). Aromatase inhibitors for prevention of breast cancer in postmenopausal women: a narrative review. Menopause, 22(3), pp.342-50.	Narrative review of the IBIS-2 and MAP.3 trials which have been assessed separately by the CGUT team.
Chen S, Liu H, Li J, and Yang G. (2015). Risk of gastric and colorectal cancer after tamoxifen use for breast cancer: A systematic review and meta-analysis. Journal of Clinical Gastroenterology, 49(8), pp.666-674.	Systematic review; studies include both women at risk of breast cancer and those with breast cancer. All included studies are pre-2012 and therefore not captured by the update search.
Cheung A M, Tile L, Cardew S, Pruthi S, Robbins J, Tomlinson G, Kapral M K, Khosla S, Majumdar S, Erlandson M, Scher J, Hu H, Demaras A, Lickley L, Bordeleau L, Elser C, Ingle J, Richardson H, and Goss P E. (2012). Bone density and structure in healthy postmenopausal women treated with exemestane for the primary prevention of breast cancer: a nested substudy of the MAP.3 randomised controlled trial. The Lancet. Oncology, 13(3), pp.275-84.	No indication that population were at increased risk of breast cancer based on family history or results of genetic tests.
Cheung A M, Robbins J, Pruthi S, Goss P E, Cardew S, Majumdar S, Khosla S, Boyd S, Burghardt A, Bordeleau L, Ingle J, Szabo E, Erlandson M, Hu H, Scher J, Richardson H, Gelmon K, Tile L, and Tomlinson G. (2012). Cortical porosity and estimated bone strength in healthy postmenopausal women treated with exemestane for the primary prevention of breast cancer: Analyses from the nested bone strength substudy of the map.3 trial (MAP3BSS). Journal of bone and mineral research, 27, pp..	Conference abstract: could not be retrieved as no longer available.
Collins I M, Milne R L, Weideman P C, McLachlan S A, Friedlander M L, Cuningham K, Hopper J L, and Phillips K A. (2013). Preventing breast and ovarian cancers in high-risk BRCA1 and BRCA2 mutation carriers. Medical Journal of Australia, 199(10), pp.680-683.	Only 3% of the population took chemoprevention drugs – no relevant data reported for the subgroup that took chemopreventative drugs.
Cossetti R, and Gelmon K A. (2015). Exemestane for breast cancer risk reduction. Breast Cancer Management, 4(3), pp.159-164.	Unclear whether all had family history as numbers not reported nor does it seem to be a criteria for inclusion.
Cuzick J, Sestak I, Forbes J F, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel R E, Minckwitz G, Bonanni B, Palva T, and Howell A. (2013). Breast cancer prevention using anastrozole in	Conference abstract: updated analysis of this abstract (Cuzick 2014) has

postmenopausal women at high risk. Cancer research, 73(24 suppl. 1), pp..	been included in this update.
Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, and Forbes J F. (2015). 16 year long-term follow-up of the IBIS-I breast cancer prevention trial. Cancer research, 75(9 suppl. 1), pp..	Conference abstract – original study (Cuzick 2015) included in this update.
Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S and Boyle P (2003) Overview of the main outcomes in breast cancer prevention trials. The Lancet, 361 (9354), 296-300 [included in 2004 original guideline]	Overview article – relevant trials included in this overview have been reviewed separately.
Danhauer S C, Legault C, Bandos H, Kidwell K, Costantino J, Vaughan L, Avis N E, Rapp S, Coker L H, Naughton M, Naylor C, Terracciano A, and Shumaker S. (2013). Positive and negative affect, depression, and cognitive processes in the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Trial. Aging Neuropsychology & Cognition, 20(5), pp.532-52.	No relevant outcomes.
Day S, and Bevers T B. (2014). Quality of life in MAP.3 (mammary prevention 3): A randomized, placebo-controlled trial evaluating exemestane for prevention of breast cancer. Breast Diseases, 26(2), pp.123-4.	Same article as Maunsell 2014.
DeCensi A, Bonanni B, Maisonneuve P, Serrano D, Omodei U, Varricchio C, Cazzaniga M, Lazzeroni M, Rotmensz N, Santillo B, Sideri M, Cassano E, Belloni C, Muraca M, Segnan N, Masullo P, Costa A, Monti N, Vella A, Bisanti L, D'Aiuto G, and Veronesi U. (2013). A phase-III prevention trial of low-dose tamoxifen in postmenopausal hormone replacement therapy users: the HOT study. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 24(11), pp.2753-60.	Unclear whether all had family history as numbers not reported.
Decensi A, Dunn B K, Puntoni M, Gennari A, and Ford L G. (2012). Exemestane for breast cancer prevention: a critical shift?. Cancer Discovery, 2(1), pp.25-40.	Critical review of the MAP.3 trial which has been excluded given no indication that the population was at increased risk of breast cancer based on family history or results of genetic testing. Though Gail score >1.66% which incorporates family history was an additional eligibility criteria, it is unclear how many subjects this data was available for as no subgroup analysis is performed.
Dunn B K, Cazzaniga M, and DeCensi A. (2013). Exemestane: one part of the chemopreventive spectrum for ER-positive breast cancer. Breast, 22(3), pp.225-37.	Dunn B K, Cazzaniga M, and DeCensi A. (2013). Exemestane: one part of the chemopreventive spectrum for ER-positive breast cancer. Breast, 22(3), pp.225-37.
Eastell R, Sestak I, Gossiel F, Patel R, Blake G, Coleman R, Howell A, Dowsett M, Forbes J, Singh S, and Cuzick J. (2013). Effect of aromatase inhibition on bone density and bone turnover in healthy postmenopausal women: Results of the international breast cancer	Conference abstract: could not be retrieved as no longer available.

intervention study II (IBIS-II). Journal of bone and mineral research, 28, pp..	
Fowler J, Mitchell K, and Bukhari M. (2014). The effect of aromatase inhibitors on different sites of the human skeleton-an observational case-control study. Annals of the rheumatic diseases, 73, pp..	Abstract only – insufficient information to assess quality of study
Gatti-Mays M E, Venzon D, Galbo C E, Singer A, Reynolds J, Makariou E, Kallakury B, Heckman-Stoddard B M, Korde L, Isaacs C, Warren R, Gallagher A, and Eng-Wong J. (2016). Exemestane use in postmenopausal women at high risk for invasive breast cancer: Evaluating biomarkers of efficacy and safety. Cancer Prevention Research, 9(3), pp.225-233.	Unclear whether all had family history as numbers not reported.
Goss P, Ingle JN, et al (2011) Exemestane for Breast Cancer Prevention in Postmenopausal Women The New England Journal of Medicine 364;25:2381-2391 [included in 2013 update].	Unclear whether subjects had family history of breast or related cancers as numbers not reported.
Goss P E. (2012). The promise of breast cancer prevention. Menopause (New York, and N.Y.), 19(12), pp.1366.	Abstract only – insufficient information to assess quality of study
Gronwald J, Robidoux A, Kim-Sing C, Tung N, Lynch H T, Foulkes W D, Manoukian S, Ainsworth P, Neuhausen S L, Demsky R, Eisen A, Singer C F, Saal H, Senter L, Eng C, Weitzel J, Moller P, Gilchrist D M, Olopade O, Ginsburg O, Sun P, Huzarski T, Lubinski J, Narod S A, Hereditary Breast Cancer Clinical Study, and Group . (2014). Duration of tamoxifen use and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Research & Treatment, 146(2), pp.421-7.	Case control study assessing duration of tamoxifen use and risk of contralateral breast cancer – comparator drug not examined
Johansson H, Bonanni B, Gandini S, Guerrieri-Gonzaga A, Cazzaniga M, Serrano D, Macis D, Puccio A, Sandri M T, Gulisano M, Formelli F, and Decensi A. (2013). Circulating hormones and breast cancer risk in premenopausal women: a randomized trial of low-dose tamoxifen and fenretinide. Breast cancer research and treatment, 142(3), pp.569-78.	Mixed population of which 23% were at increased risk of breast cancer based on 5 year Gail risk score – however, Gail strata results not reported by type of intervention received.
Land S R, Wickerham D L, Costantino JP, Ritter MW, Vogel VG, Lee M, Pajon ER, Wade JL, Dakhil S, Lockhart JB, Wolmark N and Ganz PA (2006). Patient reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention, 295 (23): 2742 – 2751 [included in 2013 update].	Unclear whether subjects had family history of breast or related cancers as numbers not reported.
Land S R, Walcott F L, Liu Q, Wickerham D L, Costantino J P, and Ganz P A. (2014). Patient-reported outcomes and behavioral risk factors as predictors of chemoprevention adherence among women in the National Surgical Adjuvant Breast and Bowel Program (NSABP) Breast Cancer Prevention P-1 trial. Journal of clinical oncology, 32(15 suppl. 1), pp..	Conference abstract – insufficient information to assess quality of study.
Litzenburger B C, and Brown P H. (2014). Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): An international, double-blind, randomised placebo-controlled trial. Breast Diseases, 25(3), pp.214-216.	Commentary
Lopez A M, Chow H H. S, Frank D, Puthi S, Boughey J, Hsu P, Guillen J, Perloff M, Ley M, and Lang J E. (2015). De-escalating doses of letrozole in post menopausal women at high risk for breast cancer. Cancer research, 75(9 suppl. 1), pp..	Conference abstract – insufficient information to assess quality of study.
Lopez A M, Pruthi S, Boughey J C, Perloff M, Hsu C H, Lang J E, Ley M, Frank D, Taverna J A, Sherry Chow, and H H. (2016). Double-blind, randomized trial of alternative letrozole dosing regimens in	No indication that population was at increased risk of breast

postmenopausal women with increased breast cancer risk. Cancer Prevention Research, 9(2), pp.142-148.	cancer based on family history.
Lorizio W, Wu A H, Beattie M S, Rugo H, Tchu S, Kerlikowske K, and Ziv E. (2012). Clinical and biomarker predictors of side effects from tamoxifen. Breast Cancer Research & Treatment, 132(3), pp.1107-18.	Only 3 women in the study were taking tamoxifen for the prevention of breast cancer; all others already had breast cancer therefore population not met.
Macis D, Gandini S, Guerrieri-Gonzaga A, Johansson H, Magni P, Ruscica M, Lazzeroni M, Serrano D, Cazzaniga M, Mora S, Feroce I, Pizzamiglio M, Sandri M T, Gulisano M, Bonanni B, and Decensi A. (2012). Prognostic effect of circulating adiponectin in a randomized 2 x 2 trial of low-dose tamoxifen and fenretinide in premenopausal women at risk for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30(2), pp.151-7.	No relevant outcomes.
Mallick S, Benson R, and Julka P K. (2016). Breast cancer prevention with anti-estrogens: review of the current evidence and future directions. Breast Cancer, 23(2), pp.170-177.	Review article – relevant articles have been reviewed by original guideline.
Maunsell E, Goss P E, Chlebowski R T, Ingle J N, Alés-Martínez J E, Sarto G E, Fabian C J, Pujol P, Ruiz A, Cooke A L, Hendrix S, Thayer D W, Rowland K M, Dubé P, Spadafora S, Pruthi S, Lickley L, Ellard S L, Cheung A M, Wactawski-Wende J, Gelmon K A, Johnston D, Hiltz A, Brundage M, Pater J L, Tu D, and Richardson H. (2014). Quality of life in MAP.3 (Mammary Prevention 3): a randomized, placebo-controlled trial evaluating exemestane for prevention of breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32(14), pp.1427-36.	No indication that population was at increased risk of breast cancer based on family history or results of genetic testing. Though Gail score >1.66% which incorporates family history was an additional eligibility criteria, it is unclear how many subjects this data was available for as no subgroup analysis is performed.
McCaskill-Stevens W, Wilson J W, Cook E D, Edwards C L, Gibson R V, McElwain D L, Figueroa-Moseley C D, Paskett E D, Roberson N L, Wickerham D L, and Wolmark N. (2013). National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene trial: advancing the science of recruitment and breast cancer risk assessment in minority communities. Clinical trials (London, and England), 10(2), pp.280-91.	No relevant outcomes
McCluggage W G, Abdulkader M, Price J H, Kelehan P, Hamilton S, Beattie J, and Al-Nafussi A. (2000). Uterine carcinosarcomas in patients receiving tamoxifen. A report of 19 cases. Int J Gynecol Cancer, 10(4), pp.280-284.	No relevant outcomes nor is the population at increased risk as specified in the review protocol.
Motion J, Ashcroft L, Dowsett M, Cuzick J, Hickman J, Evans G, Eccles D, Eeles R, Greenhalgh R, Affen J, Bundred S, Boggis C, Sergeant J, Fallowfield L, Adams J, and Howell A. (2012). The razor trial: A phase ii prevention trial of screening plus goserilin and raloxifene versus screening alone in pre-menopausal women at increased risk of breast cancer. Cancer research, 72(24 suppl. 3), pp..	Conference abstract – insufficient information to assess quality of study.
Nelson HD, Rongwei F, Griffin JC, Nygren P, Smith B and Humphrey L (2009). Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer. Ann Intern Med, 151: 703 – 715 [included in 2013 update].	Meta-analysis: not all included studies in this meta-analysis meet the update inclusion criteria. Individual studies have

	been checked and included if they meet the criteria.
Nelson H D, Smith M E, Griffin J C, and Fu R. (2013). Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Annals of Internal Medicine, 158(8), pp.604-14.	Review article – included studies have been reviewed separately.
Nichols H B, DeRoo L A, Scharf D R, and Sandler D P. (2015). Risk-benefit profiles of women using tamoxifen for chemoprevention. Journal of the National Cancer Institute, 107(1), pp.354.	No relevant outcomes.
Olin J L, St Pierre , and M . (2014). Aromatase inhibitors in breast cancer prevention. Annals of Pharmacotherapy, 48(12), pp.1605-10.	Review article – included studies have been reviewed separately.
Pujol P, Lasset C, Berthet P, Dugast C, Delaloge S, Fricker J P, Tennevet I, Chabbert-Buffet N, This P, Baudry K, Lemonnier J, Roca L, Mijonnet S, Gesta P, Chiesa J, Dreyfus H, Vennin P, Delnatte C, Bignon Y J, Lortholary A, Prieur F, Gladieff L, Lesur A, Clough K B, Nogues C, Martin A L, French Federation of Cancer, and Centres . (2012). Uptake of a randomized breast cancer prevention trial comparing letrozole to placebo in BRCA1/2 mutations carriers: the LIBER trial. Familial Cancer, 11(1), pp.77-84.	No relevant outcome and also 49% of the study population had a personal history of breast cancer.
Phillips K A, Milne R L, Rookus M A, Daly M B, Antoniou A C, Peock S, Frost D, Easton D F, Ellis S, Friedlander M L, Buys S S, Andrieu N, Nogues C, Stoppa-Lyonnet D, Bonadona V, Pujol P, McLachlan S A, John E M, Hooning M J, Seynaeve C, Tollenaar R A, Goldgar D E, Terry M B, Caldes T, Weideman P C, Andrulis I L, Singer C F, Birch K, Simard J, Southey M C, Olsson H L, Jakubowska A, Olah E, Gerdes A M, Foretova L, and Hopper J L. (2013). Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. Journal of Clinical Oncology, 31(25), pp.3091-9.	All subjects have a personal history of breast cancer.
Prasad V, and Diener-West M. (2015). Primary chemoprevention of breast cancer: Are the adverse effects too burdensome?. Cmaj, 187(9), pp.E276-E278.	Commentary
Razzaboni E, Toss A, Cortesi L, Marchi I, Sebastiani F, De Matteis , E , and Federico M. (2013). Acceptability and adherence in a chemoprevention trial among women at increased risk for breast cancer attending the Modena Familial Breast and Ovarian Cancer Center (Italy). Breast Journal, 19(1), pp.10-21.	Data only reported for one arm of the study, updated analysis (Cuzick 2014) included in 2016 update.
Reimers L, and Crew K D. (2012). Tamoxifen versus raloxifene versus exemestane for chemoprevention. Current Breast Cancer Reports, 4(3), pp.207-215.	Narrative review – references of relevant studies checked for inclusion.
Roetzheim R G, Lee J H, Fulp W, Matos Gomez, E , Clayton E, Tollin S, Khakpour N, Laronga C, Lee M C, and Kiluk J V. (2015). Acceptance and adherence to chemoprevention among women at increased risk of breast cancer. Breast, 24(1), pp.51-56	No relevant outcomes by type of chemopreventative drug received.
Segev Y, Iqbal J, Lubinski J, Gronwald J, Lynch H T, Moller P, Ghadirian P, Rosen B, Tung N, Kim-Sing C, Foulkes W D, Neuhausen S L, Senter L, Singer C F, Karlan B, Ping S, and Narod S A. (2013). The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: An international prospective cohort study. Gynecologic Oncology, 130(1), pp.127-131.	No relevant data reported for the subgroup without personal history of breast cancer and history of tamoxifen use.
Segev Y, Rosen B, Lubinski J, Gronwald J, Lynch H T, Moller P, Kim-Sing C, Ghadirian P, Karlan B, Eng C, Gilchrist D, Neuhausen S L, Eisen A, Friedman E, Euhus D, Ping S, and Narod S A. (2015). Risk factors for endometrial cancer among women with a BRCA1 or	No relevant data reported for the subgroup without personal history of breast

BRCA2 mutation: a case control study. Familial Cancer, 14(3), pp.383-391.	cancer and history of tamoxifen use.
Sestak I, Kealy R, Nikoloff M, Fontecha M, Forbes J F, Howell A, and Cuzick J. (2012). Relationships between CYP2D6 phenotype, breast cancer and hot flushes in women at high risk of breast cancer receiving prophylactic tamoxifen: results from the IBIS-I trial. British Journal of Cancer, 107(2), pp.230-3.	Study not an RCT and no relevant outcomes reported.
Sestak I. (2014). Preventative therapies for healthy women at high risk of breast cancer. Cancer management and research, 6, pp.423-30.	Narrative review – relevant references checked for inclusion separately
Sestak I, and Cuzick J. (2015). Update on breast cancer risk prediction and prevention. Current Opinion in Obstetrics & Gynecology, 27(1), pp.92-7.	Narrative review on breast cancer prevention approaches.
Signori C, DuBrock C, Richie J P, Prokopczyk B, Demers L M, Hamilton C, Hartman T J, Liao J, El-Bayoumy K, and Manni A. (2012). Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. European Journal of Clinical Nutrition, 66(8), pp.878-84.	Population defined on the basis of breast density not family history. Although number with family history is reported, this is only a very small proportion of the subjects, n<10 in all arms.
Singh S, Cuzick J, Mesher D, Richmond B, and Howell A. (2012). Effect of baseline serum vitamin D levels on aromatase inhibitors induced musculoskeletal symptoms: results from the IBIS-II, chemoprevention study using anastrozole. Breast cancer research and treatment, 132(2), pp.625-9.	Raw data for treatment groups not reported therefore not possible to calculate effect estimate comparing treatment groups; the effect estimate reported in the study itself is for within group differences from baseline rather than comparing the anastrozole arm to the placebo arm.
Thomin A, Friszer S, Fajac A, Darai E, and Chabbert-Buffet N. (2014). Hormonal prevention of breast cancer. Annales d Endocrinologie, 75(3), pp.148-55.	Narrative review – relevant references have been assessed separately.
Vachon C M, Schaid D J, Ingle J N, Wickerham D L, Kubo M, Mushiroda T, Goetz M P, Carlson E E, Paik S, Wolmark N, Nakamura Y, Wang L, Weinshilboum R, and Couch F J. (2015). A polygenic risk score for breast cancer in women receiving tamoxifen or raloxifene on NSABP P-1 and P-2. Breast Cancer Research & Treatment, 149(2), pp.517-23.	No relevant outcomes.
Veronesi U, Maisonneuve P, Sacchini V, Rotmensz N and Boyle P (2002). Tamoxifen for breast cancer among hysetertomised women. The Lancet, 359: 1122-1124 [included in 2004 original guideline]	Unclear whether participants had family history of breast/ovarian or related cancers as numbers not reported nor does it seem to be a criterion for inclusion in the study.
Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N and Boyle P (1998). Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. The Lancet, 352: 93-97 [included in 2004 original guideline]	Only 21% of the population had family history of breast or related cancers. Although outcomes are reported for the subgroup with family history, it is unclear how many of the

	21% with family history were from the tamoxifen and placebo arms.
Vicus D et al (2009) Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers Gynaecological Oncology 115;1:135-137 [included in 2013 update]	All participants had personal history of breast cancer.
Visvanathan K, Hurley P, Bantug E, Brown P, Col N F, Cuzick J, Davidson N E, Decensi A, Fabian C, Ford L, Garber J, Katapodi M, Kramer B, Morrow M, Parker B, Runowicz C, Vogel V G, 3rd , Wade J L, and Lippman S M. (2013). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology, 31(23), pp.2942-62.	Systematic review of pre-2012 studies – relevant studies have been reviewed by the original guideline.
Vogel V G. (2007). Raloxifene: a selective estrogen receptor modulator for reducing the risk of invasive breast cancer in postmenopausal women. Women's health, 3(2), pp.139-53.	Narrative review – two relevant studies have been reviewed by the original guideline.
Walcott F L, Land S R, Costantino J P, Midthune D, and Dunn B K. (2015). Vasomotor symptoms, BMI, and adherence to tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1). Journal of clinical oncology, 33(15 suppl. 1), pp..	Conference abstract – insufficient information to assess quality of study.
Walker G, Xenophontos M, Chen L, and Cheung K. (2013). Long-term efficacy and safety of exemestane in the treatment of breast cancer. Patient preference & adherence, 7, pp.245-58.	Review article – relevant studies have been reviewed by the original guideline.
Waters E A, McNeel T S, Stevens W M, and Freedman A N. (2012). Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Research & Treatment, 134(2), pp.875-80.	No relevant outcomes – study aims to assess the prevalence of use of chemopreventative agents in a cross sectional survey
Wuttke M, and Phillips K A. (2015). Clinical management of women at high risk of breast cancer. Current Opinion in Obstetrics & Gynecology, 27(1), pp.6-13.	Narrative review of breast cancer prevention guidelines from various countries.
Xu L, Zhao Y, Chen Z, Wang Y, Chen L, and Wang S. (2015). Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in BRCA1 and BRCA2: a meta-analysis. Breast Cancer, 22(4), pp.327-34.	Meta-analysis: included studies have a personal history of breast cancer.
Zucchini G, Geuna E, Milani A, Aversa C, Martinello R, and Montemurro F. (2015). Clinical utility of exemestane in the treatment of breast cancer. International Journal of Women's Health, 7, pp.551-63.	Narrative review – relevant references have been checked for inclusion separately.
Zhang Y, Simondsen K, and Kolesar J M. (2012). Exemestane for primary prevention of breast cancer in postmenopausal women. American Journal of Health-System Pharmacy, 69(16), pp.1384-8.	Narrative on benefits and risks of exemestane for primary prevention of breast cancer.
(2012). Exemestane reduces breast cancer risk in high-risk postmenopausal women. Journal of the National Medical Association, 104(1-2), pp.118.	Commentary.

1 Appendix G: Evidence tables

G.1 2 Cuzick 2015 (reported in 3 papers)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
Study type	RCT
Aim	To report an updated analysis of the IBIS-1 trial.
Patient characteristics	**Inclusion criteria** • 35 to 70 years of age • Premenopausal and postmenopausal women judged to be at increased risk of developing breast cancer based on family history of breast cancer (97%) or abnormal benign breast disease (8%) • Women had to have risk factors for breast cancer indicating at least a twofold increased risk for the disease in women aged 45-70 years, whereas this risk needed to be higher than twofold for those younger than 45 years of age **Exclusion criteria** • History of any invasive cancer excluding skin cancer • Deep vein thrombosis • Pulmonary embolism • Wanting to become pregnant **Baseline characteristics** Median age in years (IQR): Tamoxifen - 49·9 (45·9 to 55·0); Placebo - 49·9 (46·1 to 55·0) Postmenopausal, n/N (%): 3858/7154 (54) – not reported by treatment groups Median BMI in kg/cm^2 (IQR): Tamoxifen - 26·0 (23·3 to 29·7); Placebo - 26·1 (23·2 to 29·6)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	Menopausal hormone therapy use during active treatment phase of trial, n/N (%) During trial only: Tamoxifen – 1462/3579 (40·9%) Placebo – 1414/3575 (49·5%) Before trial only: Tamoxifen – 399/3579 (11·2%) Placebo – 380/3575 (10·6%) Never: Tamoxifen – 1708/3579 (47·7%) Placebo – 1769/3575 (49·5%) Hysterectomy, n/N (%): Tamoxifen – 1232/3579 (34.4%); Placebo – 1283/3575 (35.9%)
Number of Patients	- A total of 7169 women initially enrolled into the trial and randomly assigned to the 2 treatment groups - 15 were subsequently found to be ineligible because of previous breast cancer (6 in tamoxifen arm and 9 in placebo arm) - Total N therefore =7154 women; 3579 in tamoxifen arm and 3575 in placebo arm - 93% of women (n=6639 of 7154) had more than 10 years of follow up
Intervention	Oral tamoxifen 20mg daily for 5 years
Comparison	Matching placebo for 5 years
Length of follow up	• Original report (Cuzick 2002) – median follow up was 50 months (IQR: 32-67) • Updated analysis (Cuzick 2007) – median follow up of 95.6 months • Updated analysis (Cuzick 2015) - median follow up was 16 years (IQR: 14.1 – 17.6): 6639 (93%) of 7154 women had more than 10 years of follow up
Location	• 8 countries (UK, Australia, New Zealand, Finland, Spain, Switzerland, Belgium and Ireland) • 37 centres (genetic clinics and breast care clinics)
Outcomes measures and effect size	**1. Development of invasive breast cancer, n/N (%*)** *At median follow up of 50 months (Cuzick 2002)* Tamoxifen: 64/3573 (1.8) Placebo: 85/3566 (2.4) Odds ratio (95% CI): 0.75 (0.54 to 1.04)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	At median follow up of 95.6 months (Cuzick 2007) Tamoxifen: 124/3579 (3.5) Placebo: 168/3575 (4.7) *At 0-10 year follow up period (Cuzick 2015)* Tamoxifen: 141/3579 (3.9); person years of follow up – 34 663 Placebo: 188/3575 (5.3); person years of follow up – 34 411 Hazard ratio (95%CI): 0.74 (0.60 to 0.93); p= 0.0078 *≥10 year follow up period(Cuzick 2015)* Tamoxifen: 73/3343 (2.2); person years of follow up – 20 756 Placebo: 101/3295 (3.1); person years of follow up – 20 213 Hazard ratio (95%CI): 0.70 (0.52 to 0.95); p= 0.022 *Overall- at median follow up of 16 years (Cuzick 2015)* Tamoxifen: 214/3579 (6); person years of follow up – 55 419 Placebo: 289/3575 (8.1); person years of follow up – 54 624 Hazard ratio (95%CI): 0.73 (0.61 to 0.87) * % calculated by analyst **2. Development of ductal carcinoma in situ (DCIS), n/N (%*)** *At median follow up of 50 months (Cuzick 2002)* Tamoxifen: 5/3573 (0.1) Placebo: 16/3566 (0.4) Odds ratio (95%CI): 0.31 (0.12 to 0.82

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	At median follow up of 95.6 months (Cuzick 2007) Tamoxifen: 17/3579 (0.5) Placebo: 27/3575 (0.8) *At 0-10 year follow up period (Cuzick 2015)* Tamoxifen: 21/3579 (0.6); person years of follow up – 34 663 Placebo: 38/3575 (1.1); person years of follow up – 34 411 Hazard ratio (95%CI): 0.55 (0.32 to 0.93); p= 0.027 *≥10 year follow up period (Cuzick 2015)* Tamoxifen: 14/3343 (0.4); person years of follow up – 20 756 Placebo: 15/3295 (0.5); person years of follow up – 20 213 Hazard ratio (95%CI): 0.91 (0.44 to 1.89); p=0.81 *Overall – at median follow up of 16 years (Cuzick 2015)* Tamoxifen: 35/3579 (1.0); person years of follow up – 55 419 Placebo: 53/3575 (1.5); person years of follow up – 54 624 Hazard ratio (95%CI): 0.65 (0.43 to 1.00) * % calculated by analyst **3. Non-adherence to chemoprevention** *At median follow up of 50 months (Cuzick 2002)* 25% of women completed a full 5 years of treatment: 837 (23.4) in tamoxifen vs 959 (26.9%) in placebo arm Further 47% were still on treatment at the time of data lock: 1574 (44%)] in tamoxifen vs 1760 (49.4) in placebo

Bibliographic reference	Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update] Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update]. Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].
	arm. *At median follow up of 95.6 months (Cuzick 2007)* 2287 (63.9%) in tamoxifen group and 2574 (72%) in placebo group completed the full 5 years of treatment *At median follow up of 16 years (Cuzick 2015)* Not reported **4. Health Related Quality of life** Not reported **5. Overall Survival, n/N (%)** *Extracted as total deaths (various causes)* *At median follow up of 50 months (Cuzick 2002)* Tamoxifen: 25/3573 (0.7) Placebo: 11/3566 (0.3) *At median follow up of 95.6 months (Cuzick 2007)* Tamoxifen: 65/3579 (1.82) Placebo: 55/3575 (1.54) *At median follow up of 16 years (Cuzick 2015*) Tamoxifen: 182/3578 (5.1) Placebo: 166/3575 (4.6) **6. Adverse events, n/N (%)**

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	a) *All thromboembolism (includes spontaneous and occurring within 3 months of surgery of fracture)* - At median follow up of 50 months (Cuzick 2002) Tamoxifen: 43/3573 (1.2) Placebo: 17/3566 (0.48) ***b) Pulmonary embolism*- At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 13/3573 (0.36) Placebo: 10/3566 (0.28) ***c) Deep-vein thrombosis* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 24/3573 (0.67) Placebo: 5/3566 (0.14) ***d) Thrombophlebitis* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 27/3573 (0.8) Placebo: 9/3566 (0.3) ***e) All venous thrombolic events including deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis* - At median follow up of 95.6 months (Cuzick 2007)** Tamoxifen group: 117/3579 (3.3%) of which 68 was DVT/PE and 23 superficial thrombophlebitis Placebo group: 68/3575 (1.9%) of which 37 was DVT/PE and 8 superficial thrombophlebitis RR (95%CI): 1.72 (1.27 to 2.36) ***f) All cerebrovascular (stroke/cerebrovascular accirent/transient ischemic attack)* - At median follow up of 50 months (Cuzick 2002**) Tamoxifen: 16/3573 (0.4)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	Placebo: 17/3566 (0.5) ***g) Stroke or cerebrovascular accident* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 13/3573 (0.4) Placebo: 11/3566 (0.3) ***h) Transient ischaemic attack* - a*t median follow up of 50 months (Cuzick 2002)*** Tamoxifen: 3/3573 (0.1) Placebo: 6/3566 (0.2) **i) *All Cerebrovascular events including stroke, cerebrovascular accident , transient ischemic attack* - at median follow up of 95.6 months (Cuzick 2007)** • Tamoxifen group: 32/3579 (0.9%) • Placebo group: 34/3575 (1%) • Risk ratio (95% CI) 0.94 (0.56 to 1.57) ***j) Cardiac*** **At median follow up of 50 months (Cuzick 2002)** *All (myocardial infarction, coronary revascularisation, other revascularisation, other cardiovascular events, angina)* Tamoxifen: 73/3573 (2) Placebo: 63/3566 (1.8) **At median follow up of 50 months (Cuzick 2002)** *Myocardial infarction* Tamoxifen: 5/3573 (0.1) Placebo: 5/3566 (0.1)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	At median follow up of 50 months (Cuzick 2002) *Coronary revascularisation* Tamoxifen: 5/3573 (0.1) Placebo: 5/3566 (0.1) **At median follow up of 50 months (Cuzick 2002)** *Other revascularisation* Tamoxifen: 8/3573 (0.2) Placebo: 2/3566 (0.1) **At median follow up of 50 months (Cuzick 2002)** *Other cardiovascular events* Tamoxifen: 16/3573 (0.4) Placebo: 17/3566 (0.5) **At median follow up of 50 months (Cuzick 2002)** *Angina* Tamoxifen: 39/3573 (1.1) Placebo: 34/3566 (1) **At median follow up of 95.6 months (Cuzick 2007)** *All cardiac events including myocardial infarction, angina, other cardiac.* Tamoxifen group: 122/3579 (3.4%) Placebo group: 123/3575 (3.4%) Risk ratio (95% CI): 0.99 (0.77 to 1.29)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	k) *Gynaecological or vasomotor* - At median follow up of 50 months (Cuzick 2002) Tamoxifen: 2922/3573 (81.8) Placebo: 2414/3566 (67.7) ***Gynaecologic/vasomotor* – At median follow up of 95.6 months (Cuzick 2007)** Tamoxifen group: 3151/3579 (88) Placebo group: 2922/3575 (81.7) Risk ratio (95%CI): 1.08 (1.06 to 1.10) ***l) Headaches and migraines* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 997/3573 (27.9) Placebo: 1067/3566 (29.9) ***Headaches - At median follow up of 95.6 months (Cuzick 2007)*** Tamoxifen group: 1169/3579 (32.7) Placebo group: 1261/3575 (35.3) Risk ratio (95%CI): 0.93 (0.87 to 0.99) ***m) All breast complaints (multiple breast cysts) – at median follow up of 95.6 months (Cuzick 2007)*** Tamoxifen group: 693/3579 (19.4) Placebo group: 903/3575 (25.3) Risk ratio (95%CI): 0.77 (0.70 to 0.84) ***n) All fractures* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 116/3573 (3.3) Placebo: 127/3566 (3.6)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	All fractures including wrist, arm, hip and forearm – at median follow up of 95.6 months (Cuzick 2007) Tamoxifen group: 240/3579 (6.7) Placebo group: 235/3575 (6.6) Risk ratio (95%CI): 1.02 (0.86 to 1.21) ***o) Nail changes* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 148/3573 (4.1) Placebo: 96/3566 (2.7) ***p) Eye (excluding cataracts)* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 373/3573 (10.4) Placebo: 376/3566 (10.5) ***Eye complaints excluding cataracts – at median follow up 95.6 months (Cuzick 2007)*** Tamoxifen group: 947/3579 (26.6) Placebo group: 934/3575 (26.1) Risk ratio (95%CI): 1.01 (0.94 to 1.09) ***q) Cataracts* - At median follow up of 50 months (Cuzick 2002)** Tamoxifen: 38/3573 (1) Placebo: 37/3566 (1.0) ***Cataracts, n/N – at median follow up of 95.6 months (Cuzick 2007)*** Tamoxifen group: 67/3579 (1.9) Placebo group: 54/3575 (1.5) Risk ratio (95%CI): 1.24 (0.87 to 1.77)

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**

r) Development of other cancers – only most updated analysis has been extracted, median follow up of 16 years (Cuzick 2015)

	0-5 year follow up		5-10 year follow up		≥10 year follow up		Overall	
	Tamoxifen N=3579	Placebo N=3575	Tamoxifen N=3446	Placebo N=3474	Tamoxifen N=3343	Placebo N=3295	Tamoxifen N=3579	Placebo N=3575
Gynaecological cancers								
Endometrial	15	4	7	11	7	5	29	20
	OR (95%CI): 3.76 (1.20 TO 15.56)		OR (95%): 0.64 (0.21 TO 1.80)		OR (95%): 1.40 (0.38 TO 5.61)		OR (95%): 1.45 (0.79 TO 2.71)	
All other cancers (including gastrointestinal, lung, melanoma, brain, lymphoma, myeloma or leukemia but excluding non-melanoma and endometrial)	57	63	59	62	95	81	211	206
	OR (95%CI): not reported		OR (95%CI): not reported		OR (95%CI): not reported		OR (95%CI): not reported	

Source of funding	Cancer research UK and the National Health and Medical Research Council (Australia)
Comments	• Menopausal hormone therapy use was allowed during the trial (40%) • Randomisation performed centrally by the IBIS study group by telephone or fax to a central office, balanced block randomisation was used and stratified by centre. • Non-consecutive allocation sequence generated by IBIS-1 programmer before study commencement

Bibliographic reference	**Cuzick (2015) Tamoxifen for prevention of breast cancer: extended long-term follow up of the IBIS-1 breast cancer prevention trial [updated analysis included for 2016 update]** **Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial [included in 2013 update].** **Cuzick, J and IBIS investigators (2002). First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial [included in 2004 original guideline].**
	• All IBIS-1 personnel, participants and clinicians were masked to treatment allocation and only the IBIS-1 trial statistician had access to unmasked data. • Sample size of 3500 based on event rate of 6.6 cases of breast cancer per 1000 women per year which with a 50% reduction in the anastrozole group would translate to nine cases of breast cancer per 1000 women per year for placebo. • Adverse events data were collected by annual postal questionnaires which were sent directly to all participants and returned to the central office. In the non-UK centres, annual questionnaires, annual clinic visits or hospital notes were used to collect these data, supplemented by a national registry in Finland. • Results not reported by menopausal status.

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G.22 Cuzick 2014 (reported in 3 papers)

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**
Study type	RCT

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**
Aim	To assess the efficacy and safety of the aromatase inhibitor anastrozole for prevention of breast cancer in postmenopausal women who are at high risk of the disease.
Patient characteristics	**Inclusion criteria:** • Postmenopausal women; women were deemed to be postmenopausal when they were aged 60 years or older; had had a bilateral oophorectomy; were younger than 60 years, but had a uterus and had had amenorrhoea for at least 12 months; or were aged less than 60 years, had no uterus, and had a concentration of follicle stimulating hormone of greater than 30 IU/L. • Women aged 45‑60 years who had a relative risk of breast cancer that was at least two times higher than in the general population, those aged 60‑70 years who had a risk that was at least 1・5 times higher, and those aged 40‑44 years who had a risk that was four times higher. • Women who did not meet other eligibility criteria were included if the Tyrer-Cuzick model indicated a 10-year risk of breast cancer of more than 5%. **Exclusion criteria:** • premenopausal status • any previous diagnosis of breast cancer (except for oestrogen receptor-positive ductal carcinoma in situ diagnosed less than 6 months previously and treated by mastectomy) • any invasive cancer in the previous 5 years (except for non-melanoma skin cancer or cervical cancer); • present or previous use of selective oestrogen receptor modulators for more than 6 months (unless as part of IBIS-I and treatment was completed at least 5 years before study entry) • intention to continue hormone replacement therapy; • prophylactic mastectomy; • evidence of severe osteoporosis (T score <‑4 or more than two vertebral fractures); • life expectancy of fewer than 10 years; • psychologically or physiologically unfit for the study;

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**
	• or a history of gluten or lactose intolerance, or both. **Baseline characteristics, anastrozole; placebo; median (range) or n (%)** • Age (years): 59·5 (55·0–63·5); 59·4 (55·1–63·3) • Age at menopause (years): 50·0 (45·0–52·0); 49·0 (45·0–52·0) • Body-mass index (kg/m²) <25: 581 (30%); 568 (29%) 25–30: 699 (36%); 732 (38%) >30 640: (33%); 644 (33%) • Previous use of hormone replacement therapy: 893 (47%); 910 (47%) • Use of hormone replacement therapy within previous 12 months: 128 (7%); 152 (8%) • Hysterectomy: 631 (33%); 656 (34%) • Two or more first-degree or second-degree relatives with breast or ovarian cancer: 956 (50%); 938 (48%) • One first-degree relative with breast cancer at age 50 years or younger: 675 (35%); 653 (34%) • One first-degree relative with bilateral breast cancer: 164 (9%); 141 (7%) • Lobular carcinoma in situ or atypical hyperplasia: 154 (8%); 190 (10%) • Oestrogen-receptor-positive ductal carcinoma in situ treated by mastectomy within 6 months: 160 (8%); 166 (9%) • 10-year Tyrer-Cuzick risk (%): 7·6% (5·8–9·9) 7·8 (5·1–10·2)
Number of Patients	N=3864 in total underwent randomisation 1920 in anastrozole group 1944 in placebo group
Intervention	1 mg oral anastrozole everyday for 5 years

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**
Comparison	Matching placebo every day for 5 years
Length of follow up	Median follow up of 5 years (range: 3.0 to 7.1)
Location	153 centres in 18 countries
Outcomes measures and effect size	1. **<u>All invasive breast cancer - anastrozole; placebo, n/N (%)</u>** 32/1920 (2); 64/1944 (3) Hazard ratio (95%CI): 0.50 (0.32 to 0.76) 2. **<u>Ductal carcinoma in situ (DCIS)</u>** 6/1920 (<1); 20/1944 (1) Hazard ratio (95%CI): 0.30 (0.12 to 0.74) 3. **<u>Non-adherence to chemoprevention</u>** ***In Cuzick 2014*** • Reported as full 5-year adherence was 68% in the anastrozole group versus 72% in the placebo group • The main reasons for treatment discontinuation were adverse events (375/1920 [20%] in the anastrozole group; 298/1944 [15%] in the placebo group) and patient refusal (94/1920 [5%] in the anastrozole group; 98/1944 [5%] in the placebo group). • At the cutoff date, 357 women (19%) in the anastrozole group and 450 (23%) in the placebo group were continuing with treatment. ***In Spagnolo 2016*** • Reported as treatment discontinuation because of onset of CTS or other adverse events • Anastrozole: 12/1920 (0.6) • Placebo: 5/1944 (0.3) • Odds ratio (95%CI): 2.44 (0.80 to 8.85); p=0.08

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**

4. **Health Related Quality of life**
   Not reported

5. **Overall Survival**
   Extracted as total deaths (various causes) - anastrozole; placebo, n/N (%)
   18/1920 (1%); 17/1944 (1%)

6. **Adverse events**

a) Cuzick 2014

	Anastrozole n=1920	Placebo n=1944	Risk ratio (95%CI)
Endometrial cancer	3 (<1%)	5 (<1%)	0·61 (0·15–2·54)
All other cancers (including gastrointestinal, lung, melanoma, thyroid, leukemia, lymphoma or myeloma, cancer of urinary tract, nervous system, ovarian and vaginal cancer but excluding non-melanoma and endometrial)	27	45	Not reported
Carcinomatosis	1 (<1%)	1 (<1%)	1·01 (0·06–16·18)

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**

Fractures	164 (9%)	149 (8%)	1·11 (0·90–1·38)
Musculoskeletal (arthralgia, joint stiffness, pain in hand or foot, carpal tunnel syndrome or nerve compression)	1226 (64%)	1124 (58%)	1·10 (1·05–1·16)
Vasomotor (hot flushes or night sweats)	1090 (57%)	961 (49%)	1·15 (1·08–1·22)
Gynaecological (vaginal dryness, haemorrhage or bleeding, vaginal or uterine prolapse, vulvovaginal pruritus)	460 (24%)	423 (22%)	1·10 (0·98–1·24)
Hypotension	89 (5%)	55 (3%)	1.64 (1.18 – 2.28)
Myocardial infarction or cardiac failure	8 (<1%)	9 (<1%)	0.90 (0.35 – 2.23)
Thrombosis or embolism	19 (1%)	17 (1%)	1.13 (0.59 – 2.17)
Phlebitis	9 (<1%)	8 (<1%)	1.14 (0.44 – 2.95)
Cerebrovascular accident	3 (<1%)	6 (<1%)	0.51 (0.13 – 2.02)
Eye (dry eyes, conjunctivitis, glaucoma, cataract)	348 (18%)	335 (17%)	1·05 (0·92–1·21)
Infections (influenza, otitis media)	230 (12%)	217 (11%)	1·07 (0·90–1·28)

Bibliographic reference	**Cuzick 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial** **Spagnolo 2016. Anastrozole-induced carpal tunnel syndrome: results from the Intervention Breast Cancer Intervention Study II Prevention Trial (IBIS-2)** **Sestak I, Singh S, Cuzick J, Blake G M, Patel R, Gossiel F, Coleman R, Dowsett M, Forbes J F, Howell A, and Eastell R. (2014). Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial.[Erratum appears in Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncology, 15(13), pp.1460-8.**
	b) Spagnolo 2016 Incidence of CTS after 6.4 years of follow up, n (%) Anastraozole: 65/1920 (3.4) Placebo: 31/1944 (1.6) Odds ratio (95%CI): 2.16 (1.40 to 3.33); p<0.001
Source of funding	Cancer Research UK, the National Health and Medical Research Council Australia, Sanofi-Aventis and AstraZeneca.
Comments	• Eligible women were randomly assigned (1:1) by central computer allocation to either anastrozole or matching placebo. • Randomisation was stratified by country and was done with randomly chosen randomisation blocks (size six, eight, or ten) to maintain balance. • All IBIS-II personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician had access to unblinded data. • Diagnosis, management and reporting of CTS were left to local investigators and were therefore heterogeneous • All postmenopausal women

1

G.3 1 Fallowfield 2001

Bibliographic reference	**Fallowfield et al (2001) Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomised controlled trials [included in 2004 original guideline]**
Study type	Prospective cohort study
Aim	To evaluate the psychosocial implications of tamoxifen versus placebo in women who are at an increased risk of breast cancer.
Patient characteristics	**Included:** consecutive women at high familial risk of breast cancer recruited into the TAMOPLAC and IBIS trials (416 and 72 women respectively) **Women recruited into TAMOPLAC and IBIS trials before data merge:** age, familial risk of breast cancer, use of HRT and psychosocial characteristics reported as similar, although more TAMOPLAC than IBIS women were premenopausal. **Baseline characteristics, n/N (%)** Median age (years/range): Tamoxifen - 46 (33-66); Placebo - 46 (33-67) Premenopausal (%): Tamoxifen - 51.0; Placebo - 51.8 Postmenopausal or hysterectomy (%): Tamoxifen - 49.0; Placebo - 48.2 HRT before trial entry (%): Tamoxifen - 20.6; Placebo - 22.6 Family history of breast cancer (%): Mother: Tamoxifen - 73.7; Placebo - 72.7; Sister: Tamoxifen - 32.1; Placebo - 33.8
Number of Patients	**Total:** 488 **Tamoxifen:** 254 (217 [TAMOPLAC trial] 37 [IBIS trial]) **Placebo:** 234 (199 [TAMOPLAC trial], 35 [IBIS trial])
Intervention	**Tamoxifen**: psychological and sexual functioning in women at high familial risk of breast cancer randomised to tamoxifen (20mg daily) for at least 5 years
Comparison	**Placebo**: psychological and sexual functioning in women at high familial risk of breast cancer randomised to placebo for at least 5 years
Length of follow up	• Participants sent postal questionnaires every 6 months for 5 years. • Reminders were sent to non-responders after 4 weeks • 71.1% of women returned at least 8 of 10 questionnaires. 46.9% returned all questionnaires. No difference in participation between those randomised to receive tamoxifen or placebo (OR [95% CI] 1.00; [0.68-1.49]). Questionnaire return and loss to follow up • 15 women did not return any questionnaires after baseline. • 11 women withdrew from the main trials, and so did not return any questionnaires • Odds ratio (95% CI): 1.00 (0.68 to 1.49)

Bibliographic reference	**Fallowfield et al (2001) Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomised controlled trials [included in 2004 original guideline]**
Location	Royal Marsden Hospital tamoxifen RCT (TAMOPLA C), London; International Breast Cancer Intervention Study (IBIS), Manchester centre
Outcomes measures and effect size	**1. Development of invasive breast cancer** Not reported **2. Development of Ductal Carcinoma in situ (DCIS)** Not reported **3. Non-adherence to chemoprevention** • 38.2% (153 of 401, data missing for 87) of the psychosocial study participants stopped taking the trial medication before the end of the trial. • There was a reduction in adherence associated with tamoxifen (OR [95% CI]: 0.33 [0.19 to 0.57]) **4. Health related quality of life** Not reported **5. Overall survival** Not reported **6. Adverse events, n/N (%)** *a) Psychological morbidity* For those who exceeded the GHQ threshold and so were identified as probable cases of psychological morbidity. Becoming a new 'case' at 6 months was not associated with treatment group: Tamoxifen: 29/220 (13.2%) Placebo: 26/201 (12.9%) Odds ratio (95% CI): 0.72 (0.53 to 1.00) *b) Sexual activity* Throughout the trial, approximately 3/4 of the women who completed the Sexual Activity Questionnaire (SAQ). OR below is adjusted for baseline sexual activity status and time on the study. • OR (95% CI): 1.63 (0.86 to 3.08)

Bibliographic reference	Fallowfield et al (2001) Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomised controlled trials [included in 2004 original guideline]

c) Vaginal dryness

- Vaginal dryness: OR (95% CI): 0.56 (0.30 to 1.05)
- Pain during penetration: OR (95% CI): 0.87 (0.49 to 1.57)

d) Other symptoms reported

				Tamoxifen/placebo	
Symptom	**No. of patients***	**Tamoxifen %**	**Placebo %**	**Odds ratio**	**95% CI**
Weight gain	358	40.76	47.13	0.77	0.51-1.17
Join pains	356	36.26	43.1	0.75	0.49-1.15
Feeling bloated	358	34.24	39.08	0.81	0.53-1.25
Night sweats	355	43.09	28.74	1.88	1.21-2.92
Hot flashes	359	41.6	28.74	1.77	1.14-2.74
Low energy	358	27.72	40.8	0.56	0.36-0.87
Muscle stiffness	353	29.83	32.56	0.88	0.56-1.38
Leg/hand pains	356	29.67	29.89	0.99	0.63-1.56
Forgetfulness	357	30.6	28.74	1.09	0.69-1.72
Breast sensitivity/tenderness	355	22.95	36.63	0.52	0.32-0.82
Difficulty with bladder control (when laughing or coughing)	355	26.92	27.75	0.96	0.60-1.53
Brittle nails	356	31.69	22.54	1.59	0.99-2.56
Headaches	361	24.32	29.55	0.77	0.48-1.22
Vaginal dryness	359	21.74	29.14	0.68	0.42-1.09
Mood swings	358	22.4	26.29	0.81	0.50-1.31
Anxiety	355	22.53	24.86	0.88	0.54-1.44
Increase in appetite	357	19.23	25.14	0.71	0.43-1.17
Irritability	355	18.13	24.28	0.69	0.41-1.15

Bibliographic reference	Fallowfield et al (2001) Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomised controlled trials [included in 2004 original guideline]					
	Light headaches	356	16.85	23.26	0.67	0.40-1.13
	Swelling of hands or feet	356	17.58	21.84	0.76	0.45-1.29
	Depression	357	16.85	21.39	0.75	0.44-1.27
	Irregular periods	322	21.56	16.13	1.43	0.81-2.51
	Difficulty concentrating	356	16.94	19.65	0.83	0.49-1.43
	Shortness of breath	357	16.48	18.29	0.88	0.51-1.53
	Blurring of vision	354	10.56	22.41	0.41	0.23-0.74
	Heavier periods	321	13.77	16.88	0.79	0.43-1.45
	Constipation	357	12.71	17.05	0.71	0.39-1.28
	Vaginal discharge	356	17.68	10.29	1.87	1.01-3.48
	Difficulty with bladder control, not only when laughing or coughing	355	14.75	11.63	1.32	0.71-2.45
	Vaginal itching/irritation	358	16.39	9.71	1.82	0.97-3.44
	Abdominal cramps	346	12.36	13.69	0.89	0.48-1.66
	Pain/discomfort with intercourse	339	12.5	11.67	1.08	0.56-2.08
	Diarrhoea	355	7.78	8.57	0.90	0.42-1.92
	Skin rashes	356	8.24	7.47	1.11	0.51-2.41
	Tinning of hair	354	7.78	7.47	1.04	0.48-2.29
	Nausea	356	5.46	7.51	0.71	0.30-1.67
	Vaginal bleeding or spotting	357	5	8	0.60	0.25-1.42
	Cold sweats	347	9.71	2.91	3.59	1.30-9.97
	Change in voice	356	3.87	2.86	1.37	0.43-4.39
	Weight loss	349	1.69	4.09	0.40	0.10-1.58
	Decrease in appetite	348	1.13	1.75	0.64	0.11-3.88
	Vomiting	355	1.09	1.74	0.62	0.10-3.77

Bibliographic reference	**Fallowfield et al (2001) Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomised controlled trials [included in 2004 original guideline]**
	*Total numbers in each arm of study not reported b) c) and d) above has not been added to the GRADE tables given the raw data to calculate risk ratios has not been reported in the study. This has nevertheless been extracted as supporting information
Source of funding	This study was funded by the Cancer Research Campaign
Comments	• Randomisation: participants randomised but paper doesn't detail how this was done, where it was done, or who did it. • Blinding: Treatment allocation concealed from all patients and staff in the main trials. Unblinding of the data for the psychosocial study was conducted by an independent statistician. • Data by menopausal status not reported • Adverse events data collected by self-reported questionnaires

G.41 Fisher 2005 (reported in 2 papers)

Bibliographic reference	**Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]** **Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]**
Study type	Randomised Controlled Trial
Aim	To provide updated findings from the P-1 trial after 7 years of follow-up (average follow-up was 74 months)
Patient characteristics	**Inclusion criteria** • Women at increased risk of breast cancer because: • they were aged 60 years or older • they were aged 35-59 years with a 5 year predicted risk for breast cancer of at least 1.66% (according to Gail index) • had a history of lobular cancer in situ (LCIS) or atypical hyperplasia • have had a mammogram 180 days before randomisation, that was negative for breast cancer **Exclusion criteria** • Women who had taken oestrogen or progesterone replacement therapy, oral contraceptives or androgens within 3 months of randomisation • Women with a history of deep vein thrombosis or pulmonary embolism

Bibliographic reference	**Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]** **Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]**
	Baseline characteristics *Age in years, n/N (%)* 35-39: Tamoxifen – 160/6597 (2.4); Placebo – 186/6610 (2.8) 40-49: Tamoxifen – 2429/6597 (36.8); Placebo – 2414/6610 (36.5) 50-59: Tamoxifen – 2037/6597 (30.9); Placebo – 2022/6610 (30.6) 60-69: Tamoxifen – 1577/6597 (23.9); Placebo – 1592/6610 (24.1) ≥70: Tamoxifen – 394 (6); Placebo – 396 (6) Race, n/N (%) White: Tamoxifen – 6366/6597 (96.5); Placebo – 6368/6610 (96.3) African American: Tamoxifen – 111/6597 (1.7); Placebo – 1126610 (1.7) Other: Tamoxifen – 120/6597 (1.8); Placebo – 130/6610 (2) First degree relatives with breast cancer, n/N (%) One or more first degree relatives: Tamoxifen – 5049/6597 (76.5); Placebo – 5013/6610 (75.8) Prior hysterectomy, n/N (%) Tamoxifen – 2486 (37.7) Placebo – 2410 (36.5) History of local carcinoma in situ, n/N(%) Tamoxifen – 416 (6.3) Placebo – 413 (6.2)
Number of Patients	Initial participants randomised: N=13,388 Included in analysis: N=13,207 Tamoxifen N = 6597 Placebo N = 6610
Intervention	Tamoxifen – 20mg daily for at least 5 years
Comparison	Placebo
Length of follow up	Initial analysis (Fisher 1998) – average follow up was 47.7 months.

Bibliographic reference	**Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]** **Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]**
	Updated analysis (Fisher 2005) – average follow up was 74 months.
Location	USA
Outcomes measures and effect size	**1. Development of invasive breast cancer, n/N (%) –** data reported for subgroup with family history **At average follow up of 74 months (Fisher 2005)** Tamoxifen: 112/5049 (2.2) Placebo: 188/5013 (3.8) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 137/6576 (2.1) Placebo: 72/6599 (1.1) **2. Development of ductal carcinoma in situ (DCIS) -** Reported as rate of DCIS and LCIS; number of events not reported; data includes all subjects as numbers for subgroup with family history not reported. **At average follow up of 74 months (Fisher 2005)** Risk ratio (95% CI): 0.63 (0.45 to 0.89) Incidence rate in tamoxifen group: 10.2 per 1000 women Incidence rate in placebo group: 15.8 per 1000 women **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 35/6576 (0.5) Placebo: 69/6599 (1.0) Risk ratio (95% CI):0.50 (0.33 to 0.77) **3. Non-adherence to chemoprevention** **At average follow up of 74 months (Fisher 2005)** Not reported **At average follow up of 47.7 months (Fisher 1998)** *Discontinuation of treatment* • Tamoxifen: 23.7% (1559/6576)

Bibliographic reference	**Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]** **Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]**
	• Placebo: 19.7% (1300/6599) 6% participants in each study group were lost to follow up *n/N calculated by analyst **4. Health Related Quality of Life** Not reported. **5. Overall survival, n/N (%)** - Data includes all subjects not just those with family history *Extracted as total deaths (various causes)* **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 126/6597 (1.9) Placebo group: 114/6610 (1.7) Risk ratio (95% CI): 1.10 (0.85 to 1.43) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 57/6576 (0.9) Placebo: 71/6599 (1.1) Risk ratio (95% CI): 0.81 (0.56 to 1.16) **6. Adverse events*. n/N (%) –** includes all subjects not just those with family history a) Hot flushes*, % with slightly bothersome, moderately bothersome, quite a bit or extremely bothersome hot flushes assessed using quality of life questionnaire that was used as a self-reporting instrument. Some subjects opted not to complete the questionnaire thus information not available for 101 women in the placebo group and 110 in the tamoxifen group **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 81.6 (5276/6466*)

Bibliographic reference	Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update] Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]
	Placebo: 68.6 (4458/6498*) *n/N calculated by analyst **At average follow up of 74 months (Fisher 2005)** Not reported <u>b) Vaginal discharge</u>, % with slightly bothersome, moderately bothersome, quite a bit or extremely bothersome hot flushes (n/N)**: **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 55.2 (3569/6466) Placebo: 34.8 (2261/6498) *Assessed using quality of life questionnaire that was used as a self-reporting instrument. Some subjects opted not to complete the questionnaires thus information not available for 101 women in the placebo group and 110 in the tamoxifen group. **n/N calculated by analyst **At average follow up of 74 months (Fisher 2005)** Not reported <u>c) Osteoporotic fractures (hip, spine, colles)</u> **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 80/6597 (1.2) Placebo group: 116/6610 (1.8)% Risk ratio (95% CI): 0.68 (0.51 to 0.92) **At average follow up of 47.7 months (Fisher 1998)** *Fractures*

Bibliographic reference	Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update] Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]
	Tamoxifen: 111/6576 (1.7) Placebo: 137/6599 (2.1) Risk ratio (95% CI): 0.81 (0.63 to 1.05) d) Ischaemic heart disease (myocardial infarction, severe angina and acute ischemic syndrome) **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 113/6597 (1.7) Placebo group: 109/6610 (1.6) Risk ratio (95% CI): 1.03 (0.79 to 1.36) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 71/6576 (0.5) Placebo: 62/6599 (0.4) Risk ratio (95% CI):1.15 (0.81 to 1.64) e) Uterine cancer (invasive or in situ endometrial cancer) **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 54/6597 (0.8) Placebo group: 20/6610 (0.3) **At average follow up of 47.7 months (Fisher 1998)** *Invasive endometrial cancer* Tamoxifen: 36/6576 (0.5) Placebo: 15/6599 (0.2) Risk ratio (95% CI): 2.53 (1.35 to 4.97) *In situ endometrial cancer* Tamoxifen: 1/6576 (0.02) Placebo: 3/6599 (0.05)

Bibliographic reference	Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update] Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]
	Risk ratio (95% CI): 0.35 (0.01 to 4.38) f) Thromboembolic events – stroke **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 71/6597 (1.1) Placebo group: 50/6610 (0.8) Risk ratio (95% CI): 1.42 (0.97 to 2.08) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 38/6576 (0.6) Placebo: 24/6599 (0.4) Risk ratio (95% CI): 1.59 (0.93 to 2.77 g) Thromboembolic events – transient ischemic attack **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 31/6597 (0.5) Placebo group: 34/6610 (0.5) Risk ratio (95%CI): 0.91 (0.54 to 1.52) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 19/6576 (0.3) Placebo: 25/6599 (0.4) Risk ratio (95% CI): 0.76 (0.40 to 1.44 h) Thromboembolic events – pulmonary embolism **At average follow up of 74 months (Fisher 2005)**

Bibliographic reference	Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update] Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]
	Tamoxifen group: 28/6597 (0.4) Placebo group: 13/6610 (0.2) Risk ratio (95% CI): 2.15 (1.08 to 4.51) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 18/6576 (0.3) Placebo: 6/6599 (0.1) Risk ratio (95% CI): 3.01 (1.15 to 9.27) <u>i) Thromboembolic events – DVT</u> **At average follow up of 74 months (Fisher 2005)** Tamoxifen group: 49/6597 (0.7) Placebo group: 34/6610 (0.5) Risk ratio (95%CI): 1.44 (0.91 to 2.30) **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 35/6576 (0.5) Placebo: 22/6599 (0.3) Risk ratio (95% CI): 1.60 (0.91 to 2.86 <u>j) Cataracts</u> **At average follow up of 74 months (Fisher 2005)** Risk ratio (95% CI): 1.21 (1.10 to 1.34) Incidence rate in tamoxifen group: 27.5 per 1000 women Incidence rate in placebo group: 22.85 per 1000 women **At average follow up of 47.7 months (Fisher 1998)** Tamoxifen: 574/6101* (9.4) Placebo: 507/6131* (8.3) Risk ratio (95% CI): 1.14 (1.01 to 1.29)

<table>
<tr><td>Bibliographic reference</td><td>Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]

Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]</td></tr>
<tr><td></td><td>*Number at risk = number without cataracts at randomisation

<u>k) Cancers other than those of the breast and endometrium</u>

At average follow up of 74 months (Fisher 2005)

<table>
<tr><td></td><td>Tamoxifen (n=6597)</td><td>Placebo (n=6610)</td><td>Risk ratio (95%CI)</td></tr>
<tr><td>All other cancers (including gastrointestinal, lung, melanoma, brain, lymphoma, myeloma or leukemia but excluding endometrial)*

*unclear whether this includes non-melanoma and melanoma as outcome reported as ‘skin cancer’ without differentiation of type of skin cancer</td><td>178</td><td>155</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Supported by Public Health Service grants (U10-CA-37377 and U10-CA-69974) from the National Cancer Institute and the Department of Health and Human Services.</td></tr>
<tr><td>Comments</td><td>• Not all subjects had a family history of breast or related cancers - more than 75% had at least one first-degree relative with breast cancer.
• Participants were prohibited from taking oestrogen or progesterone replacement therapy, oral contraceptives or androgens while enrolled in the study.
• Blinding: double blind – not specified who was blinded. All groups received the same care apart from the intervention and participants were ‘blind’ to the treatment until the end of the 7 year follow up. Not clear whether the individuals administering the treatment were blinded to treatment allocation.
• Randomisation performed centrally and was double blinded for the original analysis/results and stratified by age, race, history of LCIS and 5 year predicted breast cancer risk.</td></tr>
</table>

Bibliographic reference	**Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study [included in 2013 update]** **Fisher et al (1998) Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study [included in 2004 original guideline]**
	• Due to the positive results for patients receiving Tamoxifen, the trial was unblinded and both patients and physicians were informed as to which arm of the trial they were in. Women in the Tamoxifen arm were given the option to continue for a total of 5 years and women in the placebo arm were given the option to begin taking tamoxifen. • No outcome data obtained from 180 due to loss to follow up in the 6th and 7th year of follow up hence number analysed = 13 207 (6597 and 6610 in tamoxifen and placebo arms respectively) • In the initial report, follow up was not available for 212 women but it has since been obtained for 32 of these women. • Power calculation not reported • Unclear whether skin cancer in the composite outcome extracted includes melanoma and non-melanoma. • Adverse events assessed using quality of life questionnaire that was used as a self-reporting instrument • Menopausal status not reported

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G.52 Powles 1998

Bibliographic reference	**Powles (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial [included in 2004 original guideline]**
Study type	Randomised controlled trial (double-blind)
Aim	To assess whether tamoxifen would prevent breast cancer in healthy women – results of planned interim analysis

Bibliographic reference	**Powles (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial [included in 2004 original guideline]**
Patient characteristics	**Included**: • Women between 30-70 yrs; no clinical/screening evidence of breast cancer; • Increased risk of breast cancer because of family history • At least one 1st degree relative aged <50 with bilateral breast cancer, • Or one affected 1st degree relative of any age + another affected 1st or 2nd degree relative; • Women with history of a benign breast biopsy who had 1st degree relative with breast cancer was included. • Post-menopausal women taking hormone replacement therapy – didn't have to stop therapy **Excluded**: • Women with history of any cancer or DVT or PE; • Pre-menopausal women considering further pregnancies or taking oral contraception **Baseline characteristics** • Median age in years (range): Tamoxifen - 47 (31-70); Placebo - 47 (30-70) • Pre/perimenopausal: Tamoxifen - 822/1250 (66); Placebo - 812/1244 (65) • Post menopausal: Tamoxifen – 416/1250 (33); Placebo – 421/1244 (34) • 1st degree relative with breast cancer <<50 yrs: Tamoxifen – 698/1250 (56); Placebo – 668/1244 (54) • 2 or more relatives with breast cancer at any age: Tamoxifen – 225/1250 (18); Placebo – 205/1244 (16) • Previous benign lump excised: Tamoxifen – 280/1250 (22); Placebo – 263/1244 (21) • On HRT at start: Tamoxifen – 187/1250 (15); Placebo – 202/1244 (16)
Number of Patients	**Total consented:** 2494 **Tamoxifen:** 1250 **Placebo:** 1244 **Removed from analysis:** 23 (participants had evidence of DCIS and 1 person randomised to placebo was found to have pre-existing invasive cancer) **Included in analysis:** 2471 **Tamoxifen:** 1238 **Placebo:** 1233
Intervention	Tamoxifen (20mg daily orally, [Tamoplac]) for 8 years
Comparison	Identical placebo (Orion Pharma)
Length of follow up	• DCIS initially an inclusion criteria, but later exclusion criteria and 22 women were excluded from analysis

Bibliographic reference	Powles (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial [included in 2004 original guideline]
	• Median follow- up of 70 months for both groups. • Follow-up assessments every 6 months. • Annual mammography. 280 women have been were reported as lost to follow up at the time of the report: Tamoxifen:141/1238 (11.4%) Placebo: 139/1233 (11.3%)
Location	Royal Marsden Hospital (UK) Sites in Italy and USA
Outcomes measures and effect size	**1. Development of invasive breast cancer and DCIS** Tamoxifen: 30/1238 (2.4%) Placebo: 32/1233 (2.6%) **2. Development of ductal carcinoma in situ (DCIS)** Tamoxifen: 4/1238 (0.3) Placebo: 4/1233 (0.3) **3. Non-adherence to chemoprevention** Tamoxifen: 497/1238 (40.1)* Placebo: 380/1233 (30.8%)** *177 stopped medication early due to non-toxic reasons and 320 due to toxic reasons including nausea (n=12), headaches (n=13), hot flushes (n=51), weight gain (n=6), period abnormality (n=18), gynaecological problems (n=69), mood change (n=8) and other or unknown reasons (n=143) **204 stopped medication early due to non-toxic reasons and 176 due to toxic reasons including nausea (n=6), headaches (n=14), hot flushes (n=13), weight gain (n=12), period abnormality (n=6), gynaecological problems (n=18), mood change (n=1), other or unknown reasons (n=106). **4. Health related quality of life** Not reported **5. Overall survival** *Reported as deaths* Tamoxifen – 9/1238 (0.7) – 4 due to breast cancer, 5 due to other causes

Bibliographic reference	Powles (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial [included in 2004 original guideline]
	Placebo – 6/1233 (0.5) – 1 due to breast cancer, 5 due to other causes **6. Adverse events** *a) Total number of other cancers** Tamoxifen: 15/1238 (1.2%) Placebo: 23/1233 (1.9%) *Excludes cancer of the endometrium but includes ovarian, gastrointestinal and other cancers (not defined) *b) Cancer of endometrium* Tamoxifen: 4/1238 (0.3%) Placebo: 1/1233 (0.1%) *f) Deep Vein Thrombosis* Tamoxifen: 4/1238 (0.3%) Placebo: 2/1233 (0.1%) *g) Pulmonary Embolism* Tamoxifen: 3/1238 (0.2%) Placebo: 2/1233 (0.2%)
Source of funding	Trial supported by the cancer research campaign
Comments	• DCIS initially and inclusion criteria, but later exclusion criteria and 22 women were excluded from analysis • Administrative errors led to 11 participants being randomised by the pharmacy – the data was censored at the time of their second randomisation • Participants randomised, but no details reported about how this was done or who did it. • Blinding: not reported • Based on accrual rate in 1993 and the relative risk of breast cancer in the study population, the study was powered to detect a 75% effect of tamoxifen in 1996 and a 50% effect in 1998 (power = 90%) • Unclear how adverse events data was collected • All included women were post-menopausal

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G.62 Sestak 2012

Bibliographic reference	**Sestak I, Harvie M, Howell A et al (2012) Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Research and Treatment. 134(2):727-34**
Study type	Secondary analysis of RCTs
Aim	To assess the effects of anastrozole on weight change in postmenopausal women compared to tamoxifen in the adjuvant setting (Anastrozole, tamoxifen, alone or in combination trial) and to placebo in the IBIS-2 trial preventive setting. Also investigated weight change in IBIS-1 study which compared tamoxifen with placebo in women at increased risk of breast cancer.
Patient characteristics	**Inclusion criteria** IBIS-1 trial • Postmenopausal women at high risk of developing breast cancer* IBIS-2 trial • High risk postmenopausal women without breast cancer* **Exclusion criteria** IBIS-1 trial • Not reported* IBIS-2 trial • Not reported* *Authors indicate additional details have been described in Cuzick 2002 (see separate evidence table) **Baseline characteristics** Not reported for this sub-analysis
Number of Patients	IBIS-1 • N=1936 in tamoxifen arm and 1922 in placebo arm • Baseline weight measurements were available for 1898 (98%) in the tamoxifen arm and 1885 (98%) in the placebo arm

Bibliographic reference	**Sestak I, Harvie M, Howell A et al (2012) Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Research and Treatment. 134(2):727-34**
	• 1369 (71%) in the tamoxifen arm and 1396 (73%) in placebo arm had a baseline and 12 month weight measurement • 606 (31%) in tamoxifen arm and 648 (33.7%) in placebo arm had baseline, 12 month and 60 month weight measurement available for analysis. IBIS-2 • N=577 in anastrozole arm and 568 in placebo arm • Baseline weight measurements were available for 574 (99.5%) in the anastrozole arm and 560 (98.6%) in placebo arm. • 364 (63.1%) in the anastrozole arm and 355 (62.5%) in the placebo arm had a baseline and 12 month measurement
Intervention	IBIS-1 • 5 years of tamoxifen (20mg per day) IBIS-2 • 5 years of anastrozole 1mg/day
Comparison	IBIS-1 • Matching placebo IBIS-2 • Matching placebo
Length of follow up	IBIS-1 • Up to 60 months IBIS-2 • Up to 12 months
Location	Various
Outcomes measures and effect size	**1. Development of invasive breast cancer** Not reported **2. Development of DCIS**

Bibliographic reference	Sestak I, Harvie M, Howell A et al (2012) Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Research and Treatment. 134(2):727-34
	Not reported **3. Non-adherence to chemoprevention** Not reported **4. Health related quality of life** Not reported **5. Overall survival** Not reported **6. Adverse events** IBIS-1 Weight change in kg (SD) *Mean weight at baseline* Tamoxifen: 71.9 (13.9); n=1898 Placebo: 71.4 (13.3); n=1885 *Mean weight change at 12 months* Tamoxifen: 0.9 (1.4); n=1369 Placebo: 1.0 (1.5); n= 1396 *Mean weight change at 60 months* Tamoxifen: 1.3 (5.6); n=606 Placebo: 1.3 (5.7); n=648 IBIS-2 1. Weight change in kg (SD)

Bibliographic reference	**Sestak I, Harvie M, Howell A et al (2012) Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Research and Treatment. 134(2):727-34**
	Mean weight at baseline Anastrozole: 73.9 (14); n=574 Placebo: 75.5 (15.9); n=560 *Mean weight change at 12 months* Anastrozole: 0.8 (5.3); n=364 Placebo: 0.5 (7.3); n=355
Source of funding	Analysis was supported by the Cancer Research UK and AstraZeneca
Comments	• Data reported from the ATAC trial has not been extracted given this study included those with early breast cancer rather than those at increased risk of cancer. • Weight was measured at entry and any subsequent clinic visits by research staff and was not a self-reported measure. Weight was measured on digital and non-digital scales and participants wore light clothes but no shoes. • For the IBIS-2 study, weight was measured at follow-up visit for those who participated in the bone sub study (anastrozole n=577; placebo n=568). • All post-menopausal women

G.71 Vogel 2010 (reported in 2 papers)

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**
Study type	Randomised Double blinded Trial
Aim	To provide an updated analysis of the effectiveness of Tamoxifen and Raloxifene in the prevention of breast cancer in women taking part in the STAR trial.
Patient characteristics	**Inclusion criteria** • A five year predicted breast cancer risk of 1.66% based on the GAIL model • ≥35 years and postmenopausal

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**
	• Not taking Tamoxifen, raloxifene, hormone therapy, oral contraceptives or androgens for at least the 3 months prior to randomisation • Not taking warfarin or cholestyramine • no history of stroke, transient ischemic attack, pulmonary embolism, or deep-vein thrombosis • No history any malignancy diagnosed in the five years prior to randomisation except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix • No uncontrolled atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension • No psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day. • Post-menopausal women aged ≥35 years or older with a history of LCIS treated by local excision only **Exclusion criteria** None specifically listed – implied by the inclusion criteria **Baseline characteristics** *Age in years, n/N (%)* ≤49: Tamoxifen – 884/9736 (9.1); Raloxifene – 878/9754 (9) 50-59: Tamoxifen – 4856/9736 (49.9); Raloxifene – 4855/9754 (49.8) 60-69: Tamoxifen – 3137/9736 (32.2); Raloxifene – 3174/9754 (32.5) ≥70: Tamoxifen – 859/9736 (8.8); Raloxifene – 847/9754 (8.7) *Race/ethnicity, n/N (%)* White: Tamoxifen – 9105/9736 (93.5); Raloxifene – 9115/9754 (93.4) African-American: 233/9736 (2.4); Raloxifene – 243/9754 (2.5) Hispanic: 192/9736 (2); Raloxifene – 193/9754 (2) Other: 206/9736 (2.1); Raloxifene – 203 (2.1) *At least one first degree relative with breast cancer, n/N (%)* Tamoxifen – 6898/9736 (71); Raloxifene – 6963/9754 (71)

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**
	History of hysterectomy, n/N (%) Tamoxifen – 4997/9736 (51.3) Raloxifene – 5037/9754 (51.6) *History of lobular carcinoma in situ, n/N (%)* Tamoxifen – 892 (9.2) Raloxifene – 889 (9.1)
Number of Patients	19490 women included in the updated analysis; 9736 in the tamoxifen group and 9754 in the raloxifene group 19471women included in the original analysis; 9726 in the tamoxifen group and 9745 in the raloxifene group
Intervention	Tamoxifen 20md/day for 5 years maximum
Comparison	Raloxifene 60mg/day for 5 years maximum
Length of follow up	Medium follow of 81 months in the updated analysis (Vogel 2010) versus 47 months in the initial report (Vogel 2006)
Location	USA; Almost 200 centres across the United States
Outcomes measures and effect size	**1. Development of invasive breast cancer, n/N (%)** – data reported for the subgroup with family history **At median follow up of 81 months (Vogel 2010)** • Tamoxifen: 165/6898 (2.4) • Raloxifene: 205/6963 (2.9) **At median follow up of 47 months (Vogel 2006)** • Tamoxifen arm: 111/6891 (1.6) • Raloxifene arm: 115/6956 (1.7) **2. Development of ductal carcinoma in situ, n/N (%)** - data reported for all subjects not just those with family history **At median follow up of 81 months (Vogel 2010)** • Tamoxifen: 70/9736 (0.7) • Raloxifene: 86/9754 (0.9)

Bibliographic reference	Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update] Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]
	• Risk ratio (95% CI): 1.22 (0.88 to 1.69) **At median follow up of 47 months (Vogel 2006)** • Tamoxifen arm: 30/9726 (0.3) • Raloxifene arm: 44/9745 (0.5) • Risk ratio (95% CI): (RR, 1.46; 0.90-2.41) **3. Non-adherence to chemoprevention -** includes all subjects not just those with family history **At median follow up of 81 months (Vogel 2010)** Not reported however since the original report and unbinding of treatment assignment, any woman who had not completed her 5-year course of tamoxifen was offered the option to switch to Raloxifene for the remaining portion of her treatment course. A total of 879 women chose this option. **At median follow of 47 months (Vogel 2006)** Reported as % with adherence to protocol • Tamoxifen arm - 68.3% • Raloxifene arm - 71.5% • Therefore number no adherent*: Tamoxifen – 3083/9726; Placebo – 2777/9745 *Calculated by analyst **4. Health related quality of life** Not reported **5. Overall survival, n/N (%) –** includes all subjects not just those with family history Extracted as total deaths **At median follow of 47 months (Vogel 2006)** • Tamoxifen arm: 101/9726 (1) • Raloxifene arm: 96/9745 (1) • Risk ratio (95% CI): 0.94 (0.71-1.26)

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**
	At median follow up of 81 months (Vogel 2010) • Tamoxifen arm: 236/9736 (2.4) • Raloxifene arm: 202/9754 (2.1) • Risk ratio (95% CI) 0.84 (0.70 to 1.02) **6. Adverse events, n/N (%) –** includes all subjects not just those with family history *a) Invasive uterine cancer* **At median follow up of 47 months (Vogel 2006)** • Tamoxifen arm: 36/9726 (0.4) • Raloxifene arm: 23/9745 (0.2) • Risk ratio (95% CI): 0.62 (0.35 to 1.08) **At median follow up of 81 months (Vogel 2010)** • Tamoxifen: 65/9736 (0.7) • Raloxifene: 37/9754 (0.4) • Risk ratio (95%CI): 0.55 (0.36 to 0.83) *b) Other cancers* *Other cancers not reported as a composite outcome and therefore not extracted.* *c) Ischemic heart disease* **At median follow up of 47 months (Vogel 2006)** Tamoxifen: 114/9726 (1.17)-->n=48 myocardial infarction, 51 severe angina, 15 acute ischemic syndromes Raloxifene: 126/9745 (1.29) --> n=37 myocardial infarction, 63 severe angina, 26 acute ischaemic syndromes Risk ratio (95%CI): 1.10 (0.85 to 1.43)

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**

At median follow up of 81 months (Vogel 2010) – authors state this outcome was not reported in the updated analysis because the updated analyses confirmed the lack of difference between treatment groups noted for this outcome in the original report (Vogel 2006).

d) Thromboembolic events

At median follow up of 47 months (Vogel 2006)

Type of event	Number of events		Risk ratio
	Tamoxifen (9726)	Raloxifene (9745)	
Stroke	53	51	0.96 (0.64 to 1.43)
Transient Ischaemic Attack	41	50	1.21 (0.79 to 1.88)
Thromboembolic events	141 (54 pulmonary embolism, 87 deep vein thrombosis)	100 (35 pulmonary embolism, 65 deep vein thrombosis)	0.70 (0.54 to 0.91)

At median follow of 81 months (Vogel 2010)

	Tamoxifen (9736)	Raloxifene (9754)	Risk ratio N (95% CI)
Thromboembolic events	202 (84 pulmonary embolism, 118 deep vein thrombosis)	154 (68 pulmonary embolism, 86 deep vein thrombosis)	0.75 (0.60 to 0.93)
Stroke and ischemic heart disease - authors state this outcome was not reported in the updated analysis because the updated analyses confirmed the lack of difference between treatment groups noted for this outcome in the original report (Vogel 2006).			

e) Osteoporotic fractures (hip, spine and colles)

At median follow up of 47 months (Vogel 2006)

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**

Type of event	Number of events		Risk ratio
	Tamoxifen (9726)	Raloxifene (9745)	
Total*	104	96	0.92 (0.69 to 1.22)
*Two women had both a hip and a spine fracture.			

At median follow up of 81 months (Vogel 2010) – authors state this outcome was not reported in the updated analysis because the updated analyses confirmed the lack of difference between treatment groups noted for this outcome in the original report (Vogel 2006).

f) Cataracts and cataract surgery

At median follow up of 47 months (Vogel 2006)

Type of event	Number of events		Risk ratio
	Tamoxifen (9726)	Raloxifene (9745)	
Developed cataracts during follow up	394	313	0.79 (0.68 to 0.92)
Developed cataracts and had cataract surgery	260	215	0.82 (0.68 to 0.99)

At median follow up of 81 months (Vogel 2010)

	Tamoxifen (8341)**	Raloxifene (8336)**	Risk ratio N (95% CI)
Developed cataracts during follow-up	739	603	0.80 (0.72 to 0.89)
Developed cataracts and had cataract surgery	575	462	0.79 (0.70 to 0.90)
**women at risk were those with no prior history of cataracts at entry			

Bibliographic reference	**Vogel et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer [included in 2013 update]** **Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial [included in 2013 update]**
Source of funding	Funding from Public Health Service grants U10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974 from the National Cancer Institute, Department of Health and Human Services.
Comments	• Randomisation - biased coin minimisation method with stratification for age, race/ethnicity, history of LCIS, 5 year predicted risk of breast cancer (Note: this information was provided as part of the 2006 publication – Vogel et al; 2006). • Blinding – double blind, participants and clinicians unaware of treatment allocation • 274 women not included due to lack of follow-up information (146 tamoxifen, 128 raloxifene); 2 women (raloxifene arm) bilateral mastectomy before randomisation. 1 woman removed from follow-up analysis as diagnosed with invasive breast cancer. • Not all subjects had family history of breast or related cancers – 71% in each arm • Since the time of the original report (Vogel 2006), follow-up information was collected on 20 women (10 from each group) who lacked follow up information at the time of the original report. One women from the Raloxifene group in the original report had been excluded from follow up analyses because she was diagnosed with invasive breast cancer before randomisation. • Power calculation not reported • Other cancers not reported as a composite outcome • Unclear how adverse events data was collected • All included women were postmenopausal

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Appendix H: GRADE profiles

H.1 Tamoxifen versus placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Placebo	Relative (95% CI)	Absolute	
Incidence of invasive breast cancer											
3[1]	randomised trials	serious risk of bias[2]	serious[3]	no serious indirectness[4]	no serious imprecision[5]	none	356/9866 (3.6%)	509/9821 (5.2%)	RR 0.7 (0.61 to 0.8)	16 fewer per 1000 (from 10 fewer to 20 fewer)	LOW
Incidence of DCIS											
3[6]	randomised trials	serious risk of bias[7]	no serious inconsistency[8]	no serious indirectness[4]	no serious imprecision[5]	none	74/11393 (0.65%)	126/1407 (1.1%)	RR:0.59 (0.44 to 0.78)	5 fewer per 1000 (from 2 fewer to 6 fewer)	MODERATE
Overall survival - Total deaths											
3[1]	randomised trials	serious risk of bias[10]	no serious inconsistency[8]	no serious indirectness[4]	serious[9]	none	317/11413 (2.8%)	286/11418 (2.5%)	RR 1.11 (0.95 to 1.3)	3 more per 1000 (from 1 fewer to 8 more)	LOW
Non-adherance to chemoprevention											
3[1]	randomised trials	serious risk of bias[11]	very serious[12]	no serious indirectness[4]	serious[9]	none	4343/11393 (38.1%)	4254/11407 (37.3%)	RR 1.02 (0.99 to 1.05)	7 more per 1000 (from 4 fewer to 19 more)	VERY LOW
Adverse events - Weight change at 60 months (Better indicated by lower values)											
1[13]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	serious[16]	none	606	648	-	MD 0 higher (0.63 lower to 0.63 higher)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Placebo	Relative (95% CI)	Absolute	
Adverse events - Venous thrombolic events - including deep vein thrombosis, pulmonary embolism, superficial thrombophelbitis											
3[1]	randomised trials	serious risk of bias[7]	no serious inconsistency[8]	no serious indirectness[4]	no serious imprecision[5]	none	303/11414 (2.7%)	203/11418 (1.8%)	RR 1.49 (1.25 to 1.78)	9 more per 1000 (from 4 more to 14 more)	MODERATE
Adverse events - Cerebrovascular events - including stroke, cerebrovascular accident and transient ischemic attack											
1[17]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	serious[9]	none	32/3579 (0.89%)	34/3575 (0.95%)	RR 0.94 (0.58 to 1.52)	1 fewer per 1000 (from 4 fewer to 5 more)	MODERATE
Adverse events - Cardiac side effects (myocardial infarction, angina, other cardiac)											
2[18]	randomised trials	serious risk of bias[25]	no serious inconsistency[8]	no serious indirectness[4]	serious[16]	none	235/10176 (2.3%)	232/10185 (2.3%)	RR 1.01 (0.85 to 1.21)	0 more per 1000 (from 3 fewer to 5 more)	LOW
Adverse events - Gynaecologic or vasomotor effects											
1[17]	randomised trials	no serious risk of bias14	n/a	no serious indirectness[4]	serious[9]	none	3151/3579 (88%)	2922/3575 (81.7%)	RR 1.08 (1.06 to 1.1)	65 more per 1000 (from 49 more to 82 more)	MODERATE
Adverse events - Headaches/migraines											
1[17]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	no serious imprecision[5]	none	1169/3579 (32.7%)	1261/3575 (35.3%)	RR 0.93 (0.87 to 0.99)	25 fewer per 1000 (from 4 fewer to 46 fewer)	HIGH
Adverse events - Breast complaints including multiple breast cysts											
1[17]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	no serious imprecision[5]	none	693/3579 (19.4%)	903/3575 (25.3%)	RR 0.77 (0.7 to 0.84)	58 fewer per 1000 (from 40 fewer to 76 fewer)	HIGH
Adverse events - Fractures including wrist, arm hip, forearm											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Placebo	Relative (95% CI)	Absolute	
2[18]	randomised trials	serious risk of bias[25]	very serious[19]	no serious indirectness[4]	serious[9]	none	320/10176 (3.1%)	351/10185 (3.4%)	RR 0.91 (0.79 to 1.06)	3 fewer per 1000 (from 7 fewer to 2 more)	VERY LOW
Adverse events - Eye complaints excluding cataracts											
1[17]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	serious[9]	none	947/3579 (26.5%)	934/3575 (26.1%)	RR 1.01 (0.94 to 1.09)	3 more per 1000 (from 16 fewer to 24 more)	MODERATE
Adverse events – Cataracts											
1[17]	randomised trials	no serious risk of bias[14]	n/a	no serious indirectness[4]	serious[9]	none	67/3579 (1.9%)	54/3575 (1.5%)	RR 1.24 (0.87 to 1.77)	4 more per 1000 (from 2 fewer to 12 more)	MODERATE
Adverse events - Gynecological cancers – endometrial											
3[1]	randomised trials	serious risk of bias[20]	no serious inconsistency[21]	no serious indirectness[4]	no serious imprecision[5]	none	87/11414 (0.76%)	41/11418 (0.36%)	RR 2.12 (1.47 to 3.07)	4 more per 1000 (from 2 more to 7 more)	MODERATE
Adverse events - All other cancers (including gastrointestinal, lung, melanoma, brain, lymphoma, myeloma or leukemia but excluding non-melanoma and endometrial											
3[1]	randomised trials	serious risk of bias[2]	no serious inconsistency[22]	no serious indirectness[4]	serious[9]	none	404/11414 (3.5%)	384/11418 (3.4%)	RR 1.05 (0.92 to 1.21)	2 more per 1000 (from 3 fewer to 7 more)	LOW
Adverse events - Hot flushes											
1[23]	randomised trials	serious risk of bias[25]	n/a	no serious indirectness[4]	no serious imprecision[5]	none	5726/6466 (88.6%)	4458/6498 (68.6%)	RR 1.29 (1.27 to 1.32)	199 more per 1000 (from 185 more to 220 more)	MODERATE
Adverse events - Vaginal discharge											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Placebo	Relative (95% CI)	Absolute	
1[23]	randomised trials	serious risk of bias[25]	n/a	no serious indirectness[4]	no serious imprecision[5]	none	3569/6466 (55.2%)	2261/6498 (34.8%)	RR 1.59 (1.52 to 1.65)	205 more per 1000 (from 181 more to 226 more)	MODERATE
Adverse events - Psychological morbidity											
1[24]	prospective cohort[26]	serious[27]	n/a	no serious indirectness[4]	serious[9]	none	29/220 (13.2%)	26/201 (12.9%)	RR 1.02 (0.62 to 1.67)	3 more per 1000 (from 49 fewer to 87 more)	VERY LOW

[1] Follow up ranged from a median of 70 months in Powles 1998, a mean of 74 months in Fisher 2005 and a median of 16 years in Cuzick 2015.
[2] Serious risk of bias - adverse events collected by self report in 1 studies and method not reported in one other study. Though there are concerns in the risk of bias of Powles 1998 (randomisation details and blinding not described), this study had only a 6% weight in the meta-analysis and therefore has not been downgraded in the meta-analysis..
[3] Serious inconsistency: I squared = 47%
[4] No serious indirectness.
[5] No serious imprecision as confidence interval does not cross the committee defined MID of no difference.
[6] Follow up ranged from a median of 47.7 months in Fisher 1998 to 70 months in Powles 1998 to a median of 16 years in Cuzick 2015.
[7] Serious risk of bias - adverse events collected by self report in 1 study and method not reported in one other study. Though there are concerns in the risk of bias of Powles 1998 (randomisation details and blinding not described), this study had only a 7% weight in the meta-analysis and therefore has not been downgraded in the meta-analysis..
[8] No serious inconsistency as I squared = 0%
[9] Serious imprecision as confidence interval crosses the committee defined MID of no difference .
[10] Serious risk of bias - unclear how this outcome was assessed/method of data collection not reported both studies. Though there are concerns in the risk of bias of Powles 1998 (randomisation details and blinding not described), this study had only a 6% weight in the meta-analysis and therefore has not been downgraded in the meta-analysis..
[11] Serious risk of bias - adverse events collected by self report in 1 study and method not reported in one other study. Though there are concerns in the risk of bias of Powles 1998 (randomisation details and blinding not described), this study had only a 9% weight in the meta-analysis and therefore has not been downgraded in the meta-analysis..
[12] Very serious inconsistency as I sqaured =98%.
[13] Follow up of 60 months (Sestak 2012).
[14] No serious risk of bias.
[15] Single study analysis.
[16] Serious imprecision as confidence interval crosses the committee defined MID of no difference .
[17] Follow up was a median of 95.6 months (Cuzick 2007).
[18] Follow up ranged from median of 95.6 months in Cuzick 2007 to mean of 74 months in Fisher 2005.
[19] Very serious risk of bias as I squared = 81%
[20]Serious risk of bias - adverse events collected by self report in 1 study and method not reported in one other study. Though there are concerns in the risk of bias of Powles 1998 (randomisation details and blinding not described), this study had only a 2% weight in the meta-analysis and therefore has not been downgraded in the meta-analysis..
[21] No serious inconsistency: I squared = 32%
[22] No serious inconsistency: I squared = 31%
[23] Fisher 1998: mean follow up of 47.7 months.
[24] Follow up of 5 years (Fallowfield 2001)
[25] Adverse events collected by self report.
[26] Overall quality rating began at low for cohort studies

1 [27] Randomisation method not described (Fallowfield 2001) and adverse events collected by self report

2

H.23 Tamoxifen versus raloxifene

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Raloxifene	Relative (95% CI)	Absolute	
Development of invasive breast cancer											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	165/6898 (2.4%)	205/6963 (2.9%)	RR 0.81 (0.66 to 0.99)	6 fewer per 1000 (from 0 fewer to 10 fewer)	MODERATE
Development of DCIS											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	70/9736 (0.72 %)	86/9754 (0.88 %)	RR 0.82 (0.6 to 1.12)	2 fewer per 1000 (from 4 fewer to 1 more)	LOW
Non-adherance to chemoprevention											
1[8]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	no serious imprecision[5]	none	3083/9726 (31.7 %)	2777/9745 (28.5 %)	RR 1.11 (1.07 to 1.16)	31 more per 1000 (from 20 more to 46 more)	MODERATE
Overall survival - Total deaths											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	236/9736 (2.4%)	202/9754 (2.1%)	RR 1.17 (0.97 to 1.41)	4 more per 1000 (from 1 fewer to 8 more)	VERY LOW
Adverse events – Stroke											
1[8]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	53/9726 (0.54 %)	51/9745 (0.52 %)	RR 1.04 (0.71 to 1.53)	0 more per 1000 (from 2 fewer to 3 more)	LOW
Adverse events - Cardiac side effects including myocardial infarction, severe angina and acute ischemic syndromes)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	Raloxifene	Relative (95% CI)	Absolute	
1[8]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	114/9726 (1.2%)	126/9745 (1.3%)	RR 0.91 (0.7 to 1.17)	1 fewer per 1000 (from 4 fewer to 2 more)	LOW
Adverse events - Thromboembolic events including pulmonary embolism, deep vein thrombosis)											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	no serious imprecision[5]	none	202/9736 (2.1%)	154/9754 (1.6%)	RR 1.31 (1.07 to 1.62)	5 more per 1000 (from 1 more to 10 more)	MODERATE
Adverse events - Uterine invasive cancer											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	no serious imprecision[5]	none	65/9736 (0.67 %)	37/9754 (0.38 %)	RR 1.76 (1.18 to 2.63)	3 more per 1000 (from 1 more to 6 more)	MODERATE
Adverse events – Fractures											
1[8]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	104/9726 (1.1%)	96/9745 (0.99 %)	RR 1.09 (0.82 to 1.43)	1 more per 1000 (from 2 fewer to 4 more)	LOW
Adverse events – Cataracts											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	no serious imprecision[5]	none	739/8341 (8.9%)	603/8336 (7.2%)	RR 1.22 (1.1 to 1.36)	16 more per 1000 (from 7 more to 26 more)	MODERATE
Adverse events - Transient ischemic attack											
1[8]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[6]	serious[7]	none	41/9726 (0.42 %)	50/9745 (0.51 %)	RR 0.82 (0.54 to 1.24)	1 fewer per 1000 (from 2 fewer to 1 more)	;LOW

[1] Vogel 2010: median follow up of 81 months.
[2] No serious risk of bias. Although power calculation not reported, this is unlikely to affect the results given the large sample size.
[3] Single study analysis.
[4] No serious indirectness, outcome reported for the subgroup with family history.
[5] No serious imprecision as confidence interval does not cross the committee defined MID of no difference.
[6] No serious indirectness. Although only 71% of the subjects included for this outcome had a family history, this is unlikely to affect the results given the majority met the family history criteria.

[7] Serious imprecision as confidence interval crosses the committee definied MID of no difference.
[8] Vogel 2006: median follow up of 47 months.

H.34 Anastrozole versus placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anastrozole	Placebo	Relative (95% CI)	Absolute	
Invasive breast cancer											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	32/1920 (1.7%)	64/1944 (3.3%)	RR 0.51 (0.33 to 0.77)	16 fewer per 1000 (from 8 fewer to 22 fewer)	MODERATE
DCIS by 5 years of f/up											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	6/1920 (0.31%)	20/1944 (1%)	RR 0.3 (0.12 to 0.75)	7 fewer per 1000 (from 3 fewer to 9 fewer)	MODERATE
Non-adherance to chemoprevention - Reported as treatment discontinuation because of onset of CTS or other adverse events											
1[6]	randomised trials	no serious risk of bias[7]	n/a[3]	no serious indirectness[4]	Serious[8]	none	12/1920 (0.63%)	5/1944 (0.26%)	RR 2.43 (0.86 to 6.88)	4 more per 1000 (from 0 fewer to 15 more)	MODERATE
Non-adherance to chemoprevention - Reported as 5 year adherance											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	1301/1920 (67.8%)	1400/1944 (72%)	RR 0.94 (0.9 to 0.98)	43 fewer per 1000 (from 14 fewer to 72 fewer)	MODERATE
Adverse events - Endometrial cancer											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	3/1920 (0.16%)	5/1944 (0.26%)	RR 0.61 (0.15 to 2.54)	1 fewer per 1000 (from 2 fewer to 4 more)	LOW
Adverse events - All other cancers (including gastrointestinal, lung, melanoma, thyroid, leukemia, lymphoma or myeloma, cancer of urinary tract, nervous system, ovarian and vaginal cancer but excluding non-melanoma and endometrial)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anastrozole	Placebo	Relative (95% CI)	Absolute	
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	27/1920 (1.4%)	45/1944 (2.3%)	RR 0.61 (0.38 to 0.97)	9 fewer per 1000 (from 1 fewer to 14 fewer)	MODERATE
Adverse events – Carcinomatosis											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	1/1920 (0.05%)	1/1944 (0.05%)	RR 1.01 (0.06 to 16.18)	0 more per 1000 (from 0 fewer to 8 more)	LOW
Adverse events – Fractures											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	164/1920 (8.5%)	149/1944 (7.7%)	RR 1.11 (0.9 to 1.38)	8 more per 1000 (from 8 fewer to 29 more)	LOW
Adverse events - Musculoskeletal (arthralgia, joint stiffness, pain in hand or foot, carpal tunnel sydrome or nerve compression											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	1226/1920 (63.9%)	1124/1944 (57.8%)	RR 1.1 (1.05 to 1.16)	58 more per 1000 (from 29 more to 93 more)	MODERATE
Adverse events - Vasomotor (hot flushes or night sweats)											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	1090/1920 (56.8%)	961/1944 (49.4%)	RR 1.15 (1.08 to 1.22)	74 more per 1000 (from 40 more to 109 more)	MODERATE
Adverse events - Gynaecological (vaginal dryness, haemorrhage or bleeding, vaginal or uterine prolapse, vulvovaginal pruritus)											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	460/1920 (24%)	423/1944 (21.8%)	RR 1.1 (0.98 to 1.24)	22 more per 1000 (from 4 fewer to 52 more)	LOW
Adverse events - Hypertension											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anastrozole	Placebo	Relative (95% CI)	Absolute	
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	no serious imprecision[5]	none	89/1920 (4.6%)	55/1944 (2.8%)	RR: 1.64 (1.18 to 2.28)	18 more per 1000 (from 5 more to 36 more)	MODERATE
Adverse events - Myocardial infarction or cardiac failure											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	8/1920 (0.42%)	9/1944 (0.46%)	RR: 0.90 (0.35 to 2.33)	0 fewer per 1000 (from 3 fewer to 6 more)	LOW
Adverse events – Thrombosis or embolism											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	19/1920 (0.99%)	17/1944 (0.87%)	RR: 1.13 (0.59 to 2.17)	1 more per 1000 (from 4 fewer to 10 more)	LOW
Adverse events – Phelebitis											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	9/1920 (0.47%)	8/1944 (0.41$)	RR: 1.14 (0.44 to 2.95)	1 more per 1000 (from 2 fewer to 8 more)	LOW
Adverse events – cerebrovascular accident											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	3/1920 (0.16%)	6/1944 (0.31%)	RR: 0.51 (0.13 to 2.02)	2 fewer per 1000 (from 3 fewer to 3 more)	LOW
Adverse events - Eyes (dry eyes, conjunctivitis, glaucoma, cataract)											
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	348/1920 (18.1%)	335/1944 (17.2%)	RR 1.05 (0.92 to 1.21)	9 more per 1000 (from 14 fewer to 36 more)	LOW
Adverse events - Infections (influenza, otitis media)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anastrozole	Placebo	Relative (95% CI)	Absolute	
1[1]	randomised trials	serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	230/1920 (12%)	217/1944 (11.2%)	RR 1.07 (0.9 to 1.28)	8 more per 1000 (from 11 fewer to 31 more)	LOW
Adverse events - continuous outcomes - Weight change - 12 months (Better indicated by lower values)											
1[9]	randomised trials	no serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[10]	none	364	355	-	MD 0.3 higher (0.63 lower to 1.23 higher)	MODERATE
Overall survival - Total deaths											
1[1]	randomised trials	no serious risk of bias[2]	n/a[3]	no serious indirectness[4]	Serious[8]	none	18/1920 (0.94%)	17/1944 (0.87%)	RR 1.07 (0.55 to 2.07)	1 more per 1000 (from 4 fewer to 9 more)	MODERATE

[1] Cuzick 2014: Median follow up of 5 years.
[2] serious risk of bias as method of data collection for adverse events not reported.
[3] Single study analysis.
[4] No serious indirectness.
[5] No serious imprecision as confidence interval does not cross the committee defined MID of no difference.
[6] Spagnolo 2016: Median follow up of 6.4 years.
[7] No serious risk of bias
[8] Serious imprecision as confidence interval crosses the committee defined MID of no difference.
[9] Sestak 2012: follow up of 12 months.
[10] Serious imprecision as confidence interval crosses the committee defined MID of no difference.

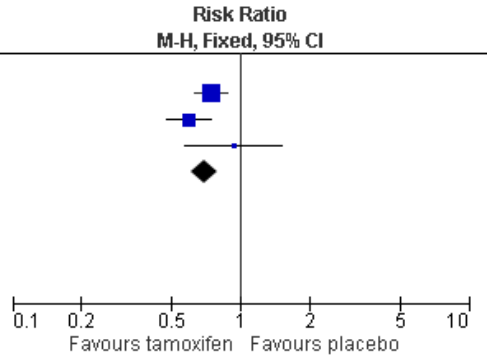
Appendix I: Forest plots

I.1 Tamoxifen versus placebo

I.1.1 Invasive breast cancer

Study or Subgroup	Tamoxifen Events	Tamoxifen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Follow up ranged from a median of 70 months in Powles 1998, a mean of 74 months in Fisher 2005 and a median of 16 years in Cuzick 2015.						
Cuzick 2015	214	3579	289	3575	56.7%	0.74 [0.62, 0.88]
Fisher 2005	112	5049	188	5013	37.0%	0.59 [0.47, 0.74]
Powles 1998	30	1238	32	1233	6.3%	0.93 [0.57, 1.53]
Subtotal (95% CI)		**9866**		**9821**	**100.0%**	**0.70 [0.61, 0.80]**
Total events	356		509			

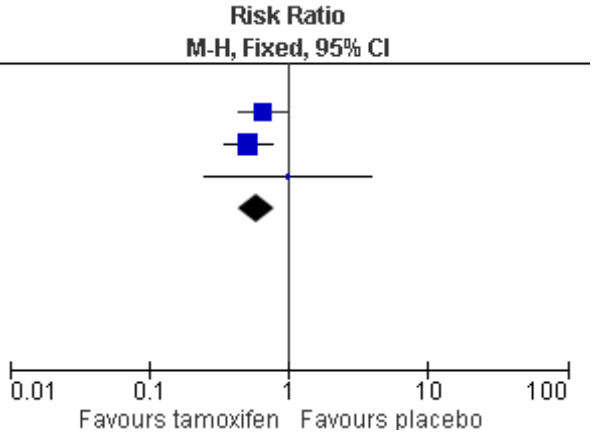
Heterogeneity: Chi² = 3.77, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 5.36 (P < 0.00001)



I.1.2 Ductal carcinoma in situ

Study or Subgroup	Tamoxifen Events	Tamoxifen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Follow up ranged from a median of 70 months in Powles 1998 to a median of 16 years in Cuzick 2015.						
Cuzick 2015	35	3579	53	3575	42.1%	0.66 [0.43, 1.01]
Fisher 1998	35	6576	69	6599	54.7%	0.51 [0.34, 0.76]
Powles 1998	4	1238	4	1233	3.2%	1.00 [0.25, 3.97]
Subtotal (95% CI)		**11393**		**11407**	**100.0%**	**0.59 [0.44, 0.78]**
Total events	74		126			

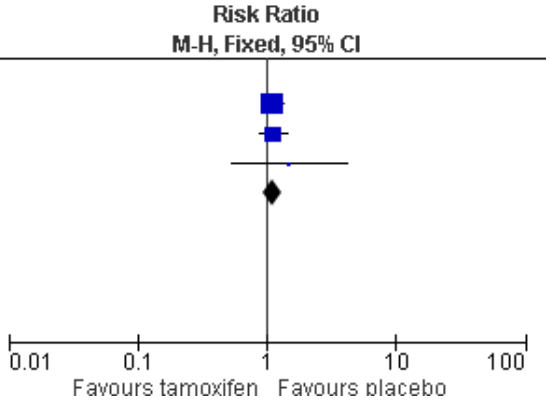
Heterogeneity: Chi² = 1.33, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.64 (P = 0.0003)



I.1.31 Overall survival

Study or Subgroup	Tamoxifen Events	Tamoxifen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.17 Total deaths: Follow up ranged from a median of 70 months in Powles 1998 to a median of 16 years in Cuzick 2015.						
Cuzick 2015	182	3578	166	3575	58.1%	1.10 [0.89, 1.34]
Fisher 2005	126	6597	114	6610	39.8%	1.11 [0.86, 1.42]
Powles 1998	9	1238	6	1233	2.1%	1.49 [0.53, 4.18]
Subtotal (95% CI)		**11413**		**11418**	**100.0%**	**1.11 [0.95, 1.30]**
Total events	317		286			

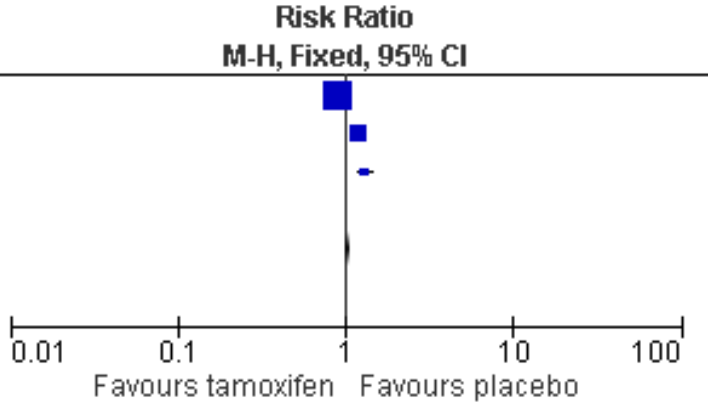
Heterogeneity: Chi² = 0.34, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)



I.1.42 Non-adherance to chemoprevention

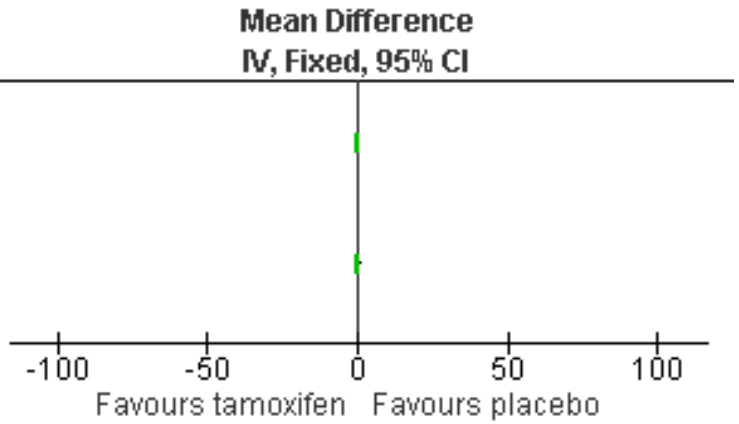
Study or Subgroup	Tamoxifen Events	Tamoxifen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cuzick 2007	2287	3579	2574	3575	60.5%	0.89 [0.86, 0.92]
Fisher 1998	1559	6576	1300	6599	30.5%	1.20 [1.13, 1.28]
Powles 1998	497	1238	380	1233	9.0%	1.30 [1.17, 1.45]
Total (95% CI)		**11393**		**11407**	**100.0%**	**1.02 [0.99, 1.05]**
Total events	4343		4254			

Heterogeneity: Chi² = 117.69, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.35 (P = 0.18)



I.1.51 Adverse events

Study or Subgroup	Tamoxifen Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.9.1 Weight change at 12 months (IBIS-1)							
Sestak 2012	0.9	1.4	1369	1	1.5	1396	-0.10 [-0.21, 0.01]
1.9.2 Weight change at 60 months (IBIS-2)							
Sestak 2012	1.3	5.6	606	1.3	5.7	648	0.00 [-0.63, 0.63]



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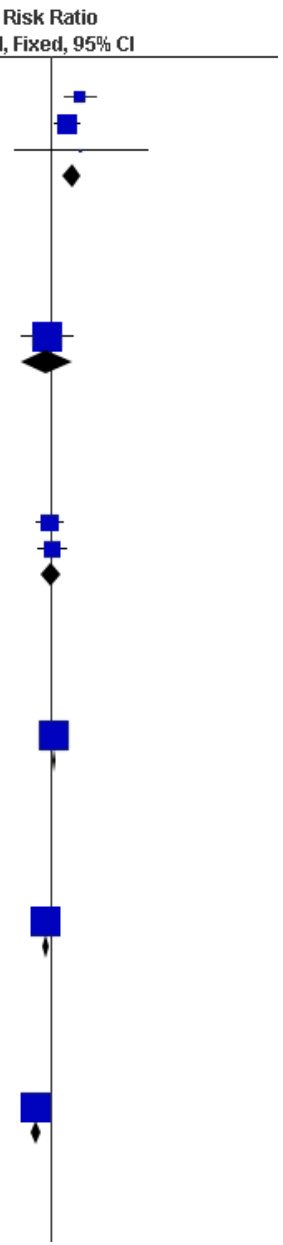
Study or Subgroup	Tamoxifen Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Venous thrombolic events - including deep vein thrombosis, pulmonary embolism, superficial thrombophelbitis						
Cuzick 2007	117	3579	68	3575	33.5%	1.72 [1.28, 2.31]
Fisher 2005	179	6597	131	6610	64.5%	1.37 [1.10, 1.71]
Powles 1998	7	1238	4	1233	2.0%	1.74 [0.51, 5.94]
Subtotal (95% CI)		**11414**		**11418**	**100.0%**	**1.49 [1.25, 1.78]**
Total events	303		203			
Heterogeneity: Chi² = 1.52, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
1.10.2 Cerebrovascular events - including stroke, cerebrovascular accident and transient ischemic attack						
Cuzick 2007	32	3579	34	3575	100.0%	0.94 [0.58, 1.52]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**0.94 [0.58, 1.52]**
Total events	32		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.10.3 Cardiac side effects (myocardial infarction, angina, other cardiac)						
Cuzick 2007	122	3579	123	3575	53.1%	0.99 [0.77, 1.27]
Fisher 2005	113	6597	109	6610	46.9%	1.04 [0.80, 1.35]
Subtotal (95% CI)		**10176**		**10185**	**100.0%**	**1.01 [0.85, 1.21]**
Total events	235		232			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.10.4 Gynaecologic or vasomotor effects						
Cuzick 2007	3151	3579	2922	3575	100.0%	1.08 [1.06, 1.10]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**1.08 [1.06, 1.10]**
Total events	3151		2922			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.42 (P < 0.00001)						
1.10.5 Headaches/migraines						
Cuzick 2007	1169	3579	1261	3575	100.0%	0.93 [0.87, 0.99]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**0.93 [0.87, 0.99]**
Total events	1169		1261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.10.6 Breast complaints including multiple breast cysts						
Cuzick 2007	693	3579	903	3575	100.0%	0.77 [0.70, 0.84]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**0.77 [0.70, 0.84]**
Total events	693		903			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.96 (P < 0.00001)						



1.10.7 Fractures including wrist, arm hip, forearm

Cuzick 2007	240	3579	235	3575	67.0%	1.02 [0.86, 1.21]
Fisher 2005	80	6597	116	6610	33.0%	0.69 [0.52, 0.92]
Subtotal (95% CI)		**10176**		**10185**	**100.0%**	**0.91 [0.79, 1.06]**
Total events	320		351			

Heterogeneity: Chi² = 5.30, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.23 (P = 0.22)

1.10.8 Eye complaints excluding cataracts

Cuzick 2007	947	3579	934	3575	100.0%	1.01 [0.94, 1.09]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**1.01 [0.94, 1.09]**
Total events	947		934			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

1.10.9 Cataracts

Cuzick 2007	67	3579	54	3575	100.0%	1.24 [0.87, 1.77]
Subtotal (95% CI)		**3579**		**3575**	**100.0%**	**1.24 [0.87, 1.77]**
Total events	67		54			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

1.10.10 Gynecological cancers - endometrial

Cuzick 2015	29	3579	20	3575	48.8%	1.45 [0.82, 2.56]
Fisher 2005	54	6597	20	6610	48.7%	2.71 [1.62, 4.51]
Powles 1998	4	1238	1	1233	2.4%	3.98 [0.45, 35.59]
Subtotal (95% CI)		**11414**		**11418**	**100.0%**	**2.12 [1.47, 3.07]**
Total events	87		41			

Heterogeneity: Chi² = 2.92, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 3.98 (P < 0.0001)

**1.10.11 All other cancers (*including gastrointestinal, lung, melanoma, brain, lymphoma, myeloma or leukemia but excluding non-melanoma and endometrial*

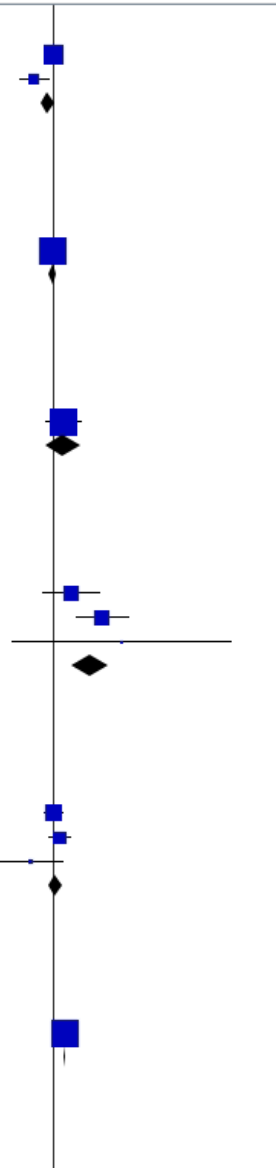
Cuzick 2015	211	3579	206	3575	53.7%	1.02 [0.85, 1.23]
Fisher 2005	178	6597	155	6610	40.3%	1.15 [0.93, 1.42]
Powles 1998	15	1238	23	1233	6.0%	0.65 [0.34, 1.24]
Subtotal (95% CI)		**11414**		**11418**	**100.0%**	**1.05 [0.92, 1.21]**
Total events	404		384			

Heterogeneity: Chi² = 2.91, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.73 (P = 0.47)

1.10.12 Hot flushes

Fisher 1998	5726	6466	4458	6498	100.0%	1.29 [1.27, 1.32]
Subtotal (95% CI)		**6466**		**6498**	**100.0%**	**1.29 [1.27, 1.32]**
Total events	5726		4458			

Heterogeneity: Not applicable
Test for overall effect: Z = 26.85 (P < 0.00001)



1.10.13 Vaginal discharge

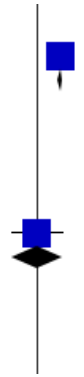
Fisher 1998	3569	6466	2261	6498	100.0%	1.59 [1.52, 1.65]
Subtotal (95% CI)		**6466**		**6498**	**100.0%**	**1.59 [1.52, 1.65]**
Total events	3569		2261			

Heterogeneity: Not applicable
Test for overall effect: Z = 22.68 (P < 0.00001)

1.10.20 Psychological morbidity

Fallowfield 2001	29	220	26	201	100.0%	1.02 [0.62, 1.67]
Subtotal (95% CI)		**220**		**201**	**100.0%**	**1.02 [0.62, 1.67]**
Total events	29		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)



*Forest plots for other comparisons (anastrozole versus placebo and tamoxifene versus raloxifene have not been presented as these were single study analysis i.e. no meta-analyses performed).

Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 13. The search strategy is shown in Table 14. The same strategy was translated for the other databases listed.

Table 13: Economic search summary

Database	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	17/05/2016	1946 to May wk 1 2016	63
MEDLINE in Process (Ovid)	17/05/2016	May 16 2016	11
Embase (Ovid)	17/05/2016	1974 to 2016 May 16	275
NHS Economic Evaluation Database (NHS EED) (legacy database)	17/05/2016	2 of 4 April 2015	1
Health Technology Assessment (HTA Database)	17/05/2016	2 of 4 April 2016	3
Pubmed	17/05/2016	n/a	133

Table 14: Economic search strategy

Database: MiP
Strategy used: atabase: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 13, 2016> Search Strategy: ---------- 1 exp Breast Neoplasms/ (0) 2 (paget* adj1 disease).tw. (381) 3 (intraductal adj1 papilloma*).tw. (33) 4 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (0) 5 ((breast or mammary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw. (21669) 6 ((duct* or intraductal or lobular or medullary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (3244) 7 or/1-6 (23990) 8 exp ovarian neoplasms/ (0) 9 (ovar$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (5365)

Database: MiP

10 (granulosa adj4 cell*).tw. (570)

11 (hboc adj1 syndrome*).tw. (15)

12 (luteoma* or luteinoma*).tw. (11)

13 (meig* adj1 syndrome).tw. (38)

14 (androblastoma* or arrhenoblastoma*).tw. (3)

15 (sertoli* adj1 leydig).tw. (40)

16 (thecoma* or (theca adj1 cell)).tw. (43)

17 or/8-16 (5874)

18 exp Prostatic Neoplasms/ (0)

19 (prostat$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (9387)

20 18 or 19 (9387)

21 exp Pancreatic Neoplasms/ (0)

22 (pancrea$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (5042)

23 (adenoma or nesidioblastoma).tw. (2859)

24 ((island or islet) adj1 cell).tw. (298)

25 or/21-24 (8110)

26 7 or 17 or 20 or 25 (43904)

27 (familial or (family adj histor$)).tw. (8848)

28 (heredit$ or inherit$ or predispos$).tw. (19366)

29 exp Genetics/ (0)

30 (genetic adj (counsel* or test* or screening)).tw. (3134)

31 (mutation$ adj1 risk*).tw. (17)

32 mutation.tw. (18420)

33 lifetime breast cancer risk*.tw. (5)

34 (inherited adj mutation*).tw. (82)

Database: MiP

35 (mutation adj carrier*).tw. (489)

36 exp Genetic Testing/ (0)

37 exp Genetic Predisposition to Disease/ (0)

38 exp Neoplastic Syndromes, Hereditary/ (0)

39 Genetic Counseling/ (0)

40 exp Genetic Techniques/ (0)

41 (BRCA1 or BRCA2 or TP53).tw. (1875)

42 Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/ (0)

43 ((high adj risk) or (increas$ adj risk)).tw. (33788)

44 exp Mutation/ (0)

45 or/27-44 (75728)

46 26 and 45 (4749)

47 7 and 46 (2842)

48 exp Chemoprevention/ (0)

49 (chemoprevent$ or chemoprophyla$).tw. (1513)

50 exp Tamoxifen/ (0)

51 (tamoxifen* or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or kessar or tamoplac or tamoxasta).tw. (1052)

52 (raloxifene or evista or keoxifene or bonmax or loxar or loxifen or optruma or raxeto).tw. (185)

53 (toremifene or estrimex or fareston).tw. (24)

54 exp Aromatase Inhibitors/ (0)

55 aromatase inhibitor$.tw. (476)

56 (reduction adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (847)

57 (exemestane$ or aromasin$).tw. (101)

58 anastr?zol$.tw. (110)

Database: MiP

59 letrozol$.tw. (252)

60 (aminoglutethimide or amino glutethimide or cytadren or orimeten* or elipt?n or rodazol).tw. (15)

61 (fadrozole or afema or arensin).tw. (9)

62 or/48-61 (3945)

63 47 and 62 (220)

64 201207*.ed. (3546)

65 201208*.ed. (28254)

66 201209*.ed. (9310)

67 201210*.ed. (180214)

68 201211*.ed. (10479)

69 201212*.ed. (10949)

70 2013*.ed. (154920)

71 2014*.ed. (157669)

72 2015*.ed. (214369)

73 2016*.ed. (81713)

74 or/64-73 (851423)

75 63 and 74 (90)

76 Economics/ (0)

77 exp "Costs and Cost Analysis"/ (0)

78 Economics, Dental/ (0)

79 exp Economics, Hospital/ (0)

80 exp Economics, Medical/ (0)

81 Economics, Nursing/ (0)

82 Economics, Pharmaceutical/ (0)

83 Budgets/ (0)

Database: MiP

84 exp Models, Economic/ (0)

85 Markov Chains/ (0)

86 Monte Carlo Method/ (0)

87 Decision Trees/ (0)

88 econom$.tw. (24270)

89 cba.tw. (250)

90 cea.tw. (1138)

91 cua.tw. (98)

92 markov$.tw. (3236)

93 (monte adj carlo).tw. (10861)

94 (decision adj3 (tree$ or analys$)).tw. (1124)

95 (cost or costs or costing$ or costly or costed).tw. (51477)

96 (price$ or pricing$).tw. (3347)

97 budget$.tw. (2875)

98 expenditure$.tw. (3820)

99 (value adj3 (money or monetary)).tw. (197)

100 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (379)

101 or/76-100 (91355)

102 "Quality of Life"/ (0)

103 quality of life.tw. (22574)

104 "Value of Life"/ (0)

105 Quality-Adjusted Life Years/ (0)

106 quality adjusted life.tw. (949)

107 (qaly$ or qald$ or qale$ or qtime$).tw. (805)

108 disability adjusted life.tw. (282)

109 daly$.tw. (247)

Database: MiP

110 Health Status Indicators/ (0)

111 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (1864)

112 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (489)

113 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (460)

114 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (3)

115 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (15)

116 (euroqol or euro qol or eq5d or eq 5d).tw. (886)

117 (qol or hql or hqol or hrqol).tw. (4344)

118 (hye or hyes).tw. (3)

119 health$ year$ equivalent$.tw. (2)

120 utilit$.tw. (17517)

121 (hui or hui1 or hui2 or hui3).tw. (123)

122 disutili$.tw. (39)

123 rosser.tw. (2)

124 quality of wellbeing.tw. (5)

125 quality of well-being.tw. (16)

126 qwb.tw. (7)

127 willingness to pay.tw. (473)

128 standard gamble$.tw. (44)

129 time trade off.tw. (79)

130 time tradeoff.tw. (8)

131 tto.tw. (77)

132 or/102-131 (41518)

Database: MiP

133 101 or 132 (127423)

134 75 and 133 (11)

135 limit 134 to english language (11)

1

Database: Embase

Strategy used:

Database: Embase <1974 to 2016 May 13>
Search Strategy:
---

1 exp breast cancer/ (346541)

2 (paget* adj1 disease).tw. (8639)

3 (intraductal adj1 papilloma*).tw. (623)

4 ((breast or mammary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw. (367767)

5 ((duct* or intraductal or lobular or medullary) adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (54591)

6 or/1-5 (486445)

7 exp ovary tumor/ (113986)

8 (ovar$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (94401)

9 (granulosa adj4 cell*).tw. (14789)

10 (hboc adj1 syndrome*).tw. (111)

11 (luteoma* or luteinoma*).tw. (242)

12 (meig* adj1 syndrome).tw. (923)

13 (androblastoma* or arrhenoblastoma*).tw. (358)

14 (sertoli* adj1 leydig).tw. (704)

15 (thecoma* or (theca adj1 cell)).tw. (1038)

16 or/7-15 (144427)

17 exp prostate tumor/ (181694)

Database: Embase

18 (prostat$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (156902)

19 17 or 18 (200468)

20 exp pancreas tumor/ (108352)

21 (pancrea$ adj4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (82745)

22 (adenoma or nesidioblastoma).tw. (53157)

23 ((island or islet) adj1 cell).tw. (9765)

24 or/20-23 (181295)

25 6 or 16 or 19 or 24 (912060)

26 (familial or (family adj histor$)).tw. (184303)

27 (heredit$ or inherit$ or predispos$).tw. (315058)

28 exp Genetics/ (688881)

29 (genetic adj (counsel* or test* or screening)).tw. (43087)

30 (mutation$ adj1 risk*).tw. (324)

31 mutation.tw. (358393)

32 lifetime breast cancer risk*.tw. (84)

33 (inherited adj mutation*).tw. (1457)

34 (mutation adj carrier*).tw. (8419)

35 genetic screening/ (56630)

36 exp Genetic Predisposition/ (93831)

37 exp cancer genetics/ (180758)

38 Genetic Counseling/ (24154)

39 exp genetic procedures/ (1408576)

40 (BRCA1 or BRCA2 or TP53).tw. (28203)

41 BRAC1 protein/ or BRCA2 protein/ or protein p53/ (102956)

Database: Embase

42 ((high adj risk) or (increas$ adj risk)).tw. (513381)

43 exp Mutation/ (879269)

44 or/26-43 (3431646)

45 25 and 44 (195624)

46 6 and 45 (117776)

47 chemoprophylaxis/ (20708)

48 (chemoprevent$ or chemoprophyla$).tw. (28346)

49 Tamoxifen/ (51720)

50 (tamoxifen* or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or kessar or tamoplac or tamoxasta).tw. (27615)

51 raloxifene/ (9972)

52 (raloxifene or evista or keoxifene or bonmax or loxar or loxifen or optruma or raxeto).tw. (4626)

53 toremifene/ (1933)

54 (toremifene or estrimex or fareston).tw. (865)

55 exp Aromatase Inhibitor/ (24639)

56 aromatase inhibitor$.tw. (8652)

57 (reduction adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw. (17409)

58 (exemestane$ or aromasin$).tw. (2152)

59 anastr?zol$.tw. (2538)

60 letrozol$.tw. (3497)

61 (aminoglutethimide or amino glutethimide or cytadren or orimeten* or elipt?n or rodazol).tw. (1833)

62 (fadrozole or afema or arensin).tw. (381)

63 or/47-62 (127842)

64 46 and 63 (11899)

65 201207*.dd. (116208)

Database: Embase

66	201208*.dd. (119118)
67	201209*.dd. (111458)
68	201210*.dd. (114155)
69	201211*.dd. (94659)
70	201212*.dd. (82655)
71	2013*.dd. (1360235)
72	2014*.dd. (1423517)
73	2015*.dd. (1986420)
74	2016*.dd. (768298)
75	or/65-74 (6176723)
76	64 and 75 (3729)
77	exp Health Economics/ (690108)
78	exp "Health Care Cost"/ (232876)
79	exp Pharmacoeconomics/ (178525)
80	Monte Carlo Method/ (26915)
81	Decision Tree/ (7524)
82	econom$.tw. (257435)
83	cba.tw. (11107)
84	cea.tw. (26464)
85	cua.tw. (1029)
86	markov$.tw. (20025)
87	(monte adj carlo).tw. (32827)
88	(decision adj3 (tree$ or analys$)).tw. (14422)
89	(cost or costs or costing$ or costly or costed).tw. (523645)
90	(price$ or pricing$).tw. (40102)
91	budget$.tw. (28313)

Database: Embase

92 expenditure$.tw. (54228)

93 (value adj3 (money or monetary)).tw. (2358)

94 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (7007)

95 or/77-94 (1305613)

96 "Quality of Life"/ (315738)

97 Quality Adjusted Life Year/ (16039)

98 Quality of Life Index/ (2064)

99 Short Form 36/ (15736)

100 Health Status/ (98297)

101 quality of life.tw. (276282)

102 quality adjusted life.tw. (11725)

103 (qaly$ or qald$ or qale$ or qtime$).tw. (11973)

104 disability adjusted life.tw. (2194)

105 daly$.tw. (2272)

106 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (28932)

107 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1729)

108 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (5819)

109 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (41)

110 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (374)

111 (euroqol or euro qol or eq5d or eq 5d).tw. (10270)

112 (qol or hql or hqol or hrqol).tw. (58199)

113 (hye or hyes).tw. (100)

114 health$ year$ equivalent$.tw. (40)

Database: Embase

115 utilit$.tw. (192864)

116 (hui or hui1 or hui2 or hui3).tw. (1544)

117 disutili$.tw. (517)

118 rosser.tw. (90)

119 quality of wellbeing.tw. (22)

120 quality of well-being.tw. (402)

121 qwb.tw. (214)

122 willingness to pay.tw. (4796)

123 standard gamble$.tw. (878)

124 time trade off.tw. (1211)

125 time tradeoff.tw. (235)

126 tto.tw. (1133)

127 or/96-126 (662042)

128 95 or 127 (1861746)

129 76 and 128 (434)

130 limit 129 to embase (407)

131 limit 130 to (conference abstract or conference paper or conference proceeding or "conference review") (129)

132 130 not 131 (278)

133 limit 132 to english language (275)

1

Database: Cochrane

Strategy used:

ID	Search	Hits
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	9677
#2	paget* near/1 disease:ti,ab,kw (Word variations have been searched)	15
#3	intraductal near/1 papilloma*:ti,ab,kw (Word variations have been searched)	4
#4	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	450
#5	(breast or mammary) near/4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis):ti,ab,kw (Word variations have been searched)	20351

Database: Cochrane

#6 (duct* or intraductal or lobular or medullary) near/4 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$):ti,ab,kw (Word variations have been searched) 1113
#7 {or #1-#6} 21894
#8 MeSH descriptor: [Ovarian Neoplasms] explode all trees 1485
#9 ovar$ near/4 cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$:ti,ab,kw (Word variations have been searched) 28589
#10 granulosa near/4 cell*:ti,ab,kw (Word variations have been searched) 119
#11 hboc near/1 syndrome*:ti,ab,kw (Word variations have been searched) 0
#12 luteoma* or luteinoma*:ti,ab,kw (Word variations have been searched) 0
#13 meig* near/1 syndrome:ti,ab,kw (Word variations have been searched) 10
#14 androblastoma* or arrhenoblastoma*:ti,ab,kw (Word variations have been searched) 0
#15 sertoli* near/1 leydig:ti,ab,kw (Word variations have been searched) 1
#16 thecoma* or theca near/1 cell:ti,ab,kw (Word variations have been searched) 19
#17 {or #8-#16} 29671
#18 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3903
#19 prostat$ near/4 cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$:ti,ab,kw (Word variations have been searched) 28578
#20 #18 or #19 31606
#21 MeSH descriptor: [Pancreatic Neoplasms] explode all trees 1057
#22 pancrea$ near/4 cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$:ti,ab,kw (Word variations have been searched) 28578
#23 adenoma or nesidioblastoma:ti,ab,kw (Word variations have been searched) 1674
#24 island or islet near/1 cell.:ti,ab,kw (Word variations have been searched) 893
#25 {or #21-#24} 31352
#26 #7 or #17 or #20 or #25 53705
#27 familial or family near histor*:ti,ab,kw (Word variations have been searched) 3363
#28 heredit$ or inherit$ or predispos$:ti,ab,kw (Word variations have been searched) 464
#29 MeSH descriptor: [Genetics] explode all trees 729
#30 genetic near counsel* or test* or screening:ti,ab,kw (Word variations have been searched) 209465
#31 mutation* near/1 risk*:ti,ab,kw (Word variations have been searched) 39
#32 mutation:ti,ab,kw (Word variations have been searched) 3925
#33 lifetime breast cancer risk*:ti,ab,kw (Word variations have been searched) 42
#34 inherited near mutation*:ti,ab,kw (Word variations have been searched) 22
#35 mutation near carrier*:ti,ab,kw (Word variations have been searched) 138
#36 MeSH descriptor: [Genetic Testing] explode all trees 476
#37 MeSH descriptor: [Genetic Predisposition to Disease] explode all trees 1588
#38 MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees 313
#39 MeSH descriptor: [Genetic Counseling] this term only 163
#40 MeSH descriptor: [Genetic Techniques] explode all trees 4956
#41 BRCA1 or BRCA2 or TP53:ti,ab,kw (Word variations have been searched) 416
#42 MeSH descriptor: [Genes, BRCA1] this term only 91
#43 MeSH descriptor: [Genes, BRCA2] this term only 67
#44 MeSH descriptor: [Genes, p53] this term only 72
#45 high near risk or increas* near risk:ti,ab,kw (Word variations have been searched) 41699
#46 MeSH descriptor: [Mutation] explode all trees 2043
#47 {or #27-#46} 247250
#48 #26 and #47 15057
#49 #7 and #48 6547
#50 MeSH descriptor: [Chemoprevention] explode all trees 1679

Database: Cochrane

#51 chemoprevent$ or chemoprophyla$.:ti,ab,kw (Word variations have been searched) 4
#52 MeSH descriptor: [Tamoxifen] explode all trees 1974
#53 tamoxifen* or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or kessar or tamoplac or tamoxasta:ti,ab,kw (Word variations have been searched) 3820
#54 raloxifene or evista or keoxifene or bonmax or loxar or loxifen or optruma or raxeto:ti,ab,kw (Word variations have been searched) 720
#55 toremifene or estrimex or fareston:ti,ab,kw (Word variations have been searched) 139
#56 MeSH descriptor: [Aromatase Inhibitors] explode all trees 476
#57 reduction near/4 cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$:ti,ab,kw (Word variations have been searched) 29012
#58 exemestane$ or aromasin$:ti,ab,kw (Word variations have been searched) 458
#59 anastr?zol$:ti,ab,kw (Word variations have been searched) 12
#60 letrozol$:ti,ab,kw (Word variations have been searched) 8
#61 aminoglutethimide or amino glutethimide or cytadren or orimeten* or elipt?n or rodazol:ti,ab,kw (Word variations have been searched) 177
#62 fadrozole or afema or arensin:ti,ab,kw (Word variations have been searched) 42
#63 {or #50-#62} 34997
#64 #49 and #63 Publication Year from 2012 to 2016 675

1

Database: Pubmed

Strategy used:

HistoryDownload historyClear history
Recent queries
Search Add to builder Query Items found Time
#50 Add Search (#47 or #49) 133 05:04:14
#49 Add Search (#45 and #48) 2 05:03:56
#48 Add Search ("2016/05/15"[Date - Entrez] : "3000"[Date - Entrez]) 1891 05:03:26
#47 Add Search (#45 and #46) 133 05:02:30
#46 Add Search publisher [sb] 496216 05:02:05
#45 Add Search (#36 and #44) 5571 05:01:36
#44 Add Search (#37 or #38 or #39 or #40 or #41 or #42 or #43) 118514 05:01:11
#43 Add Search (exemestane[Title/Abstract] OR aromasin[Title/Abstract] OR anastrozole[Title/Abstract] OR letrozole[Title/Abstract] OR aminoglutethimide[Title/Abstract] OR "amino glutethimide"[Title/Abstract] OR cytraden[Title/Abstract] OR orimeten[Title/Abstract] OR eliptin[Title/Abstract] OR elipten[Title/Abstract] OR rodazol[Title/Abstract] OR fadrozole[Title/Abstract] OR afema[Title/Abstract] OR arensin[Title/Abstract]) 5000 05:00:31
#42 Add Search (reduction[Title/Abstract]) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract]) 79301 04:57:23
#41 Add Search ("aromatase inhibitor"[Title/Abstract] OR "aromatase inhibitors"[Title/Abstract]) 5761 04:52:38
#40 Add Search (toremifene[Title/Abstract] OR estrimex[Title/Abstract] OR fareston[Title/Abstract]) 625 04:51:04

Database: Pubmed

#39 Add Search (raloxifene[Title/Abstract] OR evista[Title/Abstract] OR keoxifene[Title/Abstract] OR bonmax[Title/Abstract] OR loxar[Title/Abstract] OR loxifen[Title/Abstract] OR optruma[Title/Abstract] OR raxeto[Title/Abstract]) 2968 04:50:13

#38 Add Search (tamoxifen[Title/Abstract] OR nolvadex[Title/Abstract] OR novaldex[Title/Abstract] OR soltamox[Title/Abstract] OR tomaxithen[Title/Abstract] OR zitazonium[Title/Abstract] OR kessar[Title/Abstract] OR tamoplac[Title/Abstract] OR tamoxasta[Title/Abstract]) 19536 04:49:11

#37 Add Search (chemoprevention[Title/Abstract] OR chemopreventions[Title/Abstract] OR chemoprophylaxis[Title/Abstract] OR chemoprophylaxes[Title/Abstract]) 14492 04:47:56

#36 Add Search (#5 and #35) 49867 04:46:50

#35 Add Search (#21 and #34) 82701 04:46:23

#34 Add Search (#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33) 1426906 04:45:59

#33 Add Search ((increase[Title/Abstract] OR increased[Title/Abstract] OR increasing[Title/Abstract])) AND risk[Title/Abstract] 545875 04:44:53

#32 Add Search (high[Title/Abstract]) AND risk[Title/Abstract] 458918 04:43:49

#31 Add Search (BRAC1[Title/Abstract] OR BRAC2[Title/Abstract] OR TP53[Title/Abstract]) 7677 04:43:07

#30 Add Search (mutation[Title/Abstract]) AND (carrier[Title/Abstract] OR carriers[Title/Abstract]) 16234 04:42:39

#29 Add Search (inherited[Title/Abstract]) AND (mutation[Title/Abstract] OR mutations[Title/Abstract]) 22994 04:42:05

#28 Add Search ("lifetime breast cancer risk"[Title/Abstract] OR "lifetime breast cancer risks"[Title/Abstract]) 55 04:41:20

#27 Add Search mutation[Title/Abstract] 285793 04:40:45

#26 Add Search ((mutation[Title/Abstract] OR mutations[Title/Abstract])) AND (risk[Title/Abstract] OR risks[Title/Abstract]) 36983 04:40:18

#25 Add Search (genetic[Title/Abstract]) AND (counsel[Title/Abstract] OR counselling[Title/Abstract] OR counsellor[Title/Abstract] OR counsellors[Title/Abstract] OR test[Title/Abstract] OR tests[Title/Abstract] OR testing[Title/Abstract] OR screen[Title/Abstract] OR screening[Title/Abstract]) 111552 04:39:38

#24 Add Search (hereditary[Title/Abstract] OR inherited[Title/Abstract] OR inherit[Title/Abstract] OR predisposed[Title/Abstract] OR predispose[Title/Abstract] OR predisposition[Title/Abstract]) 177944 04:37:56

#23 Add Search (family[Title/Abstract]) AND (history[Title/Abstract] OR histories[Title/Abstract]) 70182 04:36:58

#22 Add Search familial[Title/Abstract] 93605 04:36:23

#21 Add Search (#5 or #15 or #16 or #20) 634792 04:32:41

#20 Add Search (#17 or #18 or #19) 133305 04:31:37

#19 Add Search ((island[Title/Abstract] OR islet[Title/Abstract])) AND cell[Title/Abstract] 24104 04:31:15

#18 Add Search (adenoma[Title/Abstract] OR nesidioblastoma[Title/Abstract]) 42244 04:30:46

#17 Add Search ((pancreas[Title/Abstract] OR pancreatic[Title/Abstract])) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract]) 71284 04:30:11

#16 Add Search ((prostate[Title/Abstract] OR prostatic[Title/Abstract])) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract]) 122352 04:27:48

#15 Add Search (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) 102377 04:25:21

Database: Pubmed

#14 Add Search (theca[Title/Abstract]) AND cell[Title/Abstract] 1836 04:20:34

#13 Add Search (thecoma[Title/Abstract] OR thecomas[Title/Abstract]) 386 04:19:58

#12 Add Search (sertoli[Title/Abstract]) AND leydig[Title/Abstract] 2983 04:19:26

#11 Add Search (androblastoma[Title/Abstract] OR androblastomas[Title/Abstract] OR arrhenoblastoma[Title/Abstract] OR arrhenoblastomas[Title/Abstract]) 432 04:18:59

#10 Add Search ((meig[Title/Abstract] OR meig's[Title/Abstract] OR meigs[Title/Abstract])) AND syndrome[Title/Abstract] 551 04:18:06

#9 Add Search (luteoma[Title/Abstract] OR luteomas[Title/Abstract] OR luteinoma[Title/Abstract] OR luteinomas[Title/Abstract]) 204 04:17:32

#8 Add Search (hboc[Title/Abstract]) AND (syndrome[Title/Abstract] OR syndromes[Title/Abstract]) 120 04:16:43

#7 Add Search (granulosa[Title/Abstract]) AND (cell[Title/Abstract] OR cells[Title/Abstract]) 13344 04:16:14

#6 Add Search ((ovarian[Title/Abstract] OR ovary[Title/Abstract] OR ovaries[Title/Abstract])) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract]) 87942 04:15:24

#5 Add Search (#1 or #2 or #3 or #4) 338295 04:13:10

#4 Add Search ((ductal[Title/Abstract] OR duct[Title/Abstract] OR ducts[Title/Abstract] OR intraductal[Title/Abstract] OR lobular[Title/Abstract] OR medullary[Title/Abstract])) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract]) 58825 04:12:38

#3 Add Search ((breast[Title/Abstract] OR mammary[Title/Abstract])) AND (cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplastic[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR adenocarcinomas[Title/Abstract] OR metastatic[Title/Abstract] OR metastasis[Title/Abstract] OR dcis[Title/Abstract]) 293088 04:09:40

#2 Add Search (intraductal[Title/Abstract]) AND (papilloma[Title/Abstract] OR papillomas[Title/Abstract]) 522 04:06:56

#1 Add Search ((paget[Title/Abstract] OR paget's[Title/Abstract] OR pagets[Title/Abstract])) AND disease[Title/Abstract] 7075

1

Supplementary Search Techniques:

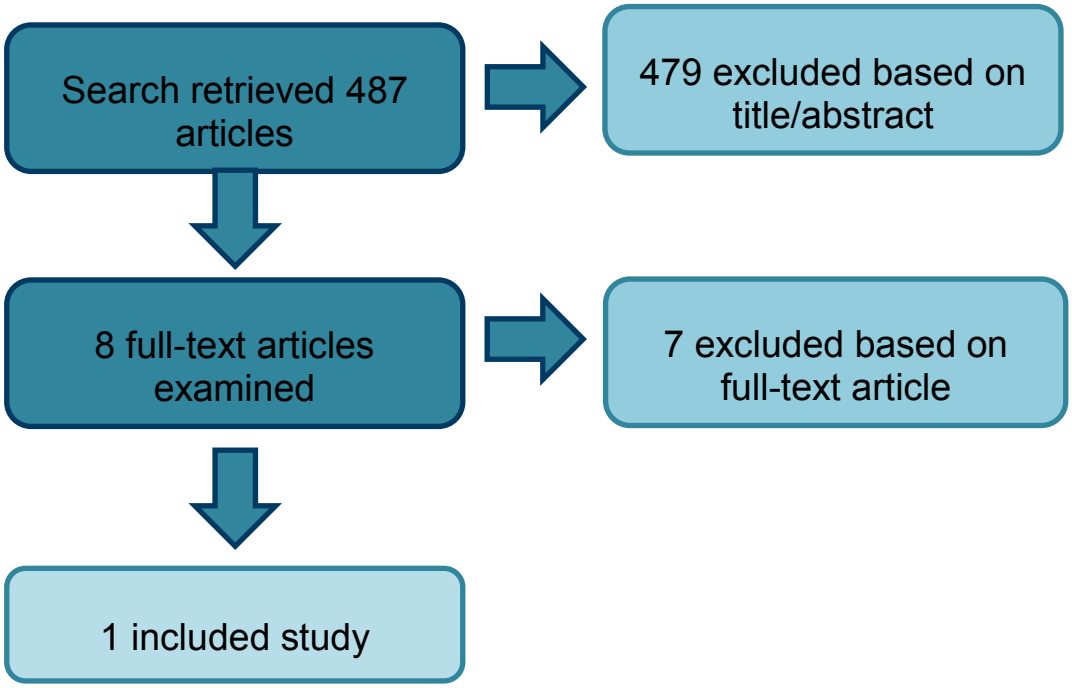
A grey literature search was performed to identify cost-effectiveness analyses referenced in articles selected for full text review.

A cost consequences model used to inform the 2013 update to the guideline was also identified as a relevant economic analysis.

2

3

Appendix K: Economic review flowchart



1 Appendix L:Economic excluded studies

2

Reference	Reason for exclusion
Blank P R, Filipits M, Dubsky P, Gutzwiller F, Lux M P, Brase J C, Weber K E, Rudas M, Greil R, Loibl S, Szucs T D, Kronenwett R, Schwenkglenks M, and Gnant M. (2015). Cost-Effectiveness Analysis of Prognostic Gene Expression Signature-Based Stratification of Early Breast Cancer Patients. PharmacoEconomics, 33(2), pp.179-190.	Does not include chemoprevention
Bozovic-Spasojevic I, Azambuja E, McCaskill-Stevens W, Dinh P, and Cardoso F. (2012). Chemoprevention for breast cancer. Cancer Treatment Reviews, 38(5), pp.329-39.	Not an economic analysis
Gabriel E M, and Jatoi I. (2012). Breast cancer chemoprevention. Expert Review of Anticancer Therapy, 12(2), pp.223-8.	Not an economic analysis
Green L E, Dinh T A, Hinds D A, Walser B L, and Allman R. (2014). Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy. Applied Health Economics & Health Policy, 12(2), pp.203-17.	Analysis is focused on a genetic test to direct chemoprevention, rather than the cost-effectiveness of chemoprevention.
Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, Wardle J, Sanderson S, Gessler S, Side L, Balogun N, Desai R, Kumar A, Dorkins H, Wallis Y, Chapman C, Taylor R, Jacobs C, Tomlinson I, Beller U, Menon U, and Jacobs I. (2015). Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. Journal of the National Cancer Institute, 107(1), pp.380.	Does not include chemoprevention
Shen Y, Qin J, and Costantino J P. (2007). Inference of Tamoxifen's Effects on Prevention of Breast Cancer from a Randomized Controlled Trial. J Am Stat Assoc, 102(480), pp.1235-1244.	Not an economic analysis
Zucchini G, Geuna E, Milani A, Aversa C, Martinello R, and Montemurro F. (2015). Clinical utility of exemestane in the treatment of breast cancer. International Journal of Women's Health, 7, pp.551-63.	Not an economic analysis

3

4

1 Appendix M: Full economic evidence tables

2 These are the full evidence tables for all included economic studies.

3 **Table 15: Economic evidence table: Noah-Vanhoucke et al, 2011**

Bibliographic reference	**Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P., & Smith, R. A. (2011). Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer, 117(15), 3322-3331.**
Evaluation design	

Interventions	Chemoprevention with tamoxifen – five year treatment
Comparators	No chemoprevention
Base-line cohort characteristics	Postmenopausal women aged <55, stratified by five-year risk of breast cancer
Type of Analysis	Cost-effectiveness
Structure	Continuous time model of breast cancer incidence, tumour growth, detection, survival, and healthcare processes.
Cycle length	N/A
Time horizon	Lifetime
Perspective	US healthcare system
Country	US
Currency unit	US dollars
Cost year	2010
Discounting	3%
Other comments	

Bibliographic reference	**Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P., & Smith, R. A. (2011). Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer, 117(15), 3322-3331.**

Results

Chemoprevention with tamoxifen compared to no treatment

Risk group, %	QALYs saved per 1000 treated women	Additional cost per treated woman ($US)	ICER ($US)
≥0	29.0	333.81	11,528.05
≥0.8	38.7	255.63	6603.31
≥1	44.1	196.07	4450.38
≥1.25	57.7	98.27	1702.04
≥1.66	84.8	-47.58	Dominates
≥2	112.3	-158.48	Dominates
≥3	119.3	-485.00	Dominates
≥4	199.8	-613.55	Dominates

Author's conclusion: The analysis indicates that the benefits of tamoxifen chemoprevention can compensate sufficiently for its side-effect profile in a postmenopausal population aged <55 years with a risk >1.66%

Data sources

Base-line data	Breast cancer incidence: Hazard rates estimated from incidence by age data from SEER from 1980 through 2004 Endometrial cancer, pulmonary embolism, deep vein thrombosis, and cataract incidence: Hazard functions approximated from incidence by age data from a review article summarising the risks and benefits of tamoxifen treatment Hysterectomy incidence: Based on cancer incidence rate data for the US Survival from breast cancer, endometrial cancer, and pulmonary embolism: Survival curves estimated using relative survival and SEER data from 1988 through 2004.
Effectiveness data	Reduction in breast cancer incidence from treatment with tamoxifen: Tamoxifen reduces the risk of ER-negative breast cancer by 48% - hazard ratio of 0.52 **Hazard ratios for adverse events – calculated using adverse event rates from four RCTs of tamoxifen:** Endometrial cancer: 2.41 Stroke: 1.39

Bibliographic reference	Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P., & Smith, R. A. (2011). Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer, 117(15), 3322-3331.	
		Pulmonary embolism: 1.79 Deep vein thrombosis: 2.05 Cataracts: 1.12 Osteoporotic fracture: 0.88 Myocardial infarction: 1.14
	Cost data	The following costs were obtained from a previous cost-effectiveness analysis of tamoxifen for chemoprevention: Breast cancer Year 1: $22,418 Year 2: $1,902 Year 3: $1,509 Years 4-10: $1,433 Endometrial cancer Year 1: $17,391 Year 2: $284 Years 3-5: $190 DVT: $6,274 PE: $16,943 Cataracts: $5,484 Stroke: Cost obtained from Medicare claims data: Year 1: $27,325 Year 2: $2,786 Tamoxifen, 1 year supply: Taken from drugstore.com 2010: $203 End of life costs: Obtained from Medicare data on expenses incurred during the final year of life: Death: $12,147 Last year of life: $39,236
	Utility data	Healthy patients: A utility value of 1 is assumed Breast cancer: Values taken from a previous cost-effectiveness analysis of digital mammography breast cancer screening: Local: 0.9 Regional: 0.75 Distant: 0.6

Bibliographic reference	**Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P., & Smith, R. A. (2011). Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer, 117(15), 3322-3331.**
	The following utility values were taken from a previous cost-effectiveness analysis of anastrozole versus tamoxifen in women with early breast cancer: Endometrial cancer: 0.839 Deep vein thrombosis: 0.729 Pulmonary embolism: 0.741 Stroke: 0.707 Common tamoxifen symptoms: 0.959 Terminal year of cancer: Taken from a cost-effectiveness analysis of preventative therapies for postmenopausal women with osteopenia: 0.23 Cataracts: Taken from a previous cost-effectiveness analysis of tamoxifen for breast cancer prevention: 0.772
Uncertainty	
One-way sensitivity analysis	Cost-effectiveness results are robust to sensitivity analysis performed for discount rate (1% to 5%) and costs (tamoxifen and cancer costs increased up to 3 times). Sensitivity analysis of side-effect hazard ratios reveals a large effect on ICERs. Varying stroke hazard ratio from 1.0 to 1.39 results in tamoxifen being dominated by no treatment at low risk thresholds (risk ≥1.25%) but remains cost saving at a risk ≥3%. Varying the hazard ratio for endometrial cancer from 2.41 to 3.96 results in tamoxifen therapy being dominated for all women at any risk threshold.
Probabilistic sensitivity analysis	N/A
Applicability	**Partially applicable** This analysis is directly relevant to the topic area, but is only partially applicable to the NHS, as it is based on the US healthcare system.
Limitations	**Minor Limitations** The analysis was determined to have only minor limitations as the model considered all relevant health outcomes and costs, and used a lifetime time horizon

Bibliographic reference	**Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P., & Smith, R. A. (2011). Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer, 117(15), 3322-3331.**
Conflicts	**N/A**

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 16: Economic evidence table – original economic analysis for 2013 update

Bibliographic reference	**A cost consequence analysis for chemoprevention for women with no personal history of breast cancer (original health economic analysis for 2013 update to CG164 – Familial breast cancer)**
Evaluation design	

Interventions	Chemoprevention (consisting of tamoxifen for premenopausal women, and an even split of tamoxifen and raloxifene for postmenopausal women)
Comparators	No chemoprevention
Base-line cohort characteristics	High risk women with no personal history of breast cancer, who have no history of increased risk of thromboembolic disease or endometrial cancer and who are eligible for the offer of chemoprevention as described by CG164.
Type of Analysis	Cost consequence
Structure	Incidence of breast cancer under current standard of care and with chemoprevention is calculated on an annual basis based on baseline incidence data and relative risk reduction of chemoprevention. Chemoprevention costs are estimated over a five-year period, dependent on treatment rates and discontinuation. Associated adverse event rates are also estimated over this period, based on baseline rates and relative risk of chemoprevention.
Cycle length	1 year
Time horizon	Lifetime
Perspective	NHS and PSS
Country	UK
Currency unit	GBP
Cost year	2013
Discounting	3.5%
Other comments	Assumption made that 25% of eligible patients will opt for chemoprevention, and 50% of patients receiving treatment will discontinue after one year.

Bibliographic reference	**A cost consequence analysis for chemoprevention for women with no personal history of breast cancer (original health economic analysis for 2013 update to CG164 – Familial breast cancer)**

Results

	Current standard of care	Chemoprevention offered	Difference
Discounted costs			
Chemoprevention drugs	£0	£79,088	£79,088
Chemoprevention monitoring	£0	£56,731	£56,731
Endometrial cancer & thromboembolic events	£24,322	£27,068	£2,746
Breast cancer	£2,649,226	£2,544,925	-£104,301
Total costs	£2,673,548	£2,707,812	£34,264
Outcomes			
Breast cancer cases	300	289	11
Endometrial cancer cases	5.00	5.60	0.60
Thromboembolic events	5.00	5.60	0.60

Author's conclusion: The overall cost per breast cancer case prevented was found to be £3,010 in the base case. Assuming a willingness to pay threshold of £20,000 per QALY, chemoprevention would need to provide a gain of 1.71 QALYs per 1,000 women to be cost effective. It is therefore likely that chemoprevention as an overall strategy is cost effective, although, due to the nature of the analysis, an exact cost-effectiveness value cannot be calculated.

Data sources

Base-line data	Annual incidence of breast cancer: No published reference is provided: 20-29 years old: 0.27% 30-39 years old: 0.47% 40-49 years old: 0.65% 50-59 years old: 0.91% 60-69 years old: 1.06% 70+ years old: 1.75% Background probability of death: Annual probability of death for each year of age taken from office for national statistics data 2009-2011 Annual probability of endometrial cancer and thromboembolic events with no chemoprevention: Taken from the placebo group result in a systematic review of comparative effectiveness of chemoprevention:

Bibliographic reference	A cost consequence analysis for chemoprevention for women with no personal history of breast cancer (original health economic analysis for 2013 update to CG164 – Familial breast cancer)	
		Probability of endometrial cancer: 0.1% Probability of thromboembolic events: 0.1% Age distribution among women aged at least 20 in England: Taken from total population data for each age group in England – ADS 2010 primary care organisations for England: 20-29: 17.0% 30-39: 17.0% 40-49: 19.1% 50-59: 15.6% 60-69: 13.9% 70+: 17.4%
	Effectiveness data	Relative risk of breast cancer for patients treated with chemoprevention: Obtained from results of two RCTs of tamoxifen (effect of raloxifene assumed to be identical): 0.65 Relative risk of endometrial cancer and thromboembolic events: Taken from a systematic review of comparative effective of chemoprevention: Endometrial cancer Tamoxifen: 2.13 Raloxifene: 1.14 Thromboembolic events Tamoxifen: 1.93 Raloxifene: 1.60
	Cost data	Annual cost of Tamoxifen and Raloxifene: Electronic drugs tariff 2012/13: Tamoxifen: £36 Raloxifene: £222 GP visit: Unit costs of health and social care 2012: £40 Breast cancer: NICE familial breast cancer costing report: £14,511 Endometrial cancer: Obtained from a systematic review of hormonal therapies for early breast cancer: £4,375 Thromboembolic events: Taken from 2011/2012 HRG costs for deep vein thrombosis: £821
	Utility data	N/A

<table>
<tr><td>Bibliographic reference</td><td>A cost consequence analysis for chemoprevention for women with no personal history of breast cancer (original health economic analysis for 2013 update to CG164 – Familial breast cancer)</td></tr>
<tr><td>Uncertainty</td><td>
<table>
<tr><td>One-way sensitivity analysis</td><td>One way sensitivity analysis revealed that the model is particularly sensitive to variations in the cost of breast cancer and the effectiveness of chemoprevention, as shown below:
<table>
<tr><th>Input parameter</th><th>Input for sensitivity analysis</th><th>Cost per breast cancer case prevented</th><th>Percentage change from base case</th></tr>
<tr><td colspan="4">Total cost of breast cancer</td></tr>
<tr><td>Base case</td><td>£14,511.45</td><td></td><td></td></tr>
<tr><td></td><td>£4,200.00</td><td>£9,522.37</td><td>216%</td></tr>
<tr><td></td><td>£20,000</td><td>-£455.61</td><td>-115%</td></tr>
<tr><td colspan="4">Relative risk reduction of chemoprevention</td></tr>
<tr><td>Base case</td><td>35%</td><td></td><td></td></tr>
<tr><td></td><td>25%</td><td>£8,194.70</td><td>172%</td></tr>
<tr><td></td><td>45%</td><td>£155.63</td><td>-95%</td></tr>
</table></td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>N/A</td></tr>
</table>
</td></tr>
<tr><td>Applicability</td><td>Partially Applicable

Study was deemed partially applicable as it does not consider all of the relevant comparators, and only considers chemoprevention as an overall strategy, rather than examining the cost effectiveness of individual chemopreventive agents.</td></tr>
<tr><td>Limitations</td><td>Minor Limitations

The analysis was determined to have only minor limitations as the model considered all relevant health outcomes and costs, and used a lifetime time horizon.</td></tr>
<tr><td>Conflicts</td><td>N/A</td></tr>
</table>

1 *Acronyms*
2 *ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life yea*

Appendix N: Economic modelling report

N.1 Introduction

Since the update to this guideline in 2013, new evidence has been published on chemoprevention using aromatase inhibitors. The evidence suggests that these agents are effective in preventing breast cancer in postmenopausal women, although there remain concerns regarding their adverse event profile, specifically reduction in bone mineral density and an increased occurrence of fractures. The original economic analysis for the 2013 update investigated the cost consequences of chemoprevention as an overall strategy (with patients receiving either tamoxifen or raloxifene) compared to no chemoprevention. This evaluation updates the original economic analysis by considering the cost consequences of three chemopreventive agents (tamoxifen, raloxifene, and anastrozole) compared to no chemoprevention in postmenopausal women at high-risk and moderate-risk of breast cancer.

N.2 Methods

N.2.1 Type of evaluation

Although this topic would be a suitable candidate for cost utility modelling, it was determined that a simple cost consequences model adapted from the analysis developed for the 2013 guideline update would be sufficient to provide estimates of incremental costs and outcomes associated with each of the comparators. This type of evaluation was chosen as the previous analysis demonstrated that chemoprevention as an overall strategy is likely to be cost effective at a threshold of £20,000 per QALY. Therefore the objective of this analysis was to compare the relative costs, benefits, and side effects of different chemoprevention in their natural units.

N.2.2 Target population

The population for this analysis is high- and moderate-risk postmenopausal women with no personal history of breast cancer, who have no history or increased risk of thromboembolic disease or endometrial cancer, and who are eligible for chemoprevention with any of the chemopreventive agents included in the analysis. Risk levels are defined according to the following lifetime risks of breast cancer from age 20:

- High risk population: 30% or greater
- Moderate risk population: Greater than 17% but less than 30%

N.2.3 Interventions

The interventions included in the analysis are the following chemopreventive agents, administered once-daily over a five year period:

- Tamoxifen 20mg
- Raloxifene 60mg
- Anastrozole 1mg

N.2.4 Comparator

The comparator in the analysis is no chemoprevention.

N.2.5 Time horizon

Since chemoprevention has the potential to reduce the long-term incidence of breast cancer, a lifetime time horizon was used in this analysis.

N.2.6 Health outcomes

The primary measure of health outcomes in the analysis is cases of breast cancer prevented as a result of chemoprevention. Secondary measures are incremental endometrial cancer cases, thromboembolic events, and fractures, compared to no chemoprevention.

N.2.7 Perspective

The analysis was conducted from the perspective of the NHS and personal and social services (PSS).

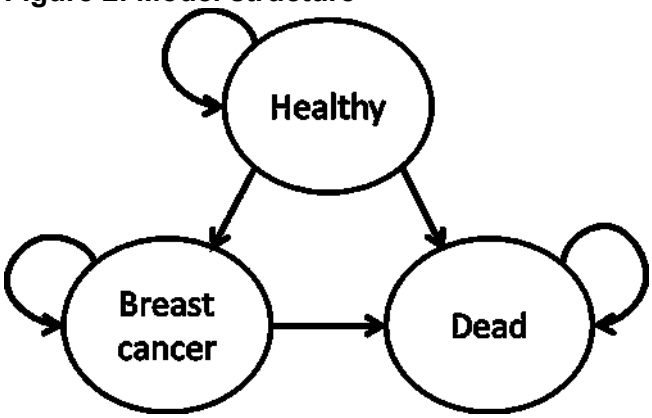
N.2.8 Discounting

A discount rate of 3.5% per annum was applied to all costs incurred after the first year.

N.2.9 Model structure

A Markov structure with a cycle length of one year was used to simulate the progression of patients over a lifetime time horizon. The model used three health states: healthy, breast cancer, and dead, as shown in Figure 2.

Figure 2: Model structure



For the no chemoprevention arm of the model, age-specific incidence rates of breast cancer and baseline mortality were used to inform progression probabilities. Each

year, living patients (either with or without breast cancer) could also experience adverse events: endometrial cancer, venous thromboembolism, or fracture. Patients could experience four categories of fracture: hip fracture, wrist fracture, vertebral fracture, or other fracture. The number of adverse events of each category per year was calculated by multiplying the number of living patients by the annual baseline probability of experiencing each event.

For the treatment arms of the model (tamoxifen, raloxifene, and anastrozole) relative risks were applied to the baseline incidence rates for breast cancer incidence, endometrial cancer, venous thromboembolism, and fracture in order to inform transition probabilities and adverse event probabilities.

N.2.10 Patient cohort characteristics

The assumption was made that patients of the age 50 and above are postmenopausal. The model simulated the progression of four patient age groups of patients: 50-59 years old, 60-69 years old, 70-79 years, and 80 years old plus, in order to capture the heterogeneity of the patient population. The distribution of patients among these age groups was derived from Office for National Statistics mid-2015 population data for females in the UK [accessed 23rd September 2016], and is shown in Table 17.

Table 17: Age distribution among women aged at least 50 in the UK

Age (years)	50-59	60-69	70-79	≥80
Proportion of women	34.6%	29.3%	20.9%	15.3%

N.2.11 Baseline breast cancer risk

Due to the scarcity of data on age-dependent baseline risk of breast cancer, five-year risks of breast cancer were generated using the BOADICEA assessment tool [http://ccge.medschl.cam.ac.uk/boadicea/] for representative high- and moderate-risk patients. Baseline risk data are displayed in Table 18. These values were converted to one year risks in order to inform transition probabilities for the model.

Patient profiles in the BOADICEA tool were selected to produce lifetime breast cancer risks which were consistent with definitions of high- and moderate-risk patients in this guideline: high-risk patients are associated with a 30% or greater risk of breast cancer from age 20 and moderate-risk patients are associated with a risk of between 17% and 30%.

The high-risk BOADICEA profile consisted of a 20 year old female patient who had not been tested for genetic mutations, but whose mother had a confirmed BRCA1 mutation. The moderate-risk profile consisted of a 20 year old female patient who had not been tested for genetic mutations, and whose mother had also not been tested, but had been diagnosed with breast cancer at age 20.

Table 18: Baseline five-year breast cancer incidence in high- and moderate-risk women

Age (years)	50-54	55-59	60-64	65-69	70-74	≥75
High-risk women	5.4%	4.7%	4.3%	3.8%	2.9%	2.6%
Moderate-risk women	2.8%	2.7%	3.0%	2.8%	2.4%	2.1%

N.2.12 Mortality rate

Age-specific mortality data for females were taken from Office for National Statistics National Life Tables: England and Wales for 2013-15 [accessed 23rd September 2016]

N.2.13 Baseline adverse event risks

Baseline risks for the incidence of endometrial cancer, thromboembolic events, and fractures were taken from the placebo arm of Cuzick et al. (2015). This study was selected as it is the analysis of tamoxifen with the largest patient numbers identified by the clinical review. Pooling of studies from the clinical literature review to derive baseline data was not possible, as analyses used varying follow-up lengths. Table 19 displays baseline adverse event incidence rates used in the model.

Table 19: Baseline incidence of adverse events

Adverse event	Endometrial cancer (median follow-up 16 years)	Thromboembolic event (median follow-up 95.6 months)	Fracture (median follow-up 95.6 months)
Incidence	0.56%	1.9%	6.57%

The distribution of fracture categories was derived from Scholes et al (2014) – an epidemiological study of the prevalence of fractures in adults aged 55 and above. Table 20 shows the relative incidence of fracture categories.

Table 20: Relative incidence of fracture categories

Fracture Category	Hip fracture	Wrist fracture	Vertebral fracture	Other fractures
Relative incidence	3.2%	22.1%	2.1%	72.6%

N.2.14 Relative risks for chemoprevention

Relative risks of breast cancer incidence and adverse event incidence were taken from the results of the clinical literature review and are shown in Table 21.

Table 21: Relative risks of breast cancer and adverse event incidence for each chemoprevention treatment

Treatment	Tamoxifen versus placebo	Tamoxifen versus Raloxifene	Anastrozole versus placebo
Breast cancer incidence	0.70	0.81	0.51
Endometrial cancer incidence	2.12	1.76	0.61
Thromboembolic event incidence	1.49	1.31	1.21
Fracture incidence	0.91	1.09	1.11

N.2.15 Adherence to chemoprevention

For the base case, the assumption was made that 50% of patients discontinued chemoprevention after one year of treatment, with the remaining 50% continuing treatment for the full 5 years. This estimate was elicited via expert opinion. It was assumed that patients discontinuing after one year had the same risk of breast cancer and adverse events as patients with receiving no chemoprevention.

N.2.16 Duration of treatment effect

The assumption was made that, in the base case, reduction in the incidence of breast cancer resulting from chemoprevention persisted over patients' lifetime. It was assumed that change in risk level of endometrial cancer and thromboembolic events caused by chemoprevention lasted for the duration of treatment (i.e. the first five years of the model), and the change in risk level of fractures lasted for five years after the end of treatment (i.e. the first ten years of the model), after which incidence rates of adverse events returned to baseline levels.

N.2.17 Costs

Annual costs of tamoxifen, raloxifene, and anastrozole were taken from the September 2016 Electronic Drug Tariff [accessed 23rd September 2016], and are shown in Table 22.

Table 22: Annual costs of chemoprevention

Treatment	Tamoxifen	Raloxifene	Anastrozole
Annual cost	£37.23	£48.62	£15.90

The assumption was made that all patients receiving chemoprevention would also incur the cost of two GP consultations per year while treatment was ongoing. The cost of a GP consultation was estimated to be £38 (including direct care staff costs and excluding qualification costs), taken from the PSSRU Unit Costs of Health and Social Care 2015. It was also assumed that patients treated with anastrozole incurred the cost of a DEXA scan at the outset of treatment, to screen patients for osteoporosis, due to concerns of reduction in bone mineral density associated with

aromatase inhibitors. The cost of a DEXA scan was estimated to be £62, taken from the NHS National Tariff Payment System 2016/17 [accessed 23rd September, 2016].

Costs associated with a case of breast cancer were taken from the model for the 2013 guideline update, which were originally derived from the NICE costing report published with the full guideline. These costs were adjusted to 2015 prices using consumer price index rates from the Office for National Statistics. Costs associated with a case of breast cancer are shown in Table 23.

Table 23: Cost components of breast cancer treatment

Category	Surgery	Radiotherapy	Chemotherapy	Other drug costs	Total
Cost	£2,824.75	£1,872.68	£3,880.35	£6,310.82	**£14,888.59**

Costs of endometrial cancer and thromboembolic events were also taken from the model produced for the 2013 update, adjusted to 2015 prices. The cost of endometrial cancer was originally sourced from Hind et al (2007). The cost of a thromboembolic event was assumed to be that of deep vein thrombosis, derived from NHS Reference Costs 2011/12. Costs of hip fracture, wrist fracture, vertebral fracture, and other fractures were taken from Dolan et al (1998), and adjusted to 2015 prices. Costs of all adverse events used in the model are shown in Table 24.

Table 24: Adverse event costs

Adverse event	Cost
Endometrial cancer	£4,684.62
Thromboembolic event	£878.92
Hip fracture	£17,139.30
Wrist fracture	£668.43
Vertebral fracture	£684.14
Other fractures	£1,911.03

N.2.18 Sensitivity analysis

Both deterministic and probabilistic sensitivity analyses were used to characterise the uncertainty surrounding the base case results of the model.

For the deterministic sensitivity analysis, cost per breast cancer case prevented was calculated compared to no chemoprevention for each intervention, under each of the following scenarios:

- Relative risks for breast cancer incidence and adverse events replaced by hazard ratios where available from the clinical literature
- Baseline incidence of breast cancer increased by 100% and reduced by 50%

- Relative risks of treatments for breast cancer incidence changed to lower and upper 95% confidence intervals
- Adherence changed to 100% and 25%
- Baseline incidence of adverse events (endometrial cancer, thromboembolic events, and fractures) increased by 100% and reduced by 50%
- Relative risks of adverse events set to lower and upper 95% confidence intervals
- Cost of treatment increased by 100% and reduced by 50%
- Costs of adverse events increased by 100% and reduced by 50%
- Cost of breast cancer increased by 100% and reduced by 50%
- Relative risks of adverse events persist for 20 years after the end of treatment
- Breast cancer treatment is associated with no chemotherapy costs (this scenario was included to reflect the fact that chemoprevention is only effective in preventing ER-positive breast cancers, which are less susceptible to treatment with chemotherapy)
- Relative risks for breast cancer, endometrial cancer and thromboembolic event incidence for raloxifene changed to those from the RUTH trial comparing raloxifene to placebo in postmenopasal women (Barrett-Connor et al, 2006). This sensitivity analysis was conducted as the committee felt that the evidence comparing raloxifene to tamoxifen may provide an unfavourable representation of the effectiveness of raloxifene in preventing breast cancer. The RUTH trial was selected as a representative study comparing raloxifene to placebo in a relevant patient population.Table 25 shows the relative risks used in this sensitivity analysis.

Table 25: Relative risk values used for deterministic sensitivity analysis of raloxifine using results from the RUTH trial

Parameter	Breast cancer incidence	Endometrial cancer incidence	Thromboembolic event incidence	Fracture incidence
Relative risk (raloxifene versus placebo)	0.57	1.24	1.45	0.92

For the probabilistic sensitivity analysis, all model input parameters were assigned probability distributions (rather than being expressed as point estimates) to reflect

the uncertainty surrounding the available clinical and cost data. 1,000 iterations of the model were run, each drawing random values from parameter distributions.

Probability parameters were assigned beta distributions in order to account for the fact that probability values must lie between 0 and 1. Cost parameters were assigned gamma distributions, to ensure that costs could not be negative. Relative risks were assigned a distribution by raising the exponential constant to the power of a normal distribution of the natural logarithm of the parameter.

Where available, standard errors or 95% confidence intervals were used to inform the shape of distributions. For parameters for which these values were not available, it was assumed that standard error was 10% of the parameter mean.

N.3 Results – high risk patients

N.3.1 Deterministic results

Base case cost results for a cohort of 1,000 high risk patients are displayed in Table 26. Results show that tamoxifen and raloxifene incur an additional cost of £97,346 and £237,865 per 1,000 patients, respectively, compared to no treatment. This additional cost is incurred primarily from costs of chemoprevention and monitoring consultations with GPs, although it partially offset by a reduction in the cost of breast cancer treatment. Conversely, anastrozole produces a cost saving of £34,539 per 1,000 patients, mostly achieved through a reduction in the cost of breast cancer treatment.

Table 27 displays health outcomes for a cohort of 1,000 patients. All chemoprevention strategies demonstrate a reduction in breast cancer cases, with anastrozole achieving the highest reduction (36 cases prevented). The incidence of adverse events is relatively uniform across all comparators, although the incidence of thromboembolic events is slightly elevated for all chemopreventive agents (in particular for tamoxifen), and the incidence of fractures is slightly decreased by tamoxifen and raloxifene, and slightly increased by anastrozole.

Table 28 displays incremental cost effectiveness results for each chemopreventive agent compared to no treatment, reported in terms of incremental cost per breast cancer case prevented. Raloxifene is associated with a substantially higher cost per case prevented than other chemopreventive agents, due to a high drug acquisition cost and a relatively low efficacy. Anastrozole is associated with a negative ICER (i.e. it dominates no chemoprevention), as it results in lower costs and fewer breast cancer cases than no treatment.

Results are also reported in terms of the QALY gain required per prevented breast cancer case for each treatment to be cost effective at a threshold of £20,000/QALY. Treatment with tamoxifen and raloxifene requires a gain of 0.23 and 1.27 QALYs per

breast cancer case prevented, respectively, while the value for anastrozole is negative, as this treatment dominates no chemoprevention.

Table 26: Cost results per 1,000 high-risk patients

Cost category	No chemoprevention	Tamoxifen	Raloxifene	Anastrozole
Chemoprevention drugs	£0	£102,947	£134,442	£43,966
Chemoprevention monitoring	£0	£210,152	£210,152	£210,152
Breast cancer	£1,525,164	£1,309,356	£1,428,772	£1,167,124
Endometrial cancer and thromboembolic events	£58,294	£64,749	£59,700	£57,854
Fractures	£276,539	£270,138	£264,795	£284,362
DEXA scans	£0	£0	£0	£62,000
Total costs	**£1,859,997**	**£1,957,343**	**£2,097,862**	**£1,825,458**

Table 27: Health outcomes per 1,000 high-risk patients

Outcome category	No chemoprevention	Tamoxifen	Raloxifene	Anastrozole
Breast cancer cases	152	131	142	116
Endometrial cancer cases	9	10	9	8
Thromboembolic events	60	63	61	61
Fractures	211	208	205	216

Table 28: Incremental cost effectiveness results compared to no treatment for high-risk patients

	Tamoxifen	Raloxifene	Anastrozole
Cost per breast cancer case prevented	£4,621	£25,387	-£984
QALY gain required per breast cancer case prevented to be cost effective at £20,000 threshold	0.23	1.27	dominant

In order to verify that chemoprevention with these agents is cost effective at a theshold of £20,000, a simple Markov chain was constructed to estimate the QALY difference between a 50 year old woman with breast cancer and a healthy 50 year old woman over the course of five years. Using an annual cycle length, with the mortality and utility inputs listed in Table 29 and a discount rate of 3.5% per year, an estimate of 1.33 incremental QALYs per breast cancer case prevented was produced. Based on this value, it is likely that, in high risk patients, chemprevention with all three agents is cost effective compared to no treatment.

Table 29: Parameters used to estimate the incremental QALYs associated with preventing a case of breast cancer

Parameter	Value	Source
Annual breast cancer-related mortality: BRCA+ women with breast cancer – 50-59 years old	5.67%	Brekelmans et al, 2007
Annual background mortality rate: 50 years old	0.21%	Office for National Satitistics – National life Tables: England and Wales
Baseline utility for individual affected with breast cancer	0.68	Peasgood et al, 2010
Baseline utility for individual without cancer but with positive BRCA test result	0.895	Grann et al, 2011

N.3.2 Sensitivity analysis

Results of one-way sensitivity analysis are displayed in Table 30. Results for anastrozole are displayed as a tornado diagram in Figure 3, to illustrate the magnitude of sensitivity across parameters. These results show that the cost effectiveness of treatment is particularly sensitive to changes in the baseline incidence and relative risks of breast cancer. This is because these parameters have a considerable impact on both the number of breast cancer cases prevented and the magnitude of costs, as breast cancer treatment constitutes a large proportion of total costs. For this reason, results are also sensitive to changes in the cost per case of breast cancer.

Comparatively, cost effectiveness results are insensitive to changes in the baseline incidence, relative risks, and costs of adverse events. This is because the majority of adverse events have a low baseline incidence rate, low cost of treatment, or relative risks for chemoprevention that do not deviate far from 1. This also explains why extending the persistence of relative risks associated with adverse events to 20 years after the end of treatment does not considerably change cost effectiveness.

Removing all chemotherapy costs for breast cancer treatment results a moderate increase in incremental costs per breast cancer case prevented. However, due to chemotherapy costs compising a relatively small proportion of total breast cancer treatment costs, these changes are unlikely to be sufficiently large to affect

decisions. This demonstrates that, even in the extreme scenario that no patients with ER-postive breast cancer receive chemoprevention, results are robust.

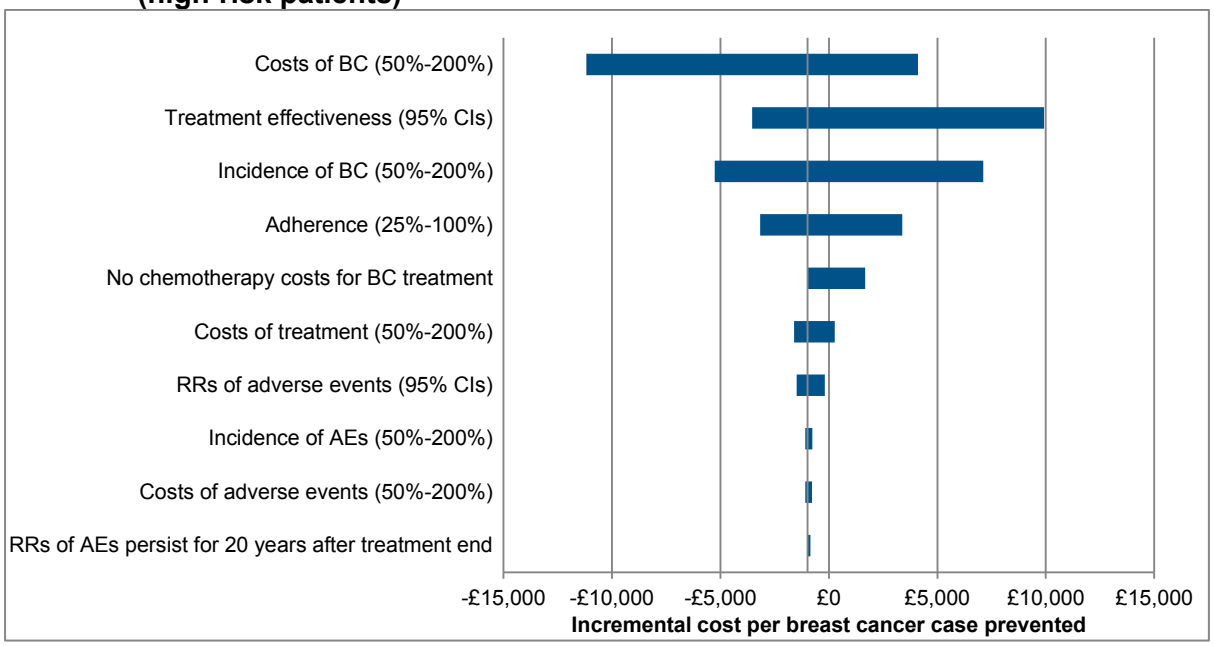
Cost effectiveness results are also relatively sensitive to changes in estimated patient adherence, as a reduction in the number of adherent patients increases drug costs, but infers no benefits in breast cancer cases prevented.

Finally, using relative risks for breast cancer and adverse event rates derived from the RUTH trial results in a considerably lower incremental cost per breast cancer case prevented, indicating that there is significant uncertainty regarding both the effectiveness and the cost effectiveness of raloxifene.

Table 30: One-way sensitivity analysis results – incremental cost per breast cancer case prevented for high-risk patients

Scenario	Tamoxifen	Raloxifene	Anastrozole
Incidence of BC reduced by 50%	£17,316	£54,990	£7,116
Incidence of BC increased by 100%	-£1,916	£10,676	-£5,266
Treatment relative risks for breast cancer incidence set to lower 95% CI	£1,104	£54,056	-£3,542
Treatment relative risks for breast cancer incidence set to upper 95% CI	£12,268	£14,820	£9,919
Adherence set to 100%	£1,948	£18,773	-£3,168
Adherence set to 25%	£9,967	£38,615	£3,385
Incidence of adverse events reduced by 50%	£4,622	£25,948	-£1,090
Incidence of adverse events increased by 100%	£4,607	£24,206	-£759
Treatment relative risks of adverse events set to lower 95% CI	£4,048	£26,395	-£1,490
Treatment relative risks of adverse events set to upper 95% CI	£5,359	£24,642	-£192
Costs of treatment reduced by 50%	£2,178	£18,213	-£1,609
Costs of treatment increased by 100%	£9,508	£39,736	£268
Costs of adverse events reduced by 50%	£4,620	£25,939	-£1,089
Costs of adverse events increased by 100%	£4,624	£24,284	-£773
Costs of breast cancer reduced by 50%	£9,744	£30,531	£4,114
Costs of breast cancer increased by 100%	-£5,624	£15,099	-£11,179
Relative risks of adverse events persist for 20 years after end of treatment	£5,034	£24,788	-£848
Breast cancer treatment is associated with no chemotherapy costs	£7,291	£28,068	£1,674
Relative risks for raloxifene taken from the RUTH trial	-	£1040	-

Figure 3: Tornado diagram of one way sensitivity analysis results for anastrozole (high-risk patients)



Mean probabilistic sensitivity analysis results are displayed in Table 31. These values show that mean probabilistic results are generally comparable to deterministic results.

Table 31: Mean PSA results for high-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Incremental cost (versus no chemoprevention)	£100,699.78	£249,453.45	-£32,489.16
Breast cancer cases prevented	21	9	35
Cost/BC case prevented	£4,758.28	£28,367.96	-£919.36
QALYs required per BC case averted to be CE	0.24	1.42	-0.05

Costs and breast cancer cases prevented for each of the 1,000 probabilistic iterations are shown in Figure 4. There is considerable overlap in the results for all chemopreventive agents, but there is a trend towards lower incremental costs and higher number of breast cancer cases for anastrozole. Moreover, anastrozole is associated with a relatively high probability of being cost saving compared to no chemoprevention (59%). Probabilistic results also show that there is an observable negative correlation between number of breast cancer cases prevented and incremental cost. This is because treatment of breast cancer comprises a large proportion of costs in the model, meaning that iterations in which a higher number of breast cancer cases are prevented are also likely to result in higher cost savings.

Figure 4: Probabilistic sensitivity analysis results – incremental cost and breast cancer cases prevented per 1,000 high-risk patients

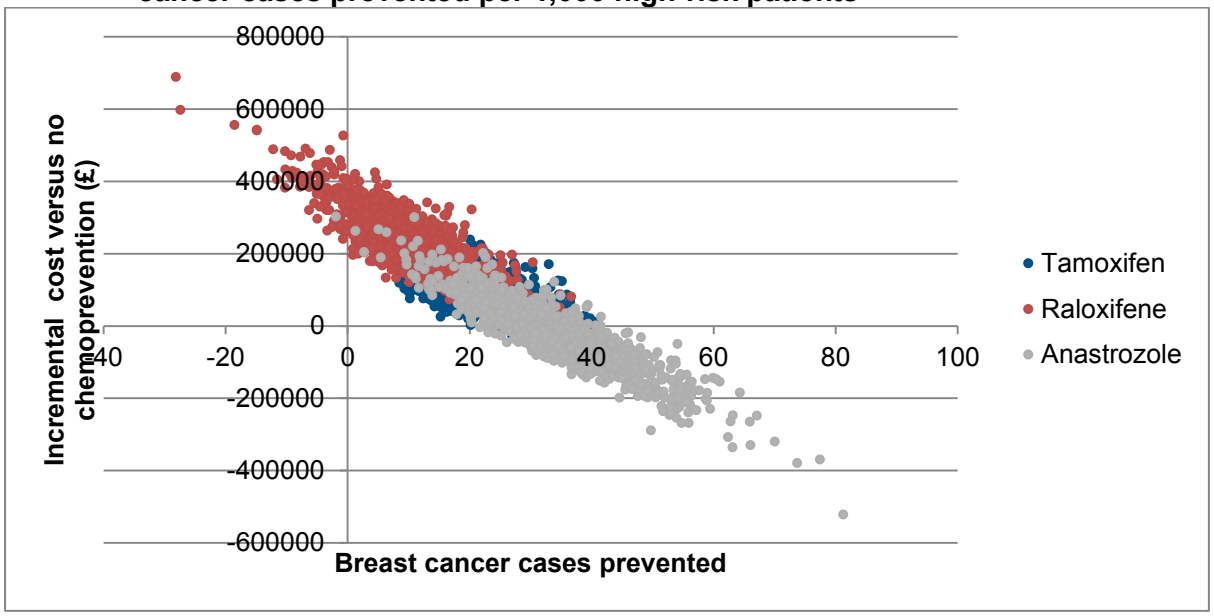
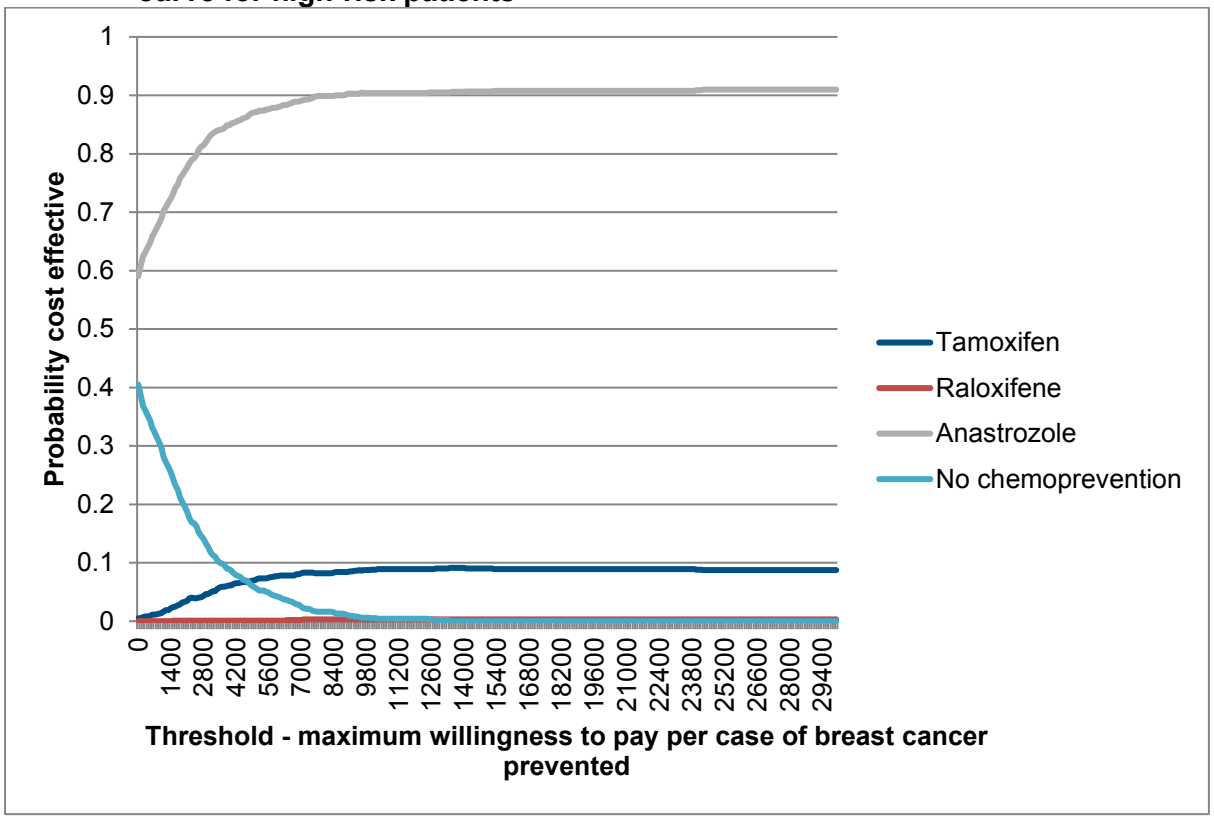


Figure 5 shows probabilistic results displayed as a cost effectiveness acceptability curve, plotting the probability of each comparator being the most cost effective option at a range of willingness to pay thresholds for the prevention of one case of breast cancer. Results show that at all thresholds anastrozole has the highest probability of being the most cost effective treatment. At a threshold of £20,000 per breast cancer case prevented, the probability of anastrozole being the most cost effective treatment is probabilities of anastrozole being the most cost effective treatment is 89%.

Figure 5: Probabilistic sensitivity analysis results – cost effectiveness acceptability curve for high-risk patients



N.4 Results – moderate risk patients

N.4.1 Deterministic results

Base case cost and health outcome results for a cohort of 1,000 moderate risk patients are presented in Table 32. Numbers of adverse events were identical to those of the high-risk cohort, so are not tabulated again. Results show that, due to the lower baseline rate of breast cancer incidence, all chemoprevention treatments are associated with a lower number of prevented breast cancer cases, and higher incremental costs than in the high-risk cohort. Anastrozole is also associated with a positive incremental costs compared to no treatment, rather than being cost saving.

However, treatment with anastrozole still results in lower total costs and a higher number of breast cancer cases prevented than tamoxifen and raloxifene. This is reflected in Table 33, which for each chemopreventive agent shows the cost per breast cancer prevented and QALYs required per breast cancer case prevented to be cost effective at a £20,000 threshold. These results indicate that, although chemoprevention is not as cost effective for moderate risk patients, anastrozole is still expected to be cost effective, both compared to no chemoprevention and compared to other chemopreventive agents.

Table 32: Cost and health outcome results per 1,000 moderate-risk patients

	No chemoprevention	Tamoxifen	Raloxifene	Anastrozole
Cost outcomes				
Cost of breast cancer treatment	£1,100,825	£942,318	£1,029,747	£839,066
Total costs	£1,435,657	£1,590,305	£1,698,837	£1,497,400
Health outcomes				
Breast cancer cases	113	97	106	87

Table 33: Incremental cost effectiveness results compared to no treatment for moderate-risk patients

	Tamoxifen	Raloxifene	Anastrozole
Cost/BC case prevented	£9,606	£36,566	£2,314
QALYs required per BC case averted to be CE	0.48	1.83	0.12

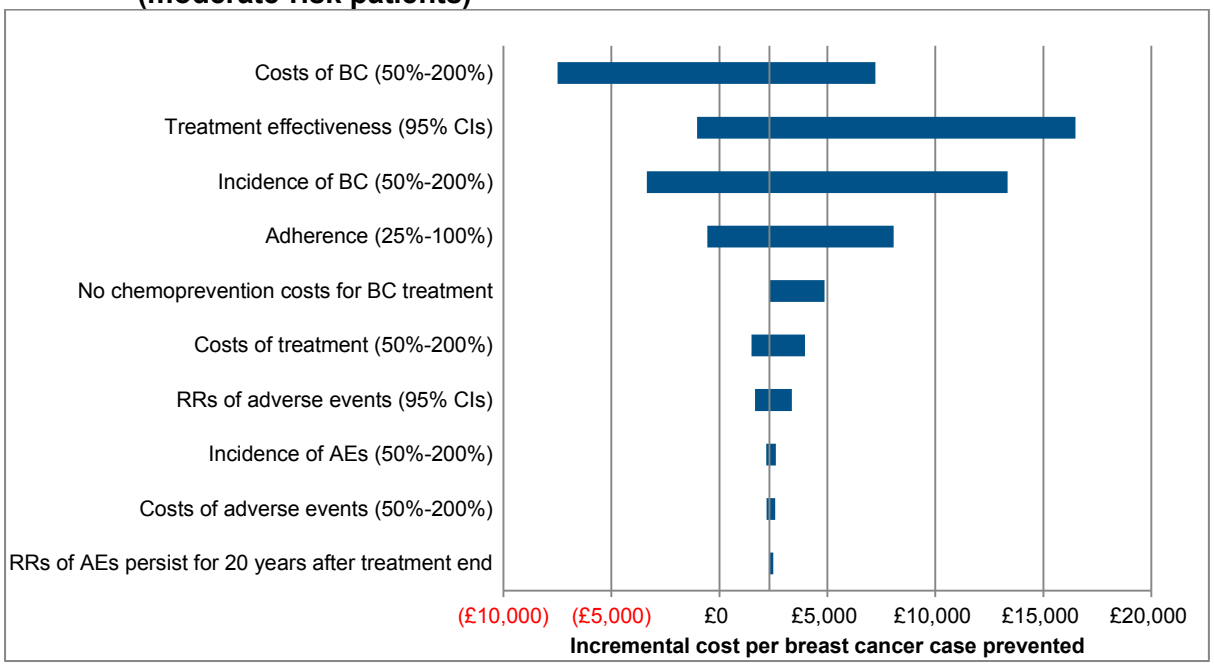
N.4.2 Sensitivity analysis

One-way sensitivity analysis results are displayed in Table 34. Results for anastrozole are displayed as a tornado diagram in Figure 6, to illustrate the magnitude of sensitivity across parameters. As with the high-risk cohort of patients, cost effectiveness results for moderate-risk patients are particularly sensitive to changes in parameters affecting the incidence or cost of breast cancer, and relatively insensitive to changes in parameters affecting incidence or cost of adverse events.

Table 34: One-way sensitivity analysis results – cost per breast cancer case prevented per 1,000 moderate-risk patients

	Tamoxifen	Raloxifene	Anastrozole
Incidence of BC reduced by 50%	£26,959	£77,256	£13,338
Incidence of BC increased by 100%	£797	£16,271	-£3,358
Treatment relative risks for breast cancer incidence set to lower 95% CI	£5,031	£73,744	-£1,032
Treatment relative risks for breast cancer incidence set to upper 95% CI	£19,536	£22,858	£16,492
Adherence set to 100%	£6,109	£27,956	-£561
Adherence set to 25%	£16,601	£53,787	£8,064
Incidence of adverse events reduced by 50%	£9,607	£37,296	£2,174
Incidence of adverse events increased by 100%	£9,588	£35,028	£2,610
Treatment relative risks of adverse events set to lower 95% CI	£8,856	£37,878	£1,648
Treatment relative risks of adverse events set to upper 95% CI	£10,572	£35,597	£3,356
Costs of treatment reduced by 50%	£6,409	£27,227	£1,490
Costs of treatment increased by 100%	£16,001	£55,246	£3,962
Costs of adverse events reduced by 50%	£9,604	£37,284	£2,176
Costs of adverse events increased by 100%	£9,609	£35,130	£2,591
Costs of breast cancer reduced by 50%	£14,529	£41,504	£7,220
Costs of breast cancer increased by 100%	-£240	£26,691	-£7,497
Relative risks of adverse events persist for 20 years after end of treatment	£10,146	£35,786	£2,493
Breast cancer treatment is associated with no chemotherapy costs	£10,146	£35,786	£2,493
Relative risks for raloxifene taken from the RUTH trial	-	£4,959	-

Figure 6: Tornado diagram of one-way sensitivity analysis results for anastrozole (moderate-risk patients)



Mean results of the probabilistic sensitivity analysis are shown in Table 35. As with the results of the high-risk patient population, these values show that deterministic and mean PSA results are largely consistent.

Table 35: Mean PSA results for moderate-risk post-menopausal patients

	Tamoxifen	Raloxifene	Anastrozole
Incremental cost (versus no chemoprevention)	£155,098	£266,093	£67,762
Breast cancer cases prevented	16	7	26
Cost/BC case prevented	£9,488	£36,912	£2,569
QALYs required per BC case averted to be CE	0.47	1.85	0.13

Figure 7 shows the results of the 1,000 probabilistic iterations for moderate risk patients plotted on a cost effectiveness plane. These results show a similar overall pattern to those of the high-risk cohort – anastrozole shows a trend towards lower costs and more cases of breast cancer prevented, though these is considerable overlap between results of different treatments. The results differ from those of the high-risk patients in that all treatments are, overall, less cost effective compared to no treatment. For this group of patients, anastrozole has an 18% probability of being cost saving compared to no treatment.

The cost effectiveness acceptability curve for moderate-risk patients (shown in Figure 8) reinforces these findings – at low thresholds no chemoprevention is the most likely option to be cost effective. However, at a relatively low threshold of £2,600 per breast cancer case prevented, anastrozole becomes the treatment with the highest probability of being cost effective.

Figure 7: Probabilistic sensitivity analysis results – incremental cost and breast cancer cases prevented per 1,000 moderate-risk patients

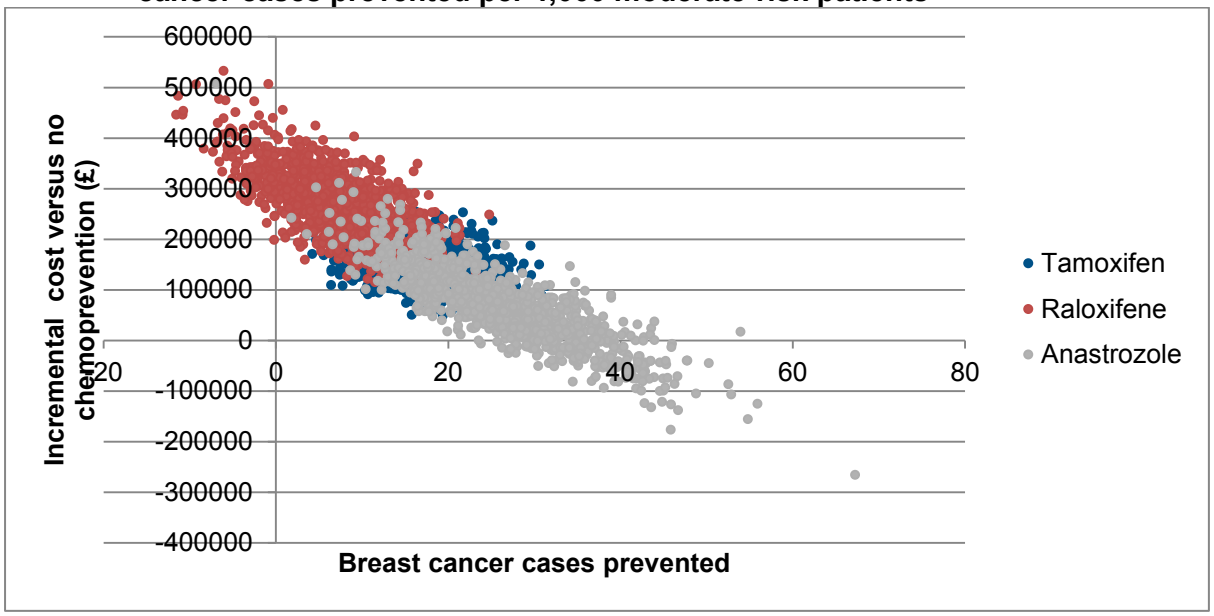
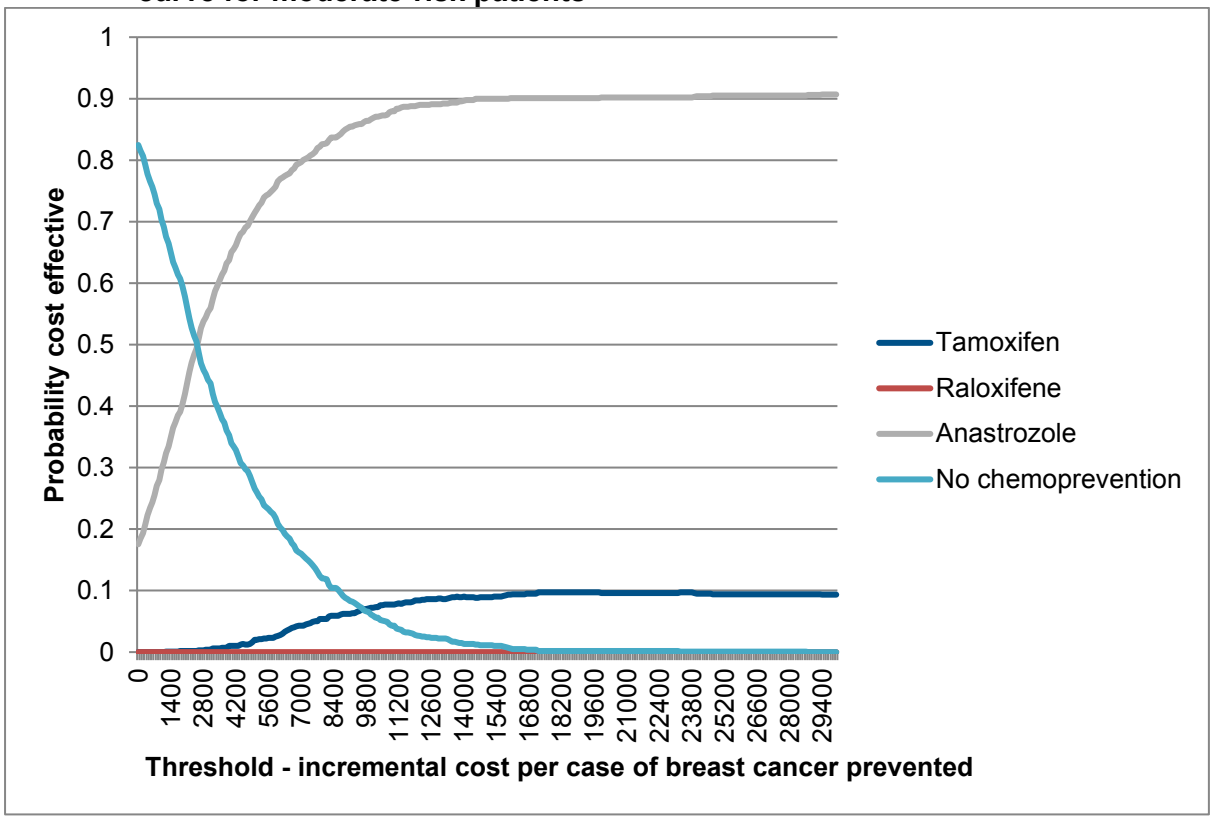


Figure 8: Probabilistic sensitivity analysis results – cost effectiveness acceptability curve for moderate-risk patients



N.5 Discussion

The results of this cost consequences analysis show that anastrozole is likely to be cost effective in preventing the incidence of breast cancer in high- and moderate-risk postmenopausal women. In the base case results, anastrozole shows improvements in both the number of breast cancer cases and total costs compared to tamoxifen and particularly raloxifene. Although results indicate that chemopreventive agents are more cost effective compared to no treatment in high-risk patients (both in terms of costs and number of breast cancer cases prevented), anastrozole is still associated with relatively a low ICER for the moderate-risk population (£2,314 per breast cancer case prevented).

Results indicate that, although associated with higher ICERs than anastrozole, tamoxifen is also likely to be cost effective (£4,621 and £9,606 per breast cancer case prevented for high- and moderate- risk patients, respectively). The cost effectiveness of raloxifene is less clear, with base case case results showing incremental costs per breast cancer case prevented of £25,387 and £36,566 for high- and moderate-risk patients. This would indicate that a gain of at least 1.27 and 1.83 QALYs, respectively, would have to be achieved per breast cancer case prevented for raloxifene to be cost effective at a threshold of £20,000. However, results of the sensitivity analysis in which data from the RUTH trial are used to inform the model indicate that raloxifene is associated with considerably lower ICERs (£668 and £4,473 for high- and moderate- risk patients). This implies that there is a high degree of uncertainty surrounding the cost effectiveness of raloxifene.

Results are robust in the sensitivity analysis, with anastrozole consistently showing the highest probability of being cost effective at any threshold in high risk patients, and the highest probability in moderate-risk patients at thresholds over £2,600 per breast cancer prevented and above.

While anastrozole results in a higher number of fractures (4 more fractures than no chemoprevention per 1,000 patients), this number is relatively low in absolute terms. Moreover, it is likely that the harm of these adverse events would be more than offset by the benefit gained in breast cancer cases prevented.

This analysis was associated with a number of limitations. First, the model assumes the same rate of mortality for healthy women and women with breast cancer, and that there is no risk of death associated with adverse events. As the primary health outcome of the analysis is breast cancer cases prevented, rather than QALYs, this assumption is unlikely to affect results considerably, although it may result in a small overestimation of the number of adverse events in treatment arms. Second, the proportion of patients discontinuing treatment after one year was based on expert assumption, as the true value is unknown. Third, the assumption was made that the benefits of chemoprevention persist over a patients' lifetime, while relative risks of adverse events either return to baseline after the end of treatment or persist for five years after the end of treatment. While these assumptions are plausible, the true

timeframe over which treatment effects persist is not precisely known (although sensitivity analysis has shown that results are generally robust to changes in these assumptions). Fourth, the assumption is made that chemoprevention affects the risks of all types of fractures equally whereas, in reality, it is likely that the incidence of fractures relating to osteoporosis are disproportionately affected. Finally, the analysis does not distinguish between different subsets of breast cancer. As chemoprevention only prevents ER-positive cancers, the incremental costs of prevented breast cancer cases are likely to differ from the average costs of breast cancer as a whole. While this assumption has been explored in sensitivity analysis by removing the cost of chemotherapy treatment (as ER-positive breast cancers are less receptive to chemotherapy), it is likely that the costs of treating breast cancer cases prevented by chemoprevention also differ in other ways.

In conclusion, although this analysis is limited to assessing the cost consequences, rather than the cost utility, of chemoprevention, it seems very likely from the results that anastrozole represens a cost effective means of preventing breast cancer in postmenopausal women, both compared to no treatment, and compared to currently recommended chemopreventive agents.

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Appendix O: Definitions of categories for risk of developing breast cancer (NICE, 2004)

	Definitions of categories for risk of developing breast cancer		
	Near population risk	Moderate risk	High risk [1]
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%
[1]This group includes people with known BRCA1, BRCA2 and TP53 mutations and those with rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11), Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).			

Appendix P: Studies by menopausal status

	Tamoxifen versus placebo	Tamoxifen versus raloxifene	Anastrozole versus placebo
Premenopausal + postmenopausal	Cuzick 2015 Fallowfield 2001		
Postmenopausal only	Sestak 2012 Powles 1998	Vogel 2010	Sestak 2012 Cuzick 2014
Premenopausal only			
Not reported	Fisher 2005		