Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Tamoxifen

Proprietary Product Name: Nolvadex/Nolvadex-D

Sponsor: Astra-Zeneca Pty Ltd

First round evaluation: 25 November 2015
Second round evaluation 21 January 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
CI	Confidence interval
CMI	Consumer medicine information
DMBA	Dimethylbenzanthracene
DVT	Deep vein thrombosis
ER	Oestrogen receptor
GCP	Good Clinical Practice
HOT	Hormone Replacement Therapy Opposed by Low Dose Tamoxifen study
HR	Hazard ratio
HRT	Hormone replacement therapy
IBIS-I	International Breast Cancer Intervention Study I
ITT	Intent-to-treat
LCIS	Lobular carcinoma in situ
MI	Myocardial infarction
NHMRC	National Health and Medical Research Council
NSABP P1	National Surgical Adjuvant Breast and Bowel Project P1 study
OR	Odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
PI	Product information
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse event
SERM	Selective oestrogen-receptor modulator
STAR	NSABP Study of Tamoxifen and Raloxifene P2 study

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
UK	United Kingdom
USA	United States of America

1. Introduction

1.1. Submission type

This is a Category 1 Application for a Type C: Extension of Indications/ Type F: Major Variation Literature Based Submission.

1.2. Drug class and therapeutic indication

Tamoxifen is a selective synthetic oestrogen-receptor modulator (SERM). It competitively inhibits the binding of oestrogen to oestrogen receptors (ERs), with mixed agonist and antagonist activity depending on the target tissue. How tamoxifen acts as an agonist in one tissue and as an antagonist in another is not understood.

The currently approved indication, as per the current PI for Nolvadex and Nolvadex-D, is:

Treatment of breast cancer

The proposed extended indication, as per the sponsor's Letter of Application, is:

Nolvadex is indicated for the primary prevention of breast cancer in women at increased risk of breast cancer. A woman could be considered at ***moderately increased risk*** *of developing breast cancer if her lifetime breast cancer risk is 1.5 to 3 times the population average and at* ***high risk*** *if her lifetime breast cancer risk is more than 3 times the population average. Validated algorithms are available that calculate breast cancer risk based on features such as age, family history, genetic factors, reproductive factors, and history of breast disease*.

Comment: This wording could be simplified to

Nolvadex is indicated to reduce the risk of breast cancer in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).

Treatment should be initiated by a specialist with expertise in managing breast cancer or familial cancer.

Use of the term risk reduction would be consistent with the terminology used by the FDA (the only regulatory body to have approved the use of tamoxifen for this indication. The information regarding 'validated algorithms' may be better placed elsewhere in the PI and would more appropriately refer to the methods of determining risk used in the key trials.

2. Clinical rationale

Tamoxifen is a nonsteroidal triphenylethylene-based drug that competes with oestrogen for binding sites in target tissues such as breast and uterus. Depending on the receptor and tissue, the effect may be oestrogen-like or anti-oestrogen. The antagonist action is thought to account for the anti-neoplastic effect in breast cancer: in women with oestrogen receptor positive (ER-positive) breast cancer, tamoxifen reduces the risk of recurrence and death when given as adjuvant therapy for early stage disease and can provide palliation in those with metastatic disease. However, not all ER-positive cancer responds to tamoxifen and resistance may develop in advanced cancers.

A central anti-oestrogen action is thought to cause the hot flushes that may occur with treatment. An agonist action in the uterus is thought to be responsible for endometrial hyperplasia, vaginal discharge and increased risk of both endometrial cancer and uterine sarcoma. Other effects of tamoxifen include increased rate of venous thromboembolic events, lowering of serum cholesterol and increased risk of cataracts. Tamoxifen may also be associated with an increased incidence of arterial thromboembolism.

Tamoxifen has been in clinical use for the treatment of breast cancer since the 1970s. It has also been approved by the Food and Drug Administration, for the indication of 'Reduction in Breast Cancer Incidence in High Risk Women' since 1998.

- *Cancer Council Australia* which recommends that women who are at high risk because of a very strong family history may benefit from hormones such as tamoxifen, usually administered over five years.[1]
- *Cancer Australia* which recommends that women over 35 years of age with moderate risk or women of any age with high risk of breast cancer (as determined by the online calculator provided – FRA-BOC), consider the use of medication, such as tamoxifen or raloxifene, to reduce risk of developing breast cancer. This requires careful assessment of risk and benefits in the individual case by an experienced medical professional.[2]
- *The American Society of Clinical Oncology* Clinical Practice Guideline which recommends: In women at increased risk of BC age ≥35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor (ER)–positive BC.[3]
- *The U.S. Preventive Services Task Force (USPSTF)* which recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene.[4]
- The UK *National Institute for Health and Care Excellence (NICE)* Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer Clinical Guideline (CG 164) from 2013 which recommends that tamoxifen for 5 years be offered to premenopausal women at high risk of breast cancer and to postmenopausal women with or without a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer.[5]

One in 8 Australian women develop breast cancer before the age of 85 and breast cancer is the second most common cause of cancer death among Australian women. Cancer Australia estimates that 4% of the Australian female population has moderately increased risk of breast cancer (risk of breast cancer up to age 75 between 1 in 8 and 1 in 4; risk 1.5 to 3 times the population average) and that 1% are potentially high risk (risk of breast cancer up to age 75 is between 1 in 4 and 1 in 2; risk may be more than 3 times the population average).

[1] Accessed November 2015 at: http://www.cancer.org.au/about-cancer/types-of-cancer/breast-cancer.html
[2] Accessed November 2015 at https://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc
[3] Accessed November 2015 at http://jco.ascopubs.org/content/31/23/2942.full
[4] Moyer V for the USPSTF Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement Ann Intern Med. 2013;159:698-708
[5] Accessed November 2015 at: http://www.nice.org.uk/guidance/cg164/chapter/1-recommendations#risk-reduction-and-treatment-strategies

For women at increased risk of breast cancer, apart from personal choices such as age of first birth, breastfeeding, body weight, and minimising alcohol intake, the main options available to reduce this risk are bilateral mastectomy or risk reducing medications. Annual breast screening (mammograms, ultrasound, and magnetic resonance imaging) may be used to enable early detection of breast cancer but there is a concern regarding interval cancers. Bilateral mastectomy is effective at reducing breast cancer risk but is generally only offered to women at very high risk of breast cancer and, in Australia, only a minority of these women undergo the procedure. Therefore, for women whose risk is not high enough to warrant a bilateral mastectomy, or for those who choose not to undergo the surgery, risk-reducing medications is the only real option to reduce the risk of breast cancer.

A study of focus groups of Australian clinicians at Family Cancer Centres in 2009 found that barriers to the use of tamoxifen included insufficient evidence of efficacy, adverse events/side effects risks outweighing benefits, drugs not approved for this indication by regulatory authorities and cost not subsidised by the PBS.[6] The meta-analysis, by Nelson et al[7], provided in the submission, found the adverse effect profile of tamoxifen to be a barrier for women at risk. Further evidence regarding the efficacy of tamoxifen has since become available with the publishing of a meta-analysis of the use of SERMS in risk reduction of breast cancer (Cuzick 2013) and the most recent report of the 20 year follow-up of the key IBIS-1 trial (Cuzick 2015). Marketing approval of tamoxifen for the indication of risk reduction of breast cancer may improve access to this option for women with increased risk of breast cancer and may facilitate discussion of this option between the clinician and woman at risk.

3. Contents of the clinical dossier

A list of the publications discussed in this report is given under References at the end of this document.

3.1. Scope of the clinical dossier

3.1.1. Scope of the clinical dossier

The following articles and reports were submitted:

- 35 articles related to controlled studies (published between 1992 and 2015)
- 1 article related to uncontrolled studies (published 2003)
- 9 articles related to data from more than one study (published between 2002 and 2013)
- Nolvadex Periodic Benefit-Risk Evaluation Report (PBRER)for the period 30 April 2013 to 29 April 2014 (International birth date 30 April 1996)

3.2. Paediatric data

The submission did not include paediatric data. The current PI includes a description of a small study of tamoxifen used in 28 girls aged 2-10 years with McCune Albright Syndrome (MAS). Tamoxifen is not currently approved for this use.

[6] Keogh L et al. Australian clinicians and chemoprevention for women at high familial risk for breast cancer. Hereditary Cancer In Clinical Practice 2009, 7:9

[7] Nelson HD, Smith MEB, Griffin JC, Fu R. Use of medications to reduce risk forprimary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(8):604-14.

3.3. Good clinical practice

The 4 randomised controlled clinical trials on which many of the publications were based were commenced prior to the implementation of the Good Clinical Practice Guideline. Documentation of ethics approval, funding source(s) and conflict of interest disclosures is provided with the publication description. In keeping with the publication dates and journal practices in the early to mid-1990s this information was not available for all publications.

4. Pharmacokinetics and Pharmacodynamics

The sponsor's Clinical Overview states that no new information regarding the Clinical Pharmacology is provided. The information provided in the sponsor's Clinical Overview regarding pharmacokinetics, pharmacodynamics and drug interactions has been directly sourced from the currently approved PI and is not repeated in full in this clinical evaluation.

In summary, tamoxifen is orally administered; absorbed from the gastro-intestinal tract (site and extent unknown, bioavailability unknown); peak levels are seen 3 to 6 hours after administration, steady state levels are seen after approximately 4 weeks; highly protein bound (99% to albumin); metabolised in the liver with a major active metabolite; excreted slowly, mainly in the faeces, with an elimination half-life of 5 to 7 days, and 10 to 14 days for the active metabolite; interactions may be seen with coumarin type anticoagulants (increased anticoagulant effect), cytotoxic agents (increased risk of thromboembolic effects), cytochrome P40 isozyme CYP3A4 inducers (reduced tamoxifen plasma level), CYP2D6 inhibitors (reduced plasma level of the active metabolite).

5. Sponsor's Literature Search

The proposed search strategy and selection criteria were provided to the TGA in March 2015. The stated intention was that the systematic literature review would assess the efficacy and safety of tamoxifen for breast cancer prevention in women at increased risk of breast cancer only. After some minor changes, a revised search strategy was approved by the TGA. The search was performed by the sponsor on April 1 2015. The submission was provided to the TGA in September 2015 and accepted for evaluation.

5.1. Search Method

[Information redacted]

5.2. Evaluator's overall conclusions on the Search Strategy

The proposed search strategy, including the selection criteria, was provided to the TGA for approval. Following some minor changes, a revised search strategy was approved by the TGA. The search strategy and selection criteria are appropriate for the proposed indication, although inclusion of publications that met all criteria except for that of 'an increased risk of developing breast cancer', such as the Italian Prevention Study, may have provided additional safety information.

5.3. Search Results

[Information redacted]

5.4. Efficacy Assessment

A total of 2827 publications were identified from the literature search once duplicates were removed (n=39). After application of the selection criteria to the studies identified through the electronic search, 16 publications/studies were identified for inclusion as evidence for the assessment of efficacy. Reasons for exclusion of the other studies are shown below.

Comment: The abstracts of 1620 of the excluded publications were read by the evaluator. This did not identify publications mistakenly excluded. It is arguable that the Italian Prevention Study should have been included, even though it did not meet the strict inclusion criteria, given that it is included in the pivotal meta-analysis. See also comments below in the Evaluator's overall conclusions on the Search Results

[Information redacted]

Another 4 publications (making a total of 20) were identified separately:

- 2 meta-analyses identified from hand searching the excluded reviews identified in the systematic literature search (Cuzick et al 2013; Nelson et al 2013)
- 1 study identified from hand searching the reference lists of recent reviews and clinical guidelines (Vogel et al 2006)
- 1 recent study providing an updated analysis of one of the trials but was not itself captured by the search (Cuzick et al 2015).

According to the dossier, the 20 identified publications present results from 4 randomised, placebo-controlled trials, and 1 randomised, controlled trial comparing tamoxifen with raloxifene. The publications present overall results, long-term results and sub-group analyses from these trials. In addition, 3 meta-analyses were identified. A search of clinicaltrials.gov was reported to not reveal any additional studies for the prevention of breast cancer in high risk women that were completed or ongoing.

The 4 randomised placebo controlled trials were:

- The International Breast Cancer Intervention Study (IBIS-I)
- The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial
- The Royal Marsden Hospital (Royal Marsden) trial
- The Hormone Replacement Therapy Opposed by Low Dose Tamoxifen (HOT) study

The randomised, controlled trial comparing tamoxifen with raloxifene was:

- The NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial

The meta-analyses were:

- Cuzick 2013, Nelson 2013, Duffy 2002

Publications included as pivotal for the assessment of efficacy were: Cuzick 2103 (meta-analysis); Cuzick 2002, 2007, and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Powles 1998 and 2007 (results of the Royal Marsden trial).

5.5. Safety Assessment

[Information redacted]

Of 2827 publications that were identified from the literature search, 2794 did not meet the safety eligibility criteria leaving 33 publications for inclusion in the safety assessment. Reasons for exclusion of the other studies are shown below.

Comment: The abstracts of 1620 of the excluded publications were read by the evaluator. This did not identify publications mistakenly excluded from the safety assessment. It is arguable that the Italian Prevention Study should have been included, even though it did not meet the strict inclusion criteria, particularly given that the HOT study was included – see further comments below.

[Information redacted]

Another 6 publications (making a total of 39) were identified separately:

- 3 meta-analyses identified from hand searching the excluded reviews identified in the systematic literature search (Cuzick et al 2013; Iqbal et al 2012; Nelson et al 2013)
- 2 literature studies identified from hand searching the reference lists of recent reviews and clinical guidelines (Legault et al 2009; Vogel et al 2006)
- 1 relevant recent literature study that provides an updated analysis of one of the trials but was not itself captured by the search (Cuzick et al 2015)

According to the dossier, the publications for the safety assessment include results from the same 4 randomised, placebo-controlled trials and randomised, controlled trial comparing tamoxifen with raloxifene that were identified through the efficacy assessment. Results from a non-randomised trial (Imperator 2003) and 5 meta-analyses (Cuzick 2013, Braithwaite 2003, Iqbal 2012, Fallowfield 2001, Nelson 2013) were also identified. A search of clinicaltrials.gov did not reveal any additional safety studies for the prevention of breast cancer in high risk women that were completed or ongoing.

Comment: Fallowfield 2001 may be more correctly described as an ancillary study to IBIS-1 and Royal Marsden rather than as a meta-analysis – see description below.

Publications identified as pivotal by the sponsor for the assessment of safety were: Cuzick 2013 (meta-analysis); Cuzick 2002, 2007, and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Reis 2001; Land 2006; Vogel 2006 and 2010.

5.6. Evaluator's overall conclusions on the Search Results

Overall, the search results were satisfactory.

5.6.1. Excluded Studies

The abstracts of 1620 of the excluded publications were read by the evaluator. This did not identify publications mistakenly excluded. It is arguable that publications related to the Italian Prevention Study should have been included, even though it did not meet the strict inclusion criteria, given that it is included in the pivotal meta-analysis. However, given that it included women who had had a hysterectomy, regardless of risk of breast cancer and given that enrolment was ceased earlier than planned, due to low recruitment numbers, it would at most be considered supportive. It is also not clear as to why the health related quality of life publication based on the NSABP P1 trial (Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659–69) was excluded, although the follow-on publication (Day 2001) was included.

5.6.2. Included Studies:

Of the included studies, Fisher 2005 may be better described as supportive rather than pivotal as the follow-up was largely unblinded. It is also arguable as to whether the HOT study should have been included (even as a secondary supportive study) given that the dose of tamoxifen used was 5mg daily (not the 20 mg daily proposed for this indication) and given that women were recruited on the basis of being post-menopausal and prepared to take HRT rather than

having an increased risk of breast cancer (that is, this study did not meet the strict inclusion criteria). Fallowfield 2001, which presents the results of a subgroup of women from the Royal Marsden and IBIS-1 studies who prospectively completed surveys of psychological well-being, is more correctly described as an ancillary study than a meta-analysis.

See Clinical Questions Search Strategies and Results 1-4.

6. Dosage selection for the pivotal studies

A dose of tamoxifen 20 mg was used in all described risk reduction studies (except for the HOT study). No rationale for this dose was provided in the related publications. A duration of treatment of 5 years was used in 3 of the 4 main trials, which was apparently based on the duration of treatment in adjuvant trials (Vogel 2010). The Royal Marsden trial had a planned duration of treatment of 8 years. No rationale for this duration of treatment was described in the publications.

The sponsor proposes a maximum dose of oral tamoxifen 20 mg daily for 5 years for the proposed indication, on the basis of the dose and duration used in the larger risk reduction trials (IBIS-1 and NSABP P1)

Comment: The proposed dose of 20 mg daily is in keeping with the publications that showed efficacy in risk reduction of breast cancer in women at increased risk. The proposed duration of 5 years is in keeping with the key trials, IBIS-1 and NSABP P1.

7. Publications included

The evaluator has reviewed each of the publications cited for safety and efficacy assessments in the dossier. A description of each publications provided in Section 17 of this evaluation report with these arranged according to the four main trials. A summary table is provided below with a description of the main trials, together with a listing of the publications based on each trial, their relationship to the main trials and the page number of the description. Summaries and descriptions of the meta-analyses are also provided.

The key publication reporting each trial, and any publications reporting extended follow-up, are described in detail. Any other publications described as pivotal by the sponsor for either the safety or efficacy assessment are also described in detail. Publications included as supportive by the sponsor are described more briefly. A short description of the 'Italian Prevention Study' is also provided to provide context to the references to this study in the pivotal meta-analyses. This trial was not included in the dossier by the sponsor as the inclusion criteria did not match the indication.

Layout of the Publication Descriptions provided in Section 17:

- A detailed description of the method for the main trial is provided in the description of the first publication. This is supplemented with information from subsequent publications where appropriate (and identified as such). The description of the trial method is not repeated for the related publications.
- All figures and Tables are copied from the relevant publication (with original captions) unless otherwise specified.
- Both safety and efficacy results are provided in the publication description
- The evaluator's assessment of the publication is provided following the publication description. It can be identified by Calibri font and title 'Allocation by sponsor and Evaluator assessment'

Table 1: Publications included in the Dossier

Publications Included	
The International Breast Cancer Intervention Study (IBIS-I) Registered with clinicaltrials.gov as NCT00002644	
Trial description	Multi-national (including Australian sites) double-blind placebo-controlled randomised trial of healthy women aged 35 to 70 years with an increased risk of breast cancer. Eligible women had to have risk factors for breast cancer, as assessed by previous history of lobular carcinoma in situ and/or family history, indicating at least a two-fold relative risk if they were aged 45 to 70 years, a four-fold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to 39 years. Pre-existing cancer was excluded by a baseline mammogram (up to 12 months before randomisation) The primary outcome measure was the frequency of breast cancer (including DCIS). Secondary endpoints were other cancers, thromboembolic events, cardiovascular events, and cause-specific mortality Predefined subgroups were oestrogen receptor status of the cancer, use of hormonal replacement therapy, and age (< 50, ≥ 50 years) 7152 women (37% from Australia and New Zealand) were recruited from 1992 to 2001 Results after 50 months, 10 years and 20 years of follow-up are presented (Cuzick 2002, 2007, 2015); these publications were included in the pivotal publications for both safety and efficacy assessment by the sponsor. A number of retrospective sub-group analyses are also presented (Sestak 2012b, Duggan 2003, Sestak 2012a, Pavla 2013, and Sestak 2006).
Related Publications	
Key Publication (s)	**Relationship to Trial**
Cuzick 2002	First publication of results (median follow-up 50 months after randomisation)
Cuzick 2007	Long term results – 10 year follow up (median follow-up 96 months after randomization)
Cuzick 2015	Extended Long term results - 20 year follow-up (median follow up 16 years)
Related Publications	
Efficacy/safety	
Sestak 2012b	Retrospective, case control, nested, sub-group analysis of the effect of the CYP2D6 phenotype on the development of ER-positive invasive breast

Publications Included	
	cancer
Safety	
Duggan 2003	Case control, nested analysis to investigate the association between acquired and inherited risk factors for VTE
Sestak 2012a	Retrospective subgroup analysis of the IBIS-1 population to assess the effect of tamoxifen on weight gain in breast cancer prevention
Palva 2013	Sub-group analysis to investigate the effects of 5 years of tamoxifen use on endometrium and gynaecological symptoms in the IBIS-1 population
Sestak 2006	Retrospective analysis of the IBIS-1 population to investigate the influence of HRT on tamoxifen-induced vasomotor symptoms
The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial clinicaltrials.gov identifier NCT00000529	
Trial description	Multicentre, double-blind placebo-controlled randomised trial in North America (USA and Canada) of healthy women aged 35 years or older with an increased risk of breast cancer. Eligible, women had to be either 60 years of age or older, or between 35 and 59 years of age with a history of lobular carcinoma in situ or a five-year predicted risk of breast cancer of at least 1.66% based on the Gail algorithm. Pre-existing breast cancer was excluded by a baseline mammogram (up to 180 days before randomisation) The primary outcome measure was incidence of breast cancer 13388 women were enrolled from 1992 to 1997 Results were published after 55 month follow-up (Fisher 1998). The trial was unblinded in 1998 after the initial analysis. Participants in the placebo group were given the opportunity either to receive a 5 year course of tamoxifen or to be randomized to the Study of Tamoxifen and Raloxifene (STAR) trial resulting in substantial crossover of placebo participants to tamoxifen or raloxifene. Results after 7 year follow-up are presented (Fisher 2005). Both of these publications were regarded as pivotal for the safety and efficacy assessment by the sponsor. A number of pre-defined and/or retrospective analyses are also presented (King 2001, Shen 2008, Reis 2001, Day 2001, Cushman 2001 & 2003, Abramson 2002 & 2006, and Chalas 2005). It was not always clear if data from the unblinded period was included in the individual publications. Of these, Reis 2001 was regarded as pivotal for the safety assessment.
Related Publications	
Key Publication (s)	**Relationship to Trial**
Fisher 1998	First publication of results (median follow-up 54.6 months after randomisation)

Publications Included	
Fisher 2005	Long term results – 7 year open follow up (mean follow-up 74 months after randomisation)
Related Publications	
Efficacy	
King 2001	Comparison of incidence of breast cancer in women with BRAC1 and BRAC2 mutations
Shen 2008	Effect of tamoxifen on time to diagnosis of breast cancer
Safety	
Reis 2001	Comparison of ischaemic cardiac events in women with or without prior CHD
Day 2001	Comparison of depressive symptoms – follow-on report of quality of life study
Cushman2001	Sub group (100) comparison of antithrombin, protein C antigen, and total protein S concentrations
Cushman 2003	Sub-group (100) comparison of total cholesterol, triglyceride levels, fibrinogen, factor VIIc, prothrombin fragments 1-2 and C-reactive protein concentrations
Abramson 2002	Screening for hypercoagulable abnormalities in 24/155 cases who developed VTE or stroke
Abramson 2006	Assess relationship between risk of VTE and Factor V Leiden and prothrombin mutations in 76/81 cases.
Chalas 2005	Comparison of benign gynaecological conditions
The NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial Registered at clinicaltrials.gov identifier NCT01579734 and the European Institute of Oncology as IEO S51/200	
Trial description	Randomised double-blind controlled trial in North America (USA and Canada) comparing tamoxifen and raloxifene for the prevention of breast cancer in healthy women at increased risk of breast cancer Eligible women had to be ≥ 35 years of age, post-menopausal and have a 5 year predicted risk of breast cancer of at least 1.66% based on the Gail algorithm. Pre-existing breast cancer was excluded by a baseline mammogram (up to 180 days before randomisation) Primary end point was invasive breast cancer 19747 women were enrolled from 1999 After un-blinding of the NSABP P1 trial in 1998, participants in the placebo group were given the opportunity either to receive a 5 year course of tamoxifen or to be randomized to the Study of Tamoxifen and

Publications Included	
	Raloxifene (STAR) trial Results were published after 47month follow-up (Vogel 2006). The trial was un-blinded in 2006 after this initial analysis. At this time, 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 - 879 women chose this option. Results after 10 year follow-up are also presented (Vogel 2010). Quality of life and psychological wellbeing studies (Land 2006, Legault 2009) are presented together with a subgroup analysis (Runowicz 2011) This trial was not regarded as pivotal for efficacy. The following publications were regarded as pivotal for the safety assessment: Vogel 2006 and 2010, Land 2006
Related Publications	
Key Publication (s)	**Relationship to Trial**
Vogel 2006	First publication of results (median follow-up 47 months after randomisation)
Vogel 2010	Long term results – 10 year follow up (median follow-up 81 months after randomisation)
Related Publications	
Safety	
Land 2006	Comparison of patient-reported symptoms for the whole STAR cohort; quality of life assessments in a convenience sample of the cohort
Legault 2009	Ancillary study to compare the effects of tamoxifen and raloxifene specific cognitive function in a convenience sample of the cohort
Runowicz 2011	Comparison of the gynaecological conditions reported in post-menopausal women with intact uterus
Publications using results from both NSABP P1 and STAR The following publications used data from both the NSABP P1 and STAR trials. None of these were regarded as pivotal for either safety or efficacy assessment by the sponsor	
Publication Identifier	**Publication objective (results of NSABP P1 and STAR used)**
Freedman 2011	Mathematical modelling used to develop and risk/benefit matrix
Cecchini 2012	Retrospective analysis of the relationship between BMI and invasive breast cancer in the NASBP P1 and STAR cohorts
Goetz 2011	Retrospective sub-group (age > 50 years) analysis of the effect of CYP2D6 genotypes and inhibitors

Publications Included	
The Royal Marsden Hospital (Royal Marsden) trial Registered at controlled-trials.com as ISRCTN07027313	
Trial description	Double-blind placebo controlled randomised trial in the UK of healthy women aged 30 to 70 years with an increased risk of breast cancer. This started as a pilot study in 1986 that evolved into a larger trial. Eligible, women had to have at least 1 of the following: ≥ 1 first-degree relative who was younger than 50 years when diagnosed with breast cancer; or a first-degree relative with bilateral breast cancer; or a first-degree relative with breast cancer who was diagnosed at any age plus ≥ 1 other affected first- or second-degree relative with breast cancer; or a history of benign breast biopsy and a first-degree relative with breast cancer 2494 women were enrolled from 1986 to 1996. Results of the pilot study (2012 women) were published in 1994 (Powles 1994). Results of the full cohort were published after 70 months follow-up (Powles 1998a) and 10 years follow-up (Powles 2007). Of these, Powles 1998a and Powles 2007 are regarded as pivotal to the efficacy assessment by the sponsor. A number of cohort and sub-group analyses (Kote Jarai 2007, Jones 1992, Kedar 1994, Powles 1996 and 1998b, Chang 1996 and 1998) and one ancillary study (Fallowfield 2001) are presented. These are regarded as supportive publications by the sponsor.
Related Publications	
Key Publication (s)	**Relationship to Trial**
Powles 1998a	First publication of results (median follow-up 70 months after randomisation)
Powles 2007	Long term results – 10 year follow up (median follow-up 13 years after randomisation)
Related Publications	
Efficacy	
Kote-Jarai 2007	Proportion of BRAC1/2 mutations in the 70 women who developed breast cancer at the time of the interim analysis (1998)
Safety	
Jones 1992	Sub group analysis (approximately 200) of the effects of tamoxifen on the levels of fibrinogen, anti-thrombin III, Protein C, Protein S and cross linked fibrin degradation products (XL-FDP).
Kedar 1994	Cohort study of 111 women from the pilot study to assess the effect of preventative tamoxifen on the uterus and ovaries (ultrasound, endometrial biopsies)

Publications Included	
Powles 1994	Description of pilot study (1986 to 1993) with results for 2012 women; median duration of follow-up not described
Powles 1996	Sub-group analysis of convenience sample of 179 women to assess the effect of preventative tamoxifen on bone mineral density
Chang 1996	Sub-group analysis of the interaction between HRT and tamoxifen on serum cholesterol, fibrinogen, antithrombin III (AT III) and bone mineral density (BMD) in postmenopausal healthy women
Chang 1998	Sub-group analysis of women who became amenorrhoeic during treatment with tamoxifen or placebo to assess the effect pf preventative tamoxifen on endometrial thickness
Powles 1998b	Sub-group analysis of post-menopausal healthy women to identify the incidence of endometrial thickening, polyps and cysts by transvaginal ultrasound screening and to evaluate the possible benefit from the use of intermittent norethisterone (NE) in women with persistent changes
Fallowfield 2001	Ancillary study of the psychosocial implications of tamoxifen in a convenience sample of participants in the Royal Marsden and IBIS-1 trials
Other studies – HOT, The Italian Study, Imperato	
Publication Identifier	**Publication description**
HOT DeCensi 2013	Randomised double blind placebo controlled study of the effect of tamoxifen **5 mg** daily on occurrence of breast cancer in healthy post-menopausal women on HRT. The trial is registered with clinicaltrials.gov as NCT01579734 and the European Institute of Oncology as IEO S51/200. Eligible women were postmenopausal women undergoing hormone replacement therapy (HRT) or prepared to commence HRT. The primary outcome was the incidence of breast cancer. A 5-year intervention period and maximum of 10 year follow-up period was planned. 1884 women were enrolled from 2002 to 2007. Recruitment was stopped prior to the planned enrolment of 8500 participants due to low recruitment following negative publicity regarding HRT.
Italian Prevention Study	Randomised DB placebo controlled study of the effect of tamoxifen 20mg on occurrence of breast cancer in healthy women who had had a hysterectomy
Imperato 2003	Cohort study of the effect of tamoxifen (±HRT) on risk factors for cardiovascular disease (lipid profile) in women with an increased risk of breast cancer who had previously had hysterectomy and oophorectomy for a benign pathology. This safety study investigated was conducted in Italy between 1992 and 1998.
Meta-analyses	

Publications Included	
Publication Identifier	**Publication description**
Efficacy/safety	
Cuzick 2013	Meta-analysis to assess the effectiveness of **all currently available selective oestrogen receptor modulators** (SERMs) on breast cancer incidence. Includes individual patient data from IBIS-I, NSABP P1, Royal Marsden, Italian, STAR, together with several other trials not involving the use of tamoxifen. Regarded as pivotal for both safety and efficacy by the sponsor.
Nelson 2013	Systematic review to update evidence about the effectiveness and adverse effects of medications (tamoxifen and raloxifene) to reduce breast cancer risk, patient use of such medications, and methods for identifying women at increased risk for breast cancer for the U.S. Preventive Services Task Force (USPSTF). Includes data from IBIS-I, NSABP P1, Royal Marsden, Italian, STAR together with two studies regarding the use of raloxifene
Safety	
Iqbal 2012	Systematic review to determine the risk of endometrial cancer, deep vein thrombosis and pulmonary embolism in women <50 years given tamoxifen for breast cancer prevention. Includes published data from IBIS-I, NSABP P1, Royal Marsden. This meta-analysis provides a summary of these three trials together with a discussion of the differences with respect to method and inclusion criteria. It also provides a formal assessment of bias in each trial.
Braithwaite 2003	Meta-analysis of English-language RCTs of the use of Tamoxifen in breast cancer treatment and breast cancer risk reduction to determine the relative risk of potentially life-threatening vascular and neoplastic outcomes. Includes published data from IBIS-I, NSABP P1, Royal Marsden
Duffy 2002	Mathematical modelling of the possible effect of tamoxifen in women with BRAC1 or BRAC2 mutations. Includes published data from the risk reduction studies NSABP P1 and the Italian Prevention Study.

8. Clinical efficacy

8.1. Publications identified through the literature search in support of efficacy

For the indication of the primary prevention of breast cancer in women at increased risk of breast cancer

There were 20 identified publications, presenting results from 4 randomised, placebo-controlled trials (IBIS-1, NSABP P1, Royal Marsden), and 1 randomised, controlled trial comparing tamoxifen with raloxifene (STAR). The publications present overall results, long-term results and sub-group analyses from these trials. In addition, 3 meta-analyses were identified (Cuzick 2013, Nelson 2013, and Duffy 2002)

Summaries of these publications are provided by the sponsor in the Clinical Overview.

Comment: The evaluator has reviewed each of the publications cited for the efficacy assessment. A description of each publication is provided in Section 17 of this evaluation report with these arranged according to the four main trials. A summary table is provided above with a description of the main trials, together with a listing the publications based on each trial, their relationship to the main trials and the page number of the description.

8.2. Pivotal Publications

Publications included as pivotal for the assessment of efficacy were: Cuzick 2013 (meta-analysis); Cuzick 2002, 2007, and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Powles 1998 and 2007 (results of the Royal Marsden trial) – see table below.

Table 2: Pivotal publications included for efficacy assessment

Publication Identifier	Publication description
Meta-analyses	
Cuzick 2013	Meta-analysis to assess the effectiveness of **all currently available selective oestrogen receptor modulators** (SERMs) on breast cancer incidence. Includes individual patient data from IBIS-I, NSABP P1, Royal Marsden, Italian, STAR, together with several other trials not involving the use of tamoxifen. Regarded as pivotal for both safety and efficacy by the sponsor.
The International Breast Cancer Intervention Study (IBIS-I)	
Cuzick 2002	First publication of results (median follow-up 50 months after randomisation)
Cuzick 2007	Long term results – 10 year follow up (median follow-up 96 months after randomization)
Cuzick 2015	Extended Long term results - 20 year follow-up (median follow up 16 years)
The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial	
Fisher 1998	First publication of results (median follow-up 54.6 months after randomisation)
Fisher 2005	Long term results; 7 year open follow up (mean follow-up 74 months after randomisation)
The Royal Marsden Hospital (Royal Marsden) trial	
Powles 1998a	First publication of results (median follow-up 70 months after randomisation)
Powles 2007	Long term results; 10 year follow up (median follow-up 13 years after randomisation)

Comment: Of the included 'pivotal' publications:

- The objective of the meta-analysis Cuzick 2013 was to assess the effectiveness of all SERMs in the reduction of breast cancer. It used individual participant data from nine prevention trials comparing four selective oestrogen receptor modulators

(SERMs; tamoxifen, raloxifene, arzoxifene and lasofoxifene) with placebo, or in one study with tamoxifen compared to raloxifene. Of the studies comparing tamoxifen to placebo, one study (the Italian Prevention study) did not have increased risk of breast cancer as one of the inclusion criteria.

- The second report of the NSABP P1 trial, Fisher 2005, may be better described as supportive rather than pivotal as the follow-up was open and affected by both potential bias and crossover from placebo to tamoxifen following unblinding of the NSABP P1 trial in 1998.

  Of note is that the publication Iqbal 2012, a meta-analysis included for the safety assessment, provides a discussion of the differences between the three main tamoxifen breast cancer risk reduction trials (IBIS-1, NSABP P1, and Royal Marsden), summarises the key results from each trial and provides a formal assessment of the risk of bias in each trial.

8.3. Assessment of Efficacy

Comment: The following assessment is copied from the Clinical Overview. Having reviewed the cited publications, the Clinical Overview and the Summary of Clinical Efficacy, the evaluator is of the opinion that the sponsor has provided a fair summary and interpretation of the results of the included publications with regard to the effect of tamoxifen on the incidence of breast cancer. A more comprehensive assessment of efficacy would, however, also include the effect, or lack of effect, on mortality and quality of life and the adherence of women to the treatment regimen - see Clinical Question Efficacy 2-4. The results regarding these measures are described by the evaluator in the section *Evaluator's conclusions on clinical efficacy*. Additional comments with regard to the outcome measure of the incidence of breast cancer are included where the opinion of the evaluator differs from that of the sponsor or where the evaluator considers further information to be relevant.

8.3.1. Pivotal efficacy trials

The IBIS-1 (N=7154), NSABP P (N=13,388), and Royal Marsden (N=2471) trials were double-blind placebo-controlled randomised trials of tamoxifen (20 mg per day) for the prevention of breast cancer in women with an increased risk of breast cancer. Two trials (IBIS-I, NSABP-1) treated participants for 5 years and one trial (Royal Marsden) treated participants for 8 years. For IBIS-I and NSABP P1, tamoxifen was supplied by AstraZeneca (formerly Zeneca Pharmaceuticals, Wilmington, USA) and for the Royal Marsden trial, by Orion Pharmaceuticals, Espoo, Finland. IBIS-I was an international trial, NSABP P1 was conducted in the USA and Canada, and the Royal Marsden trial was conducted in the UK.

Pivotal publications from the IBIS-1, NSABP P1, and Royal Marsden trials included 1 publication of the initial analysis, followed by ≥ 1 publication of longer term follow up. For IBIS-1, the 3 pivotal publications represent a median follow up of approximately 4 years, 8 years, and 16 years, respectively (Cuzick 2002, 2007, 2015). For NSABP P1, the median follow up times for the publications were 4 years (Fisher 1998) and 6 years,(Fisher 2005) and for the Royal Marsden trial, the median follow up times were 6 years(Powles 1998a) and 13 years (Powles 2007).

Comment: The NSABP P1 trial was unblinded in 1998. Participants from the placebo arm were given the option of 5 years of tamoxifen or participation in the STAR trial. Ongoing follow-up was open.

Cuzick 2013 was considered a pivotal publication as it was a meta-analysis of individual participant data obtained from 28,193 women from the IBIS-1, NSABP P1, and Royal Marsden trials, all in women at increased risk of breast cancer, and a randomised controlled trial in women at normal risk (the Italian Prevention trial). The primary endpoint was incidence of all

breast cancer (including ductal carcinoma in situ) during a 10 year follow up period. Analysis was conducted based on the intent-to-treat (ITT) principle.

Comment: Cuzick 2013 used individual participant data from nine prevention trials comparing four selective oestrogen receptor modulators (SERMs; tamoxifen, raloxifene, arzoxifene, and lasofoxifene) with placebo, or in one study with tamoxifen (STAR), with the objective of assessing the effectiveness of all SERMs in the reduction of breast cancer. Of the included studies comparing tamoxifen to placebo, one study (the Italian Prevention study) did not have increased risk of breast cancer as an inclusion criterion. Although not explicitly stated by the sponsor, results presented appear to be those from the meta-analysis that relate to tamoxifen. See Clinical Question Efficacy 1

The primary efficacy outcome of all pivotal publications was incidence of breast cancer. Breast cancers were detected in all trials by annual mammography during the active treatment period and throughout follow up. Analyses were generally performed using the ITT analysis population.

8.3.1.1. Appraisal of the quality of included studies

IBIS-1, NSABP P1, and Royal Marsden all started recruiting patients before the International Conference on Harmonisation Good Clinical Practice (GCP) guideline was published in 1996 (Royal Marsden started in 1986 and IBIS-I and NSABP started in 1992) and therefore GCP compliance was not stated in the pivotal publications. However, all pivotal trials were approved by the local ethics committees.

All trials included in the Cuzick meta-analysis were of high quality with a low risk of bias. Randomisation was completed centrally and participants and investigators were blinded to treatment allocation in all trials. In the IBIS-I, Royal Marsden, and Italian trials, outcome assessors were also blinded to treatment; in the NSABP P1 this information was not reported. Withdrawals and loss to follow-up were low in the IBIS-I trial and were low until un-blinding in the NSABP-1 trial (between years 6 and 7). In the Marsden trial, withdrawals were higher for tamoxifen versus placebo (25.6 versus 14.1%) which may be related to the longer treatment period (8 years instead of 5).

Comment: The pivotal RCTs were assessed using the Cochrane Collaboration's tool to assess the risk of bias in the meta-analysis Iqbal 2013. Using allocation concealment and adequate blinding as the major criteria for risk assessment, all studies met either good or fair criteria (the NSABP P1 trial was included only to the date of un-blinding).

The reporting of study treatment discontinuations, compliance and withdrawals was variable in the RCTs. In the NSABP P1 trial (to un-blinding in 1998), complete follow-up was available on approximately 92% participants. Of these, 19.7% of women in placebo and 23.7% in tamoxifen stopped their assigned treatment, 7.2% withdrew consent in each arm and an additional 2.3% were lost to follow-up. In the IBIS-1 trial, follow-up for 10 years was said to be available for 93% of participants. Of these, 72% women in the placebo group and 63.9% women in the tamoxifen group completed 5 years of treatment. In the Royal Marsden study, 35.5% of women did not complete the planned 8 years of treatment (25.8% of the tamoxifen group and 14.3% of the placebo group, P=0.002).

8.3.1.2. Participant demographics and disease stage

The IBIS-1, NSABP P1, and Royal Marsden trials all included women at an increased risk of breast cancer. Each trial defined breast cancer risk differently: IBIS-I included women with a two-fold relative risk if they were aged 45 to 70 years, a four-fold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to 39 years; NSABP P1 included

women aged ≥60 years or aged 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66%, or a history of lobular carcinoma in situ (LCIS) or atypical hyperplasia; and Royal Marsden included healthy women aged 30 and 70 years old with a high risk of developing breast cancer based on family history.

All trials excluded women with breast cancer, a history of invasive cancer, severe concurrent illness, pregnancy, and current or past deep vein thrombosis (DVT) or pulmonary embolism (PE). Other criteria included no use of oral contraceptive (NSABP-1, Marsden), recent or current HRT (NSABP-1), current anticoagulant use (IBIS-I), life expectancy <10 years (IBIS-1 and NSABP-1) and not accessible for follow up (NSABP-1).

The majority of women in all trials were aged 59 years or below. NSABP-1 included the largest proportion of women aged 60 years or over (30%). All trials included women with some family history of breast cancer, with one trial (Royal Marsden) exclusively recruiting women with family history. In NSABP P1, the majority of women were White (96%) and the rest of the participants were African American (1.7%) or other race (1.8%); race was not reported in the IBIS-I trial or the Royal Marsden trial.

Women using HRT were eligible for inclusion in 2 trials (IBIS-I, Royal Marsden), but the majority of women in the Royal Marsden trials had never used HRT (85.0%). Two thirds of women in IBIS-I and a third of women in NSABP-1 had had a hysterectomy. A small proportion of women in NSABP-1 had a history of atypical hyperplasia or lobular carcinoma in situ. Women in IBIS-I who had a history of either of these conditions were also eligible for inclusion, but the proportion of affected women was not reported.

8.3.2. Efficacy results

Findings from the efficacy analysis provide good evidence for the use of tamoxifen for the primary prevention of breast cancer in women at increased risk of breast cancer. Despite the use of different methods to calculate breast cancer risk, and different inclusion and exclusion criteria, the key publications consistently showed reductions in breast cancer incidence and oestrogen receptor (ER)-positive breast cancer in particular, with tamoxifen when compared with placebo.

The Cuzick 2013 meta-analysis of individual data from the IBIS-I, NSABP P1, Royal Marsden, and Italian trials provides the most robust efficacy data for this submission. In this meta-analysis of 28,193 women who were randomised to tamoxifen or placebo and followed up for 10 years, overall breast cancer incidence was significantly reduced in the tamoxifen group compared with the placebo group (431 events versus 634 events, $p<0.0001$). When the results were stratified by tumour type, tamoxifen significantly reduced the incidence of ER-positive cancers (219 versus 396, $p<0.0001$) and non-invasive cancers (77 versus 112, $p=0.009$), but not ER-negative cancers (116 versus 103, $p=0.4$).

The pivotal meta-analysis is supported by the results of the long-term follow up of the individual trials. Compared with placebo, overall breast cancer incidence was significantly lower with tamoxifen in IBIS-I, numerically lower in NSABP P1 (risk ratios [RR] not reported), and not significantly different in Royal Marsden. Invasive breast cancer was significantly lower with tamoxifen in IBIS-I, NSABP P1, and during the post-treatment period in Royal Marsden, and non-invasive breast cancer was significantly lower with tamoxifen in IBIS-I and NSABP P1 (not reported in Royal Marsden). In all trials, the incidence of ER-positive cancers was significantly lower with tamoxifen whereas there were no significant treatment-related differences for ER-negative cancers.

Table 3: Analysis of Cuzick, IBIS-1, NSABP and Royal Marsden

	Cuzick meta-analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,192 Events	Placeb n=14,214 Events	Tamox n=3579 Events	Placeb n=3575 Events	Tamox n=6597 Events	Placeb n=6610 Events	Tamox n=1238 Events	Placeb n=1233 Events
Risk factor	HR (95% CI)		HR (95% CI)		RR (95% CI)		HR (95% CI)	
All breast cancer	431	634	251	350	205	343	96	113
	0.67 (0.59-0.76)		0.71 (0.60-0.83)		NR		NS	
Invasive breast cancer	NR		214	289	145	250	38[e]	56[e]
			0.73 (0.61-0.87)		0.57 (0.46-0.70)		0.67 (0.44-1.01)[e]	
Non-invasive cancers	77	112	35	53	60	93	NR	
	0.72 (0.57-0.92)		0.65 (0.43-1.00)		0.63 (0.45-0.89)			
Oestrogen receptor-positive cancers	219	396	160	238	70	182	53	86
	0.56 (0.47-0.67)		0.66 (0.54-0.81)		0.38 (0.28-0.50)		0.61 (0.43-0.86)	
Oestrogen receptor-negative cancers	116	103	50	47	56	42	24	17
	NS		NS		NS		NS	

CI = confidence interval, HR = hazard ratio, IBIS-I = International Breast Cancer Intervention Study I, NS = not significant, NR = not reported, NSABP P1 = National Surgical Adjuvant Breast and Bowel Project P1 study placeb = placebo, Royal Marsden = Royal Marsden Hospital primary prevention trial, RR = risk ratio, tamox = tamoxifen.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Royal Marsden primary prevention trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years

[e] Results shown for posttreatment period only. During treatment, invasive breast cancer incidence was not significantly different between the tamoxifen and placebo groups.

Comment: Regarding the above table: the rows (Non-invasive cancers + ER + cancers + ER – cancers) do not always add up to the totals 'All breast cancer' but are as provided in the publications. The ER status was not available for all cancers.

Comment: The timing of the finding of a significant reduction in the incidence of invasive breast cancer has varied between the trials:

- The first report of the NSABP P1 trial, after a median follow-up of 55 months from randomisation (Fisher 1998), found a significant reduction in invasive breast cancer
- The first report of the IBIS-1 trial, after a median follow-up of 50 months (Cuzick 2002), found a reduction in the incidence of breast cancer but an increase in mortality in the tamoxifen arm. The subsequent reports after median follow-up of 96 months (Cuzick 2007) and 16 years (Cuzick 2015) confirmed a significant reduction in the occurrence of breast cancer with this also reaching significance for the sub-groups of invasive breast cancer and ER positive breast cancer in the latter report. Overall mortality was slightly increased in the tamoxifen arm but the difference was not statistically significant. The first report of the results of the Royal Marsden trial, after median follow-up of 70 months (Powles 1998), did not find a reduction in the incidence of breast cancer. The subsequent report, after a median follow-up of 13 years from randomisation (Powles 2007), also did not show a reduction in the

occurrence of invasive breast cancer with tamoxifen treatment but did find a significant reduction in the occurrence of ER positive breast cancer in the tamoxifen arm with most of the reduction occurring during the post-treatment phase.

Consistent with the findings of the pivotal publications, two additional meta-analyses reported a significant reduction in breast cancer incidence with tamoxifen compared with placebo. The Nelson 2013 meta-analysis reported a significantly lower incidence of invasive breast cancer (RR 0.70; 95% CI 0.59-0.82) and ER-positive breast cancer (RR 0.58, 95% CI 0.42-0.79) in the tamoxifen group compared with the placebo group but no significant treatment differences were observed for ER-negative breast cancer or non-invasive breast cancer. Similarly, the Duffy 2002 meta-analysis reported a significantly lower incidence of ER positive breast cancer (RR 0.41, 95% CI 0.24-0.96) but not ER-negative breast cancer with tamoxifen versus placebo.

Comment: Nelson 2013 describes a comprehensive systematic review of the use of tamoxifen and raloxifene in breast cancer risk reduction. It includes published data from IBIS-1, NSABP P1, Royal Marsden, the Italian Prevention Study and STAR. In the section on efficacy, it found that tamoxifen reduced the incidence of invasive breast cancer (risk ratio [RR], 0.70 [95% CI, 0.59 to 0.82]; 4 trials; 7 cases in 1000 women over 5 years) and the results for ER positive cancer as given above.

The main aim of the Duffy 2002 publication was to calculate estimates of the likely effect of tamoxifen administration in mutation carriers. To do this, the authors used results from a number of 'randomised' preventive, including the first report of the NSABP P1 trial and the Italian Prevention Study, and therapeutic trials using tamoxifen combined with published tumour surveys giving the oestrogen receptor status of tumours in BRCA1 and BRCA2 mutation positive women in mathematical modelling . In the process of doing this, the authors found that the results of the first report of the NSABP P1 trial and the Italian Prevention Study showed a significant overall reduction in incidence of 59% (RR=0.41, 95% CI 0.24 – 0.96) in ER positive breast cancer.

In the STAR trial, which compared the effect of tamoxifen on breast cancer incidence with raloxifene, the incidence of breast cancer overall was significantly higher in the raloxifene group than the tamoxifen group (RR 1.24, 95% CI 1.05-1.47); however, the incidence of non-invasive breast cancer was not significantly different between the treatment groups (Vogel 2006 and Vogel 2010).

Comment: In the first report of the STAR trial, after 47 months of follow-up (Vogel 2006), there was no significant difference in the primary outcome variable of invasive breast cancer between the tamoxifen and raloxifene arms (RR, 1.02; 95% CI, 0.82-1.28). With this publication, the STAR trial was unblinded in 2006 and 879 participants were known to crossover to raloxifene. The next report, after median follow-up of 81 months (Vogel 2010), found a significant reduction in the incidence of invasive breast cancer in the tamoxifen arm (RR raloxifene: tamoxifen is 1.24, 95% CI, 1.05–1.47). Against this was a significant increase in endometrial cancer, other gynaecological conditions and VTE in the tamoxifen arm.

8.3.2.1. Persistence of efficacy and/or tolerance effects

Comment: The following paragraph on the duration of effect has been copied from the Summary of Clinical Efficacy:

The effects of tamoxifen on breast cancer prevention are long lasting and extend for up to 15 years after treatment ends. In IBIS-I, the study participants have now been followed up for up to 20 years; significantly fewer breast cancer events were reported for tamoxifen versus placebo in both the first 10 years and in the last 10 years of follow up, indicating that the benefits of tamoxifen treatment last long after the end of the treatment period. In the Royal Marsden trial, a significant difference

in ER-positive tumours was not observed for tamoxifen versus placebo until the post-treatment follow up period; in the NSABP P1 trial, the benefit of tamoxifen was constant over the 7-year study period.

8.3.2.2. Comparison of results in sub-populations

Menopausal status

In the Cuzick 2013 meta-analysis, tamoxifen was the only drug shown to be effective for the primary prevention of breast cancer in premenopausal women. In the final report of IBIS-I, tamoxifen significantly reduced the risk of breast cancer in premenopausal women compared with placebo (RR 0.65, 95% CI 0.45 to 0.91). In postmenopausal women, there was no significant difference between the treatment groups (RR 0.79, 95% CI 0.59 to 1.06). Although this suggests that tamoxifen might be more effective at preventing breast cancer in premenopausal women, findings from the Royal Marsden trial found that tamoxifen significantly reduced the risk of breast cancer in premenopausal and postmenopausal women. No subgroup analyses of pre and postmenopausal women were reported in the NSABP P1 trial.

Comment: The evaluator was unable to locate the discussion of the relative effect of tamoxifen in pre- and post-menopausal women in the Cuzick 2013 meta-analysis. In Cuzick 2015, the final report of the IBIS-1 trial, results are given according to the age group rather than menopausal status: women ≤ 50 years HR 0.62, 95% CI 0.48-0.79; women >50 years HR 0.78, 95% CI 0.63-0.97). In Powles 2007, a significant reduction in all breast cancer events was found in premenopausal women (14 v 28, HR 0.5, 95% CI 0.26-0.95. P 0.03) and a reduction, that did not reach significance in post-menopausal women 9 versus 19 (HR 0.46, 95% CI 0.21-1.02, P0.06). Given these results, the evaluator considers any discussion of a difference in effect between post-menopausal and pre-menopausal women to be speculative. (TGA Clinical Question Efficacy 2 re data discrepancies)

Concomitant use of HRT

Evidence from the IBIS-I trial suggests that tamoxifen may be more effective in reducing the risk of breast cancer in women who are not taking HRT. In IBIS-I, there were significantly fewer breast cancers in the tamoxifen group compared with the placebo group in women who did not use HRT at any time during the trial (141 versus 225, hazard ratio [HR] 0.62, 95% CI 0.50-0.76, p=0.0001). This contrasts to their findings in women who used HRT during the trial, where the difference between the treatment groups was not significant (110 versus 124, HR 0.88, 95% CI 0.68-1.13, p=0.31). These finding were consistent over the 20 year study period with the same pattern being observed during the first and last 10 years.

Findings from the Royal Marsden trial contrast with the IBIS-I trial and instead found similar significant reductions in the risk of breast cancer among women using HRT (RR 0.46, 95% CI 0.23-0.91), and those not using HRT (RR 0.51, 95% CI 0.25-1.05).

The HOT study, which investigated the efficacy of 5 mg tamoxifen versus placebo in postmenopausal women on HRT, also reported a significant difference in breast cancer incidence between tamoxifen versus placebo in women who had been on HRT <5 years but not in women who had been on HRT ≥5 years, again suggesting that the efficacy of tamoxifen for the prevention of breast cancer may be limited in women who were on HRT. However, the dose of tamoxifen was 5 mg and so women on HRT may have benefited from a higher dose of tamoxifen.

Comment: The HOT trial recruited women who were postmenopausal and either on, or willing to take, HRT. An increased risk of breast cancer was not one of the inclusion criteria. This, together with the low dose of tamoxifen used, makes it difficult to generalise the results of this study to the proposed indication.

The proposed PI includes the statement: *For the primary prevention of breast cancer, the efficacy and safety of concomitant use of tamoxifen and hormone replacement*

therapy or oral contraceptives is unknown. There is some evidence that hormone replacement therapy may reduce the effectiveness of tamoxifen but this was only shown in one primary prevention trial.

Age

No age-related effects of tamoxifen on breast cancer incidence have been reported.

Comment: Women aged less than 30 years were excluded from the trials

Lobular carcinoma in situ and atypical hyperplasia

A history of LCIS or atypical hyperplasia substantially raises the risk of future invasive breast cancer. In NSABP-1, there was a 75% breast cancer risk reduction in women with a history of atypical hyperplasia (RR 0.25, 95% CI 0.10-0.52) and a 37% risk reduction was observed in women with no history of atypical hyperplasia (RR 0.63, 95% CI 0.50-0.78). The RRs for women with and without a history of LCIS were similar. Subgroup analyses of women with and without a history of LCIS or atypical hyperplasia were not reported in the IBIS-I or Royal Marsden publications.

Family history

Women treated with tamoxifen in the pivotal trials experienced a risk reduction in ER-positive breast cancer, regardless of family history. Close to a quarter of participants in NSABP-1 had no family history of breast cancer, while participants in Royal Marsden had one to three or more first-degree relatives diagnosed. For those with a strong family history, data suggest that long-term therapy with tamoxifen can reduce the occurrence of invasive breast cancer by around 40% (AstraZeneca PBRER).

Comment: The PBRER states that *'For those with a strong family history, data suggest that long-term therapy with tamoxifen can reduce the occurrence of invasive breast cancer by around 40%*.' [page 39(54)]. From the context, this appears to be based on the results of the NSABP P1 study (see Table 3 Fisher 2005 and Clinical Question Efficacy 3). Of note is that multiple risk factors would have been required for eligibility in this trial for most participants. The analysis provided in Fisher 2005 presents risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer. Determining the effect of tamoxifen in women with a strong family history of breast cancer on this data would be speculative.

The Royal Marsden trial only included women with a family history of breast cancer. It found overall a statistically significant reduction in the incidence of ER positive breast cancer of around 50%. The breakdown according to the number of first and/or second degree relatives with breast cancer found a similar reduction but this did not reach statistical significance.

It is appropriate that the proposed PI makes no statement regarding the effect of tamoxifen on women with a strong family history.

BRAC1 and BRAC 2 Mutations

Comment: These sub-groups are not discussed in the Clinical Overview and not described in the main reports of the pivotal studies. The following discussion is provided by the evaluator.

BRCA1 and BRCA2 are genes in which germline mutations result in a greatly increased risk of developing breast cancer and ovarian/fallopian tube cancer. The average cumulative risk of developing breast cancer by age 70 years has been estimated to be 57% (80% by age 80) for

women with a BRCA1 mutation and 49% (88%) for women with a BRCA2 mutation.[8] Several publications provided in the dossier attempted to determine the effect of tamoxifen in this sub-group.

A retrospective cohort study of the NSABP P1 trial using data until unblinding in 1998 (King 2001) found that most breast cancers were BRCA 'wild type' (182/211 in the placebo arm and 87/109 in the tamoxifen arm). Of the 211 participants in the placebo arm who developed breast cancer, 3 were found to have the BRCA1 mutation and 8 the BRCA2 mutation. Of the 109 participants in the tamoxifen arm who developed breast cancer, 5 were found to have a BRCA1 mutation and 3 a BRCA2 mutation. A similar analysis of the Royal Marsden cohort at the time of the initial report in 1998 (Kote-Jarai 2007) found that only 4 (6%) of the 70 patients (DNA samples available for 62) who developed breast cancer were found to have BRCA 1 or BRCA 2 mutations (1 in BRCA I, 3 in BRCA2). Given the small numbers of patients with breast cancer who were also found to have these mutations, no conclusions can be drawn as to the efficacy of tamoxifen in this group.

In Duffy 2002, results from a number of 'randomised' preventive or therapeutic trials using tamoxifen were combined with the published tumour surveys providing the oestrogen receptor status of tumours in women with BRCA1 and BRCA2 mutations and used in mathematical modelling to obtain estimates of the likely effect of tamoxifen administration in mutation carriers. The speculative results of this study were that '*any preventive benefit of tamoxifen in women positive for the high risk BRCA1 mutation is likely to be modest, but that a larger benefit of the order of a 25 – 35% reduction in incidence may be conferred in BRCA2 mutation carriers*' with this due to the lesser effect of tamoxifen in prevention or treatment of ER negative cancers, which are more common in BRCA1 mutation carriers.

See Clinical Question Efficacy 4

8.4. Evaluator's conclusions on clinical efficacy

For the indication of the primary prevention of breast cancer in women at increased risk of breast cancer

The evaluator agrees with the sponsor that tamoxifen is efficacious in the reducing the incidence of breast cancer in women aged more than 30 years who were at increased risk of breast cancer. The meta-analysis Nelson 2013 estimated that tamoxifen reduced the incidence of invasive breast cancer by 7 to 9 cases in 1000 women over 5 years compared with placebo. Cuzick 2015 estimates that the number needed to treat for 5 years to prevent one breast cancer in the next 20 years was 22 (95% CI 19–26)and the number needed to treat to prevent one invasive oestrogen receptor-positive breast cancer was 29 (95% CI 26–34).

The reduction in breast cancer incidence was mainly through the reduction in the incidence of ER positive cancers. The meta-analysis Cuzick 2013 found that for the tamoxifen versus placebo trials included (Royal Marsden, NSABP P1, IBIS-1 and the Italian Prevention study), the reduction in the Hazard Ratio was 33% ($p<0{\cdot}0001$) for all breast cancers and 44% ($p<0{\cdot}0001$) for ER positive breast cancer. A non-significant increase in ER-negative tumours was also described. The reduction in incidence persisted throughout the follow-up periods of the pivotal studies (for median of 13 and 16 years for those trials that remained blinded), suggesting that tamoxifen has not simply delayed the onset of breast cancers. It is unclear from currently available evidence as to whether menopausal status or the concurrent use of HRT may alter the effect of tamoxifen on the incidence of breast cancer.

[8] Management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation: a systematic review. Cancer Australia 2013. Accessed Nov 2015 at - http://guidelines.canceraustralia.gov.au/guidelines/media/high%20risk_systematic_review_jan_2014.pdf

The evaluator is of the opinion that other measures of efficacy (mortality and quality of life) that were not discussed in the Clinical Overview but were examined in the pivotal trials should also be included in the assessment of efficacy (Clinical Question Efficacy 5 and 6). The results for these outcome measures, as available, are described below.

8.4.1. Mortality

Each of the pivotal trials (IBIS-1, NSABP P1, and Royal Marsden) included breast cancer specific and overall mortality as a secondary outcome measures. The most recent publication for each trial (Cuzick 2015, Fisher 2005, and Powles 2007) reported no significant difference in overall mortality with tamoxifen compared to placebo – see table below.

Table 4: Mortality Results from NSABP P1, Royal Marsden, and IBIS-1 Trials

	NSABP P1		Royal Marsden		IBIS-1	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
	n=6466	n=6498	1238	1233	n=3573	n=3566
Deaths, all cause - number (%)	57 (0.9)	71 (1.1)	54 (4.4)	54 (4.4)	182 (5.1)	166 (4.7)
RR, OR (95% CI)	RR 0.81 (0.56-1.16)		NA		OR 1.1, (0.88-1.37)	
Deaths, breast cancer specific - number (%)	3 (0.05)	6 (0.09)	12 (1.0)	9 (0.7)	31 (0.9)	26 (0.7)
OR, (95% CI)	NA		NA		NA	

Table constructed from Table 3 Powles 2007, Table 7 Cuzick 2015 and text Fisher 2005. Note that after 1998, women in the placebo arm of the NSABP P1 trial could crossover to the tamoxifen arm

The pivotal meta-analysis (Cuzick 2013) commented that '*No trial was designed to look at mortality as an endpoint, and no effect of any SERM was reported for all causes of death*' and that '*No effect on breast cancer death was reported in the tamoxifen trials*'. The Nelson 2013 systematic review also found that tamoxifen did not reduce breast cancer–specific mortality (RR 1.07, 95%CI 0.66-1.74) or all-cause mortality (RR 1.07, 95%CI 0.90-1.27).

8.4.2. Quality of Life

Quality of life was a secondary outcome measure in the NSABP P1 trial. This outcome was not reported in the main publications related to this trial. A publication of the analysis of the results for 11,064 women for the first 36 months of follow-up was separately reported in

> Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659–69.

This publication was not included by the sponsor (see Clinical Question Search Strategy and Results 3). From the publically available abstract of this publication, no differences were found between placebo and tamoxifen groups using the quality of life measures of Center for Epidemiological Studies-Depression Scale (CES-D) and the Medical Outcomes Study 36-Item Short Form Health Status Survey (MOS SF-36); more women on tamoxifen reported problems of

sexual functioning; and the mean number of symptoms reported using a symptom checklist was consistently higher in the tamoxifen group and was associated with vasomotor and gynaecologic symptoms.

Fallowfield 2001 describes an ancillary study of a convenience sample of 488 women enrolled in the Royal Marsden and IBIS-1 trials who completed a set of questionnaires regarding psychosocial and sexual well-being, and a symptom checklist, by post every 6 months for 5 years from commencement of their participation in the trial. This study found that preventative treatment with tamoxifen in women at increased risk of breast cancer was not associated with changes in psychological or sexual well-being, despite women in the tamoxifen group being more likely to report vasomotor symptoms (night sweats, hot flushes, and cold sweats) and vaginal discharge.

8.4.3. Adherence to the Regimen

Efficacy of tamoxifen for the proposed indication will depend on whether outcome of the risk-benefit discussion between the prescriber and the individual woman indicates that prescription is appropriate and then on whether the woman takes tamoxifen as prescribed.

Available information would indicate that adherence to the treatment regimen (tamoxifen 20 mg daily for 5 or 8 years) was low, although this measure together with treatment discontinuations was poorly described in the pivotal trials. The information available is provided below:

- In the Royal Marsden trial, 35.5% of women did not complete the planned 8 years of treatment (25.8% of the tamoxifen group and 14.3% of the placebo group, P=0.002).
- The meta-analysis Nelson 2013 found that '*In NSABP P-1, 41% of participants took 100% of study medication and 79% took at least 76% of study medication at 36 months. Forgetting was the primary reason for nonadherence for 62% of women at 36 months '*(page 608). In Day 2001, it was reported that 3539 women in the NSABP P1 trial completed an 'Off therapy form' after discontinuing treatment with tamoxifen early and that '*The most frequent reasons for going off therapy were nonmedical in nature (1667 women [47.1%]), perceived toxic effects (921 women [26.0%]), and various protocol and non-protocol medical conditions (841 women [23.8%])'* (page 1620).
- A sub-group analysis of Finnish women participating in the IBIS-1 trial (N= 96, 45 were treated with tamoxifen and 51 with placebo) found that women in the tamoxifen group were significantly more likely to discontinue the study compared to the placebo group (20/45, 44% compared to 11/51, 22%, p=0.017). The most common reason for discontinuation in the tamoxifen group was vasomotor symptoms (10/20). The median time for discontinuation in the tamoxifen group was 15 months (range 2-60months) compared to 30 months (range 14-44) in the placebo group (Palva 2013).

Nelson 2013 also reviewed women's responses to the risk/benefit of tamoxifen and found that '*A study of women with elevated risk scores reported that 12% of women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided. Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining. However, 90% of women stated that they would take a medication with the same benefit as tamoxifen if it had no side effects, and one half would take a medication with the same side effects as tamoxifen if it could eliminate the chance of getting breast cancer'.* (page 608).

From this it would appear that it would be common for women at increased risk of breast cancer to either decline, or fail to complete, a 5 year course of tamoxifen. This will reduce the potential for any efficacy benefits to be realised (see also Clinical Question Efficacy 7). No analysis of the actual duration of tamoxifen therapy against efficacy in reduction of the incidence of breast cancer is presented in the publications provided.

8.4.4. Summary

Use of tamoxifen (20 mg daily for 5 years) has been associated with a clinically and statistically significant decrease in the incidence of invasive breast cancer (mainly through a reduction in the incidence of ER positive cancer) in women at increased risk of breast cancer. Although tamoxifen treatment was not apparently associated with a decrease in psychosocial wellbeing during treatment, adherence to the planned regimen was low across the trials. The reduction in the incidence of invasive breast cancer did not translate to a reduction in either all-cause or breast-cancer specific mortality during follow-up of up to 20 years.

The incidence of invasive breast cancer observed in the tamoxifen arms of the pivotal trials is lower than that of the placebo arms but is not reduced to zero. Therefore, it may be more appropriate to use the terminology of 'primary risk reduction' rather than 'primary prevention' in the proposed indication. It would also be appropriate that the lack of demonstrated efficacy on mortality be included in the PI.

9. Clinical safety

9.1. Studies providing evaluable safety data

The publications for the safety assessment include results from the same 4 randomised, placebo-controlled trials 4 randomised, placebo-controlled trials (IBIS-1, NSABP P1, Royal Marsden), and 1 randomised, controlled trial comparing tamoxifen with raloxifene (STAR) that were identified through the efficacy assessment. The Hormone Replacement Therapy Opposed by Low Dose Tamoxifen (HOT) study, a nonrandomised trial (Imperato 2003) and 5 meta-analyses (Cuzick 2013, Braithwaite 2003, Iqbal 2012, Fallowfield 2001, Nelson 2013) were also included for the safety assessment

Summaries of these publications are provided by the sponsor in the Clinical Overview. Descriptions of each publication are provided in Section 18 of this evaluation Report; see Table *Publications included in the dossier* above.

Comment: Fallowfield 2001 is more correctly described as an ancillary study to the IBIS-1 and Royal Marsden trials than as a meta-analysis – see description below

9.1.1. Pivotal Publications

Publications identified as pivotal by the sponsor for the assessment of safety were: Cuzick 2103 (meta-analysis); Cuzick 2002, 2007, and 2015 (results of the IBIS-1 trial); Fisher 1998 and 2005 (results of the NSABP P1 trial); Reis 2001; Land 2006; Vogel 2006 and 2010 (results of the STAR trial).

Table 5: Pivotal publications for the assessment of safety

Meta-analyses	
Cuzick 2013	Meta-analysis to assess the effectiveness of all currently available selective oestrogen receptor modulators (SERMs) on breast cancer incidence. Includes individual patient data from IBIS-I, NSABP P1, Royal Marsden, Italian, STAR, together with several other trials not involving the use of tamoxifen. Regarded as pivotal for both safety and efficacy by the sponsor.
The International Breast Cancer Intervention Study (IBIS-I)	
Cuzick 2002	First publication of results (median follow-up 50 months after randomisation)

Cuzick 2007	Long term results; 10 year follow up (median follow-up 96 months after randomization)
Cuzick 2015	Extended Long term results; 20 year follow-up (median follow up 16 years)
The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial	
Fisher 1998	First publication of results (median follow-up 54.6 months after randomisation)
Fisher 2005	Long term results; 7 year open follow up (mean follow-up 74 months after randomisation)
Reis 2001	Comparison of ischaemic cardiac events in women with or without prior CHD
The NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial	
Vogel 2006	First publication of results (median follow-up 47 months after randomisation)
Vogel 2010	Long term results; 10 year follow up (median follow-up 81 months after randomisation)
Land 2006	Comparison of patient-reported symptoms for the whole STAR cohort; quality of life assessments in a convenience sample of the cohort

Comment: Of the included 'pivotal' publications, as with the efficacy assessment:

- The objective of the meta-analysis Cuzick 2013 was to assess the effectiveness of all SERMs in the reduction of breast cancer. Not all of the results provided separate out those for participants receiving tamoxifen.
- Fisher 2005 may be better described as supportive rather than pivotal as the follow-up was largely open and affected by crossover following unblinding of the NSABP P1 trial in 1998.
- The STAR trial only included post-menopausal women (a subset of the proposed population) and included an active comparator arm (raloxifene). In Land 2006, the quality of life assessment was performed on a small sub-group, 1983 of the total cohort of 19747

9.2. Assessment of Safety

Tamoxifen is a selective oestrogen receptor modulator (SERM) and has been used for several decades in the treatment of advanced breast cancer and to reduce breast cancer recurrence in the adjuvant setting. Recognised adverse effects include hot flushes, fatigue, night sweats, abnormal vaginal bleeding and discharge together with potentially life threatening complications of VTE and uterine cancer. The dossier seeks to establish the safety of tamoxifen as per the safety profile described in the approved PI and in the PBRER and through publications that relate to the safety profile when used for the specific indication of reducing the risk of breast cancer in women at increased risk of breast cancer.

Comment: The following assessment is copied predominantly from the Clinical Overview. Some additional information is copied from the Summary of Clinical Safety (as indicated). Having reviewed the cited publications and the Clinical Overview, the evaluator is of the opinion that the sponsor has provided a fair summary and interpretation of the results of these publications. Comments are included where the opinion of the

evaluator differs from that of the sponsor or where the evaluator considers further information to be relevant.

The safety of tamoxifen for the prevention of breast cancer was assessed using adverse event outcome measures including all-cause mortality, cancers other than breast cancer, thromboembolic events, cerebrovascular events, and cardiovascular events. A total of 39 publications were identified to support this application, which collectively covered the following studies: 5 meta-analyses, 4 randomised, placebo-controlled trials, 1 randomised, controlled trial comparing tamoxifen with raloxifene, and 1 non-randomised trial. Included publications were classified as pivotal, primary supporting, or secondary supporting based on the quality of safety data and their relevance to the application. Pivotal publications provide key evidence to support the safety analysis for the proposed indication for the use of tamoxifen for the primary prevention of breast cancer. In total, 10 pivotal publications were identified which report results from 3 key RCTs and 1 meta-analysis. The 3 RCTs providing key evidence for the safety analysis were IBIS-I, NSABP P1, and STAR.

The pivotal meta-analysis included in this application analysed individual participant data from IBIS-1 and NSABP P1, as well as the Royal Marsden Study and the Italian trial. Although the Royal Marsden Study was included in this pivotal meta-analysis, publications reporting results from the Royal Marsden Study did not report hazard ratios or risk ratios for the safety data. Therefore, safety data from the Royal Marsden Study are included in this safety summary as primary supporting publications. The Italian trial participants did not fulfil the inclusion criteria of this submission (that is, women who were at increased risk of breast cancer) and therefore this trial will only be mentioned when it is included as part of the primary prevention meta-analyses.

Primary supporting publications included 2 publications from the Royal Marsden trial, 1 from the NSABP P1 study, 1 from the HOT study, and 4 meta-analyses.

Secondary supporting publications included retrospective subgroup analyses, case control studies, and smaller cohort analyses from IBIS-I (5 publications), NSABP P1 (5 publications), the Royal Marsden trial (7 publications), the STAR trial (3 publications), and a nonrandomised trial (1 publication).

The quality of the evidence is discussed below and a tabulated view of all literature studies included in the assessment of safety.

Comment: The evaluator has reviewed each of the publications cited for the safety assessment. A summary table is provided above in Table *Publications included in the dossier* with a description of the main trials, together with a listing of the publications based on each trial, their relationship to the main trials.

9.2.1. Pivotal safety trials

The pivotal safety publications including this submission have collectively enrolled 40,032 women at increased risk of breast cancer (IBIS-1, N=7154; NSABP P1, N=13,388; and STAR, N=19,490), of whom 19,996 were randomised to oral tamoxifen 20 mg daily for 5 years (IBIS-I, n=3579; NSABP P1, n=6681; and STAR n=9736). IBIS-I was an international trial and NSABP P1 and STAR were conducted in the USA and Canada. Tamoxifen was supplied by AstraZeneca (formerly Zeneca Pharmaceuticals, Wilmington, USA) in all three studies.

Comment: The STAR trial randomised post-menopausal women at increased risk of breast cancer to 5 years treatment with tamoxifen or raloxifene. It did not include a placebo arm.

Pivotal publications from the IBIS-1, NSABP P1, and STAR trials included 1 publication of the initial analysis, followed by ≥1 publication of longer term follow up. For IBIS-1, the 3 pivotal publications represent a median follow up of approximately 4 years (Cuzick 2002), 8 years (Cuzick 2007), and 16 years (Cuzick 2015), respectively. For NSABP P1, the median follow up

for the publications was 4 years (Fisher 1998) and 6 years (Fisher 2005), and for the STAR trial, the median follow up was 3½ years (Vogel 2006) and almost 7 years (Vogel 2010). Pivotal publications also included 1 publication from the NSABP P1 which focussed on cardiovascular events (Reis 2001) and 1 publication from the STAR trial which investigated quality of life and symptoms (Land 2006).

Comment: Both the NSABP P1 trial and the STAR trial were un-blinded following publication of the initial analysis, with subsequent open follow-up. This occurred in 1998 for NSABP P1 and women from the placebo arm were offered 5 years treatment with tamoxifen or enrolment in the STAR trial. Un-blinding occurred in 2006 in the STAR trial and almost 900 women are known to have crossed over to the raloxifene arm.

The safety outcomes varied between the trials but included mortality, endometrial changes, endometrial cancer, other cancers (that is, not breast or endometrial cancer), ischaemic cerebrovascular events (stroke), cardiovascular events including myocardial infarction (MI), thromboembolic events (DVT and PE), fractures, cataracts, and symptoms.

Cuzick 2013 was considered a pivotal publication as it was a meta-analysis of individual participant data obtained from the IBIS-1, NSABP P1, and Royal Marsden trials, all in women at increased risk of breast cancer, and a RCT in women at normal risk (Italian trial). The safety endpoints included all-cause mortality, endometrial cancer, other cancers, DVT or PE, cardiovascular events, fractures, and cataracts during a 10 year follow up period. Analysis was conducted based on the ITT principle.

1.1.1.1. Appraisal of the quality of included studies

The IBIS-I, NSABP P1, STAR, and Royal Marsden trials were of high quality with a low risk of bias. Randomisation was completed centrally and participants and investigators were blinded to treatment allocation in all trials. In the IBIS-I and Royal Marsden trials, outcome assessors were also blinded to treatment; in the NSABP P1 this information was not reported. Withdrawals and loss to follow-up were low in the IBIS-I trial and were low until un-blinding in the NSABP-1 trial (between years 6 and 7). In the Marsden trial, withdrawals were higher for tamoxifen versus placebo (25.6% versus 14.1%) which may be related to the longer treatment period (8 years instead of 5).

1.1.1.2. Patient demographics and disease stage

The IBIS-1, NSABP P1, STAR, and Royal Marsden trials all included women at increased risk of breast cancer. Each trial defined breast cancer risk differently: IBIS-I included women with a two-fold relative risk if they were aged 45 to 70 years, a four-fold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to39 years; NSABP P1 included women aged ≥ 60 years or aged 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66%; STAR included postmenopausal women who were aged 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66%, or a history of LCIS or atypical hyperplasia; and Royal Marsden included healthy women aged 30 and 70 years old with a high risk of developing breast cancer based on family history.

All trials excluded women with breast cancer, a history of invasive cancer, severe concurrent illness, pregnancy, and current or past DVT or PE. Other criteria included no use of oral contraceptive (NSABP-1, STAR, Marsden), recent or current hormone replacement therapy (HRT; NSABP-1, STAR), current anticoagulant use (IBIS-I, STAR), life expectancy <10 years (IBIS-I and NSABP-1) and not accessible for follow up (NSABP-1).

The majority of women in all trials were aged 59 years or below. NSABP-1 and STAR included the largest proportion of women aged 60 years or over (30% to 40%). All trials included women with some family history of breast cancer, with one trial (Royal Marsden) exclusively recruiting women with family history. In NSABP and STAR, the majority of women were white (93% to

96%) and the rest of the participants were African American, Hispanic or other race; race was not reported in the IBIS-I trial or the Royal Marsden trial.

Comment: From the meta-analysis Iqbal 2012 '*Overall, about one quarter of the women in the NSABP Pl study had no family history of breast cancers whereas 97% women in the IBIS-1 and 99% women in the Royal Marsden study reported a family history of breast cancer*'. Of note is that the pivotal trials were commenced prior to the ready availability of testing for BRCA mutations.

Women using HRT were eligible for inclusion in 2 trials (IBIS-I, Royal Marsden), but the majority of women in the Royal Marsden trials had never used HRT (85.0%). Two thirds of women in IBIS-I and a third of women in NSABP-1 had had a hysterectomy. A small proportion of women in NSABP-1 had a history of atypical hyperplasia or lobular carcinoma in situ. Women in IBIS-I who had a history of either of these conditions were also eligible for inclusion, but the proportion of affected women was not reported.

9.3. Adverse drug reactions

9.3.1. Common adverse drug reactions

The most common adverse events reported in the publications included in the safety analysis, and occurring more frequently during treatment with tamoxifen than placebo, were those associated specifically with the pharmacological action of the drug such as vasomotor symptoms (hot flushes, night sweats), menstrual abnormalities\irregularities, vaginal discharge, and vaginal dryness (Powles 1994, Sestak 2006, Cuzick 2007, DeCensi 2013). The most common adverse events reported in the STAR study, and occurring more frequently in the tamoxifen group than the raloxifene group, were vasomotor symptoms, bladder problems, hot flushes, vaginal discharge, vaginal bleeding, gynaecological problems, and leg cramps (Land 2006, Runowicz 2011).

Comment: The most common adverse events associated with tamoxifen (hot flushes, menstrual irregularities, vaginal discharge, vasomotor symptoms, gynaecological problems) mainly occurred during the active treatment period (see Table 3, Powles 2007). Additional information regarding the frequency of these adverse events as reported in the pivotal trials is provided in the table below:

Table 6: Frequency of Common Adverse Events

T=Tamoxifen and P=placebo

	NSABP P1		Royal Marsden		IBIS-1	
	T	P	T	P	T	P
Symptoms (%)	n=6466	n=6498	n=1238	n=1233	n=3573	n=3566
Vasomotor symptoms, including hot flashes					68.6	51.5
Hot flashes/flushes	80.6	68.6	48.3	32		
Menstrual			40.1	35.6		

	NSABP P1		Royal Marsden		IBIS-1	
irregularities						
Vaginal discharge	55.2	34.5	25.9	13.5	28.7	14.08

Table constructed from Table 3 Powles 2007, Table 6 Cuzick 2002 and Table 10 Fisher 1998. Cells are left blank where the information was not available in the publication

9.3.2. Deaths

No significant differences in the incidence of death were observed between tamoxifen and placebo or tamoxifen and raloxifene in the pivotal studies.

Comment: A longer discussion of deaths reported in the trials is warranted. This is provided by the evaluator:

The initial report of the IBIS-1 trial (Cuzick 2002) found a significant excess of deaths from all causes in the tamoxifen group (25 versus 11, p=0·028). By the time of the final report (Cuzick 2015), a total of 348 deaths had been reported: 182 [5·1%] of 3579 women in the tamoxifen group and 166 [4·6%] of 3575 women in the placebo group. There was no significant difference in mortality between the two groups (OR 1·10 [95% CI 0·88–1·37], p=0·4). The initial report of the NSABP P1 trial prior to un-blinding and potential crossover(Fisher 1998) reported 71 deaths occurred among 6466 participants in the placebo group and 57 occurred among 6498 women in the tamoxifen group (RR=0.81; 95% CI=0.56–1.16). The initial report of the Royal Marsden trial reported 6 deaths in the placebo group and 9 in the tamoxifen group. At the time of the most recent report (Powles 2007), 54 deaths had been reported in each group.

Review of the deaths, as reported in the individual publications, did not reveal a preponderance of deaths due to particular causes in the tamoxifen group.

- Cuzick 2015 found no significant differences in other cancers or causes of death. Five women in the tamoxifen group died from endometrial cancers (four within the first 10 years) compared with none in the placebo group (p=0·06). There was no significant difference in the incidence of endometrial cancer between the tamoxifen and placebo groups in this trial. There were 4 deaths due to VTE in the tamoxifen group compared to 3 in the placebo group.
- Fisher 2005 found that death rates were similar in the two groups (RR = 1.10, 95% CI = 0.85 to 1.43). No cause-specific category of death exhibited a statistically significant difference between the groups. Three deaths were related to pulmonary embolism and nine to stroke in the tamoxifen group compared to one and three respectively in the placebo group. There was one death due to uterine cancer in the placebo group and none in the tamoxifen group.

Comment: A discussion of mortality has also been provided by the evaluator in the section *Evaluator's conclusion on clinical efficacy* above.

9.3.3. Serious adverse events

The number and percentage of serious adverse events (SAEs) in the placebo-controlled breast cancer primary prevention trials are shown in the table below. In the publications included in the safety analysis, SAEs that were significantly higher in the tamoxifen group than the placebo group included endometrial cancer, thromboembolic events (DVT and PE), and cataracts. All of these events are described as adverse drug reactions in the current Nolvadex PI.

Comment: Gynaecological conditions, other than uterine cancer, and procedures were also significantly more common with tamoxifen than placebo. This has not been

presented by the sponsor. It is included by the evaluator below. See also Clinical Question Safety 1.

Other reported SAEs included other cancers (that is, not breast or endometrial cancer), ischaemic cerebrovascular events (stroke), cardiovascular events including MI, and fractures, but these events were not significantly different between the tamoxifen and placebo groups.

Table 7: Summary of serious adverse events from the Clinical Overview; Primary prevention trials

	Cuzick meta-analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
Risk factor	Tamox n=14192	Placeb n=14214	Tamox n=3579	Placeb n=3575	Tamox n=6597	Placeb n=6610	Tamox n=1238	Placeb n=1233
All-cause mortality	214 (1.5%)	218 (1.5%)	182 (5.1%)	166 (4.6%)	126 (1.9%)	114 (1.7%)	54 (4.4%)	54 (4.4%)
Endometrial cancer	67 (0.6%)	31 (0.3%)	29 (0.8%)	20 (0. 6%)	53 (0.8%)	17 (0.3%)	13 (1.1%)	5 (0.4%)
Other cancers	372 (2.6%)	367 (2.6%)	351 (9.8%)	315 (8.8%)	178 (2.7%)	155 (2.3%)	64 (5.2%)	70 (5.7%)
DVT	131 (1.0%)	82 (0.6%)	50 (1.4%)	29 (0.8%)	49 (0.7%)	34 (0.5)	13 (1.1%)	9 (0.7%)
PE			30 (0.8%)	22 (0.6%)	28 (0.4%)	13 (0.2%)		
Stroke	NR	NR	30 (0.8%)	28 (0.8%)	71 (1.1%)	50 (0.8%)	10 (0.8%)	16 (1.3%)
TIA	NR	NR	NR	NR	31 (0.5%)	34 (0.5%)	NR	NR
Ischaemic heart disease/cardiovascular events	144 (1.1%)	130 (1.0%)	141 (3.9%)	153 (4.3%)	113 (1.7%)	109 (1.6%)	21 (1.7%)	26 (2.1%)
MI	NR	NR	13 (0.4%)	17 (0.5%)	43 (0.6%)	44 (0.7%)	NR	NR
Cataracts	654 (6.4%)	583 (5.7%)	67 (1.9%)[e]	54 (1.5%)e	574 (9.4%)[f]	507 (8.3%)[f]	12 (1.0)	3 (0.2%)
Fractures	731 (7.2%)	791 (7.8%)	240 (6.7%)[e]	235 (6.6%)[e]	80 (1.2%)	116 (1.8%)	28 (2.3%)	33 (2.7%)

DVT = deep vein thrombosis, IBIS = International Breast Cancer Intervention Study, MI = myocardial infarction, NR = not reported, NSABP P1 = National Surgical Adjuvant Breast and Bowel Project P1 study, PE = pulmonary embolism, placeb = placebo, Royal Marsden = Royal Marsden chemoprevention trial, tamox = tamoxifen, TIA = transient ischaemic attack.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Marsden primary prevention trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.[14]

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.[17]

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years.[19]

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years.[21]

[e] results from earlier analysis; median follow up was 8 years.[16]

[f] results from earlier analysis; n=6101 tamoxifen and 6131 placebo; the median follow up was 4 years[18]

Comment: As with the less serious adverse effects, the occurrence of the serious adverse effects seemed largely limited to the active treatment phase (see Table 5, Iqbal 2012).

9.3.4. Specific Serious Adverse Events

9.3.4.1. Endometrial cancer

The incidence of endometrial cancers was significantly higher in the tamoxifen group than the placebo group in the NSABP P1 trial (2.24 versus 0.68 per 1000 women; RR 3.28, 95% CI 1.87-6.03) and the Cuzick 2013 meta-analysis (0.6% versus 0.3%, HR 2.18, 95% CI 1.39 to 3.42; p=0.001), but not the IBIS-I trial (0.8% versus 0.6%, odds ratio [OR] 1.45, 95% CI 0.79 to 2.71, p=0.19). In the STAR trial, the incidence of endometrial cancers was significantly less for raloxifene than tamoxifen (1.23 versus 2.25 per 1000 women, RR 0.55; 95% CI, 0.36 to 0.83, p=0.003).

The risk of endometrial cancer varied with age. In the Iqbal 2012 meta-analysis, women aged <50 years who received tamoxifen did not have a significantly increased risk of endometrial cancer compared with placebo (RR 1.19, 95% CI 0.53-2.65; p=0.6; 2 RCTs) whereas women >50 years had a significantly increased risk of endometrial cancer (RR 3.32, 95% CI 1.95-5.67; p<0.0001; 2 RCTs).

Endometrial changes and cancers are identified risks of Nolvadex treatment. The Nolvadex PI states: 'An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with Nolvadex treatment'. Collectively, the publications included in the safety analysis are consistent with the current PI and show that there is an increased risk of endometrial cancer in women treated with tamoxifen for primary prevention of breast cancer. However, the risk is low, particularly in women <50 years old.

Comment: The proposed PI (in the section Adverse Effects) includes the above table and this additional information under the sub-heading 'Primary prevention of breast cancer':

Tamoxifen significantly increased the incidence of endometrial cancer, deep vein thrombosis, and pulmonary embolism compared with placebo, but the absolute increase in risk was small.

and

Women under 50 years old

A meta-analysis of prevention trials stratified by age (Iqbal 2012) showed that while women over 50 years old at randomisation had a significantly increased risk of endometrial cancer compared with placebo (RR 3.32, 95% CI 1.95-5.67; p<0.0001), women aged under 50 years did not (RR 1.19, 95% CI 0.53-2.65; p=0.6). Similarly, women under 50 did not have a significantly increased risk of pulmonary embolism compared with placebo (RR 1.16, 95% CI 0.55-2.43; p=0.60) and their risk of deep vein thrombosis was only significantly increased during the active treatment phase (RR 2.30, 95% CI 1.23-4.31; p=0.009) but not after treatment had ended.

Judging whether a risk is 'small' or 'low' is subjective. The above information could also be described as indicating that, with the use of tamoxifen for risk reduction, the absolute risk of endometrial cancer overall may be doubled and may be tripled in women over 50 years of age. A number of the publications in the dossier make the argument that the endometrial cancers diagnosed were usually diagnosed early and had good prognosis, although there were a small number of uterine sarcomas described. The PBRER provided in the submission makes a similar argument:

'*With appropriate counselling and close monitoring by treating physicians, early detection is possible. For early-stage endometrial cancer (stage I and II), surgery alone or in combination with local therapy is generally curative (Rauh-Hain 2010). Therefore, with close monitoring for these uncommon/rare events, the clear benefits in risk reduction for breast cancer in postmenopausal women outweigh the associated risks of uterine cancers*'

It is essential that information regarding this important risk is explicitly included in the risk-benefit discussion between the prescribing clinician and patient and is included in both the PI and the CMI.

9.3.4.2. Other Gynaecological Conditions and Procedures

These adverse effects are not presented by the sponsor in the Clinical Overview or the Summary of Clinical Safety. Given the impact on the women involved, the data is presented by the evaluator.

NSABP P1 trial

Chalas 2005 analysed all women with an intact uterus at enrolment in the NSABP P1 trial (N=8309) with mean follow up was 4.2 years. This publication reported that, compared with women taking placebo, pre- and post-menopausal women taking tamoxifen had a significantly greater incidence of endometrial polyps, leiomyomas, endometriosis, gynaecologic surgical procedures, including hysterectomy (see table below).

Table 8: Number and average annual rate per 1000 participants of gynaecologic conditions and procedures by menopausal status at entry

	Premenopausal			Postmenopausal			Total		
	Rate per 1000			Rate per 1000			Rate per 1000		
Condition or procedure	Placebo	Tamoxifen	RR (95% CI)	Placebo	Tamoxifen	RR (95% CI)	Placebo	Tamoxifen	RR (95% CI)
Conditions									
Leiomyomas	31.07	41.33	1.3 (1.14-1.55)	13.19	18.08	1.4 (1.04-1.80)	23.25	31.21	1.3 (1.17-1.54)
Ovarian cysts	17.77	25.95	1.5 (1.20-1.78)	4.96	5.96	1.2 (0.76-1.92)	12.21	17.27	1.4 (1.18-1.70)
Polyps	12.98	25.03	1.9 (1.55-2.41)	8.69	20.66	2.4 (1.76-3.24)	11.14	23.17	2.1 (1.74-2.45)
Endometriosis	5.30	10.07	1.9 (1.35-2.70)	1.60	4.15	2.6 (1.29-5.58)	3.71	7.55	2.0 (1.50-2.78)
Endometritis	2.09	1.72	0.8 (0.41-1.64)	0.27	0.27	1.0 (0.07-14.26)	1.31	1.11	0.8 (0.44-1.62)
Procedures									
Curettage	21.75	32.06	1.5 (1.23-1.77)	8.66	32.85	3.8 (2.86-5.09)	16.04	32.39	2.0 (1.74-2.35)
Hysterectomy	19.23	29.93	1.6 (1.29-1.88)	7.41	16.25	2.2 (1.60-3.13)	14.10	24.16	1.7 (1.46-2.02)
Bilateral oophorectomy	13.89	20.75	1.5 (1.19-1.87)	4.69	9.94	2.1 (1.39-3.27)	9.91	16.11	1.6 (1.34-1.98)
Laparoscopy	10.54	13.28	1.3 (0.96-1.65)	4.03	8.83	2.2 (1.40-3.51)	7.72	11.38	1.5 (1.17-1.85)
Hysteroscopy	4.30	5.90	1.4 (0.91-2.09)	1.73	5.98	3.5 (1.82-6.99)	3.20	5.93	1.9 (1.33-2.62)

These findings were consistent with reports from the other trials.

- Royal Marsden Trial (Powles 1994): In the initial report of the Royal Marsden trial, Powles 1994, malignant ovarian cysts were more common in the tamoxifen group for premenopausal women (P<0.01), fibroids were more common in the tamoxifen group for both pre-and post-menopausal women (P<0.01 for both) and hysterectomy was more common in the tamoxifen group (P<0.05).
- IBIS-1 trial (Cuzick 2002): The initial report of this trial found that in 3573 women taking tamoxifen compared to 3566 women on placebo, the following gynaecological conditions were more common in women taking tamoxifen: abnormal bleeding (842 versus 678, P< 0.0001), endometrial polyps (130 versus 65, P< 0.0001), and ovarian cysts (101 versus 42, P< 0.0001). A number of gynaecological procedures were also more common in the tamoxifen group: hysteroscopy (228 versus 138, P< 0.0001), pelvic ultrasound (209 versus 132, P< 0.0001), dilation and curettage (178 versus 94, P< 0.0001), hysterectomy (154 versus 104, P = 0.002) and oophorectomy (103 versus 67, P = 0.006).
- STAR Trial (Runowicz 2011, Vogel 2010). These publications reported that, compared to women taking raloxifene, the following conditions were more common in women taking tamoxifen:
  - hysterectomy for conditions other than invasive cancer : 5.41 per 1000 for raloxifene and 12.08 per 1000 for tamoxifen (RR 0.45; 95% CI, 0.37- 0.54)
  - leiomyoma (RR 0.55; 95% CI, 0.49-0.62), ovarian cysts (RR 0.60; CI, 0.49- 0.74), polyps (RR 0.30; 95% CI, 0.25- 0.35),
  - endometriosis (RR 0. 32; 95% CI, 0.24-0.43),
  - Surgical procedures including dilation and curettage (RR, 0.30; 95% CI, 0.26-0.35), hysteroscopy (RR 0.29; 95% CI, 0.24-0.35), and bilateral salpingo-oophorectomy or oophorectomy (RR 0.50; 95% CI, 0.42- 0.60).

Comment: Given the inconvenience and potential distress of these gynaecological conditions and procedures, separate mention of them is warranted in the PI under the sub-

heading of sub-heading 'Primary prevention of breast cancer' in the sections Precautions and Adverse Events.

9.3.4.3. Ischaemic cerebrovascular and thromboembolic events

In this submission, the incidences of DVT and PE were significantly higher in the tamoxifen group than the placebo group in the IBIS-I trial (DVT: OR 1.73, 95% CI 1.07 to 2.85, p=0.02; PE: OR 1.37, 95% CI, 0.76 to 2.49) and the NSABP P1 trial (DVT: RR 1.44, 95% CI 0.51 to 0.92; PE: RR 2.15, 95% CI 1.08-4.51). The incidence of DVT in the STAR trial was significantly lower in the raloxifene group than the tamoxifen group (RR 0.72, 95% CI 0.54 to 0.95) whereas there was no significant difference in the incidence of PE between the groups (RR 0.80, 95% CI 0.57–1.11).

In the Cuzick 2013 meta-analysis, the combined incidence of DVT and PE was significantly higher in the tamoxifen group than the placebo group (1% versus 0.6%, OR 1.60, 95% CI 1.21-2.12). Women <50 years had a low risk of DVT and PE. In the Iqbal 2012 meta-analysis, women <50 years who received tamoxifen only had a significantly increased risk of DVT during the active treatment phase (RR 2.30, 95% CI 1.23-4.31; p=0.009; 2 RCTs). Women <50 years who received tamoxifen did not have a significantly increased risk of PE compared with placebo (RR 1.16, 95% CI 0.55-2.43; p=0.60; 2 RCTs).

Factors associated with developing a major venous thromboembolism were major surgery, immobilisation, or fracture of a lower extremity (OR 4.7, 95% CI 2.2 to 10.1).

The incidence of stroke was not significantly different between the tamoxifen group and the placebo group in the IBIS-I trial (OR 1.07, 95% CI 0.62-1.86, p=0.80) or the NSABP P1 trial (RR 1.42, 95% CI 0.97-2.08).

Ischaemic cerebrovascular and thromboembolic events are identified risks of Nolvadex treatment. The Nolvadex PI states '*There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism, occurring commonly during Nolvadex therapy'*. Collectively, the publications included in this safety analysis show that tamoxifen increases the risk or DVT and PE when given to women at increased risk of breast cancer for the primary prevention of breast cancer. However, the risk is low, and is restricted to the active treatment phase in women < 50 years old. Furthermore, there is no evidence to suggest that tamoxifen causes stroke in these women.

9.3.4.4. Cataracts

In this submission, cataracts were significantly more frequent in the tamoxifen group than the placebo group in NSABP P1 (27.75 versus 22.85 per 1000 women; RR 1.21, 95% CI 1.10-1.34) and the Cuzick 2013 meta-analysis (6.4% versus 5.7%, OR 1.10; 95% CI 1.01-1.21; p=0.04) but no significant difference was observed between the treatment groups in the IBIS-I trial (1.9% versus 1.5%, RR 1.24, 95% CI 0.87 to 1.77). In STAR, the incidence of cataracts was significantly lower in the raloxifene group than the tamoxifen group (RR 0.80, 95% CI 0.72–0.89); likewise, the incidence of cataract surgeries was also significantly lower in the raloxifene group than the tamoxifen group (RR 0.79, 95% CI 0.70–0.90).

The risk of developing cataracts is described in the current PI: 'Cataracts have commonly been reported in association with the administration of Nolvadex'. Collectively, the studies included in the safety analysis of this submission are consistent with the current PI and show that tamoxifen increases the risk of cataracts in women who are at increased risk of breast cancer. However, the difference in the incidence of cataracts between tamoxifen and placebo is less than 1%.

Comment: The proposed PI includes the above statement in the Precautions section and is not clearly associated with use of tamoxifen in risk reduction. However, the table above (Summary of adverse events from Clinical Overview in this evaluation report) that details the relative numbers of cataracts observed in the pivotal trials has been

included in the proposed PI (in the Primary prevention of breast cancer subsection of the Adverse Effects section).

9.3.4.5. Other cancers (excluding breast cancer and endometrial cancer)

Cancer incidences were similar for the tamoxifen and placebo groups in the IBIS-I trial, the NSABP P1 trial, and in the Cuzick 2013 meta-analysis. In the STAR trial, no significant differences in the incidence of other cancers were observed between the raloxifene and tamoxifen groups. Thus, there was no evidence in the primary prevention trials to suggest that tamoxifen causes other cancers in women who are at increased risk of breast cancer.

9.3.4.6. Ischaemic heart disease/ cardiovascular events

The incidence of ischaemic heart disease/cardiovascular events was similar for the tamoxifen and placebo groups in IBIS-I, the NSABP P1 trial, and the Cuzick 2013 meta-analysis. Similar results were observed when subgroups in the NSABP P1 trial were stratified according to cardiovascular risk at baseline. Thus there was no evidence in the primary prevention trials to suggest that tamoxifen causes ischaemic heart disease or other cardiovascular events in women who are at increased risk of breast cancer.

MI

The incidence of MI was not significantly different between the tamoxifen and placebo groups in IBIS-I or NSABP P1. The incidence of MI was not reported in the other trials. Thus, there was no evidence in the primary prevention trials to suggest that tamoxifen causes MI in women who are at increased risk of breast cancer.

9.3.4.7. Fractures

No significant differences in the incidence of fractures were observed in IBIS-I, NSABP P1, or the Cuzick 2013 meta-analysis. Thus, there was no evidence in the primary prevention trials to suggest that tamoxifen affects fracture risk in women who are at increased risk of breast cancer.

Comment: A differential effect of tamoxifen on bone density according to menopausal status was demonstrated in a sub-group of the Royal Marsden trial (Powles 1996). This found that in premenopausal women, the mean spinal and hip BMD for women on tamoxifen were significantly less than for women on placebo. In postmenopausal women, there was a significant increase in BMD at both the lumbar spine and the hip in the tamoxifen group and a small but not significant decrease in BMD at the lumbar spine and hip, so that there was a significant increase in BMD in the tamoxifen group compared to the placebo group. Presentation of results regarding osteoporotic fractures was not broken down according to menopausal status in Cuzick 2013, IBIS-1 and NSABP P1. A differential effect according to menopausal status cannot therefore be excluded. Given the reduction in bone density in pre-menopausal women, information related to this should be included in the precautions section of the PI.

9.3.4.8. Weight gain

Weight gain has been reported in two publications in this safety analysis. In a retrospective subgroup analysis of postmenopausal women enrolled in the IBIS-I trial no difference was observed between the tamoxifen and placebo groups (Sestak 2012a). However, in women enrolled in the Marsden trial who had not used HRT, the incidence of weight gain was significantly lower in the tamoxifen group compared with the placebo group ($p<0.025$) (Powles 1994). Thus, there was no evidence in the primary prevention trials to suggest that tamoxifen causes weight gain in women at increased risk of breast cancer.

9.4. Clinical laboratory evaluations

Laboratory evaluations have been reported in 5 publications in this safety analysis. Collectively, these publications suggest that tamoxifen treatment lowers C-reactive protein, fibrinogen,

cholesterol, antithrombin, and protein S, fibrinogen, and antithrombin levels. In contrast, Factor VII coagulant activity, fragment 1-2, triglycerides, protein C, and the activated protein C ratio appear to be unaffected by tamoxifen treatment.

Comment: Additional information regarding laboratory investigations was provided in the Summary of Clinical Safety:

Subgroup analyses of NSABP P1 at 1 study site in the USA (N=111) showed that there were significant decreases in median C-reactive protein, fibrinogen, cholesterol, antithrombin, and protein S after 6 months of treatment compared with the placebo group (Cushman 2001; Cushman 2003). There were no significant differences in treatment effects on factor VII coagulant activity, fragment 1-2, triglycerides, protein C or the APC ratio (Cushman 2001, Cushman 2003).

A subgroup analysis of postmenopausal women enrolled in the Royal Marsden trial showed that serum cholesterol, fibrinogen, and antithrombin significantly decreased from baseline in the tamoxifen group (Chang 1996). Addition of tamoxifen to HRT resulted in a further decrease in serum cholesterol.

Comment: This did not translate to a reduced risk of ischaemic cardiac events.

In a subgroup analysis of women enrolled in the Royal Marsden trial, plasma fibrinogen significantly decreased from pretreatment levels in the tamoxifen group for both premenopausal and postmenopausal women (Jones 1992). For antithrombin and protein S, there were no significant decreases in premenopausal women, but there were significant decreases from baseline in postmenopausal women. For protein C, no significant differences were observed in pre or postmenopausal women.

In a separate analysis of women enrolled in the Royal Marsden pilot trial who had been on treatment for ≥ 3 months and never used HRT, fibrinogen and antithrombin III were lower in the tamoxifen group compared with the placebo group and the fibrinogen/antithrombin III ratio was significantly lower in the tamoxifen group at 6 months but not 12, 18 or 24 months (Powles 1994). Non-fasting plasma cholesterol was significantly lower in the tamoxifen group compared to baseline.

Comment: Many of the differences described were statistically significant but too small to be clinically important, or the publication made no attempt at clinical correlation (see descriptions of individual publications in Section 18). Abramson 2006 looked for a relationship between hypercoagulability factor mutations (Factor V Leiden and prothrombin mutations) and the development of VTE during tamoxifen therapy in a nested blinded case controlled retrospective analysis of the NSABP P1 trial. The conclusion was that venous thromboembolic events were associated with the use of tamoxifen and BMI, but not hypercoagulability factor mutation status and that screening for these mutations prior to initiating treatment with tamoxifen would not be of benefit.

9.5. Safety in special groups and situations

9.5.1. Race

In NSABP P1 and STAR, the majority of women were White (93% to 96%) and the rest of the participants were African American, Hispanic or other race; race was not reported in the IBIS-I trial or the Royal Marsden trial. Thus, for the primary prevention of breast cancer, safety data in non-white women is limited.

9.5.2. Age

The Iqbal meta-analysis showed that the risk of endometrial cancer, DVT, and PE was not significantly different to placebo in women aged <50 years who took tamoxifen for the primary prevention of breast cancer.

The safety of tamoxifen for the primary prevention of breast cancer in women under 30 years old is unknown.

Comment: The NSABP P1 and IBIS-1 trials excluded women aged less than 35 years; the Royal Marsden trial excluded women aged less than 30 years.

9.6. Post-marketing experience

Comment: Information regarding post-marketing experience has been provided in the Summary of Clinical Safety and in the Periodic Benefit-Risk Evaluation Report (PBRER) for the period 30 April 2013 to 29 April 2014. Of note is that tamoxifen for the indication of primary prevention of breast cancer in women at increased risk of breast cancer is only approved in the USA. Post-marketing experience is therefore largely limited to the use of tamoxifen in the treatment of breast cancer.

The following information has been collated from the PBRER and PI.

9.7. Patient exposure

THE PBRER provides the following information:

The total worldwide exposure to Nolvadex for the period of 30 April 2013 to 29 April 2014 was calculated from the number of tablets delivered to wholesalers worldwide during the period. A daily dose of 20 mg has been assumed. The total worldwide exposure, for this PBRER reporting period, has been estimated by AstraZeneca to be 293,040 patient-years.

It has not been possible to estimate the total worldwide exposure since launch in 1973 to 29 April 2014 as the AstraZeneca legacy systems and documents containing early data are now not available. However, it has been possible to calculate exposure since the beginning of 2001 to 29 April 2014; patient exposure for this period has been estimated by AstraZeneca to be 5.9 million patient years.

Marketing approval(s): *Nolvadex 10 mg was first approved for marketing in the United Kingdom (UK) on 30 August 1973, Nolvadex 20 mg was first approved on 29 January 1982 and both are currently approved in over 60 countries including some European Union (EU) member states. Nolvadex 30 mg and 40 mg were subsequently approved in a small number of countries but most of these approvals are now withdrawn and the use of these tablets has ceased. These withdrawals have been motivated by commercial reasons, and are not related to any safety concerns.*

9.8. Summary of safety concerns

Nolvadex has no Patient Risk Management Plan (PRMP) and has not been required to provide a risk management plan for this submission.

A number of important identified and important potential risks, and missing information, have been identified in the PBRER based on pre- and post-approval experience of the use of tamoxifen. Information regarding these has been summarised from the PBRER.

9.8.1. Important identified risks:

9.8.1.1. Ischaemic cerebrovascular events and thromboembolic events

There is evidence of ischaemic cerebrovascular events and thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism), occurring commonly during Nolvadex therapy. When Nolvadex is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

The current and proposed PI states in the Adverse Effects section:

> *There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism, occurring commonly during Nolvadex therapy. When Nolvadex is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring*

9.8.1.2. Endometrial cancer and uterine sarcoma

Incidences of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) have been reported in association with Nolvadex treatment.

The PBRER notes that most studies have found that the increased risk of developing endometrial carcinoma in postmenopausal women treated with tamoxifen is 2-3 times higher than that of an age matched population, and the level of risk is dose and time dependent. Premenopausal women have no known increased risk of uterine cancer. The ATLAS trial, in which tamoxifen was used for the treatment of breast cancer, showed an increased risk of endometrial cancer for those treated for 10 years versus 5 years: RR1.74 (1.30—2.34, p=0.0002).

Endometrial cancer is listed in the Nolvadex CDS with a frequency of 'uncommon'. Uterine sarcoma is listed in the Nolvadex CDS with a frequency of 'rare'.

The current and proposed PI states in the Adverse Effects section:

> *An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with Nolvadex treatment.*

The Precautions section of the PI advises that:

> *Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine cancer have been reported. Patients receiving Nolvadex should have routine gynaecological care and report any abnormal vaginal bleeding to their physician.*

The CMI advises:

> *If you have any unusual vaginal bleeding or other gynaecological symptoms (such as pelvic pain or pressure) when you are taking Nolvadex or anytime afterwards, tell your doctor. This is because a number of changes to the lining of the womb (endometrium) may occur, some of which may be serious and could include cancer.*

9.8.1.3. Hepatic injury

The same statement is made in the PBRER and PI:

> *Nolvadex has been associated with changes in liver enzyme levels and with a spectrum of more severe liver abnormalities which in some cases were fatal, including fatty liver, cholestasis and hepatitis, liver failure, cirrhosis, and, hepatocellular injury (including hepatic necrosis).*

The PBRER also notes that hepatic injury is listed in the Nolvadex CDS with a frequency of 'Rare' (>0.01% and <0.1%) and suggests: *If a decision to prescribe Nolvadex is made, then regular monitor of liver function and early stopping of Nolvadex therapy in patients exhibiting worsening liver function may be appropriate.*

Comment: Hepatic dysfunction was not described as a safety measure in the publications presented in this submission

9.8.1.4. Important potential risks:

Paediatric use:

The use of Nolvadex is not recommended in children, as safety and efficacy have not been established.

Second primary tumours:

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment of breast cancer patients with Nolvadex. According to the PBRER, no causal link has been established and the clinical significance of these observations remains unclear. The incidence of non-breast or uterine cancers was not reported to be higher in the tamoxifen arms of the placebo controlled trials in this submission.

9.8.1.5. Missing information:

Pregnancy: Nolvadex is contraindicated for use during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken Nolvadex, although no causal relationship has been established.

Lactation: It is not known if Nolvadex is excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue Nolvadex should take into account the importance of the drug to the mother

9.9. Effectiveness of risk minimisation

From the PBRER:

> *The safety profile of Nolvadex has been well characterised in over 40 years of clinical use. It is therefore considered that the routine risk minimisation activities (eg, Product labelling) are appropriate for the product and no additional risk minimisation activities (e.g., healthcare professional or patient communications/educational materials) were implemented during the reporting period.*

9.10. Post-marketing adverse events

The appendix of the PBRER included in the dossier provides tabulated cumulative summaries of:

1. Case reports containing Serious Adverse Events (SAEs) from AstraZeneca-sponsored interventional clinical trials from the Development International Birth Date (DIBD) to the
2. Case reports of serious and non-serious adverse events from spontaneous sources from IBD to the PBRER data lock point (29 April 2014)

These tables have been summarised by the evaluator to include System Organ Class and Preferred Terms for the most common events or events of special interest, where the evaluator has defined these as events identified as important risks or events that were reported in the pivotal publications. These tables have been included below.

Overall, the cumulative listings are consistent with the Important Identified Risks in the PBRER and with the Precautions and Adverse Events as described in the PI. Serious adverse events described in the PBRER and current PI as associated with tamoxifen use that were not described in the publications presented in the dossier included: ischaemic cerebrovascular events; isolated reports of skin reactions such as erythema multiforme and Stevens-Johnson syndrome;

uncommon reports of interstitial pneumonitis, liver injury (as described above under Important Identified Risks) and rare reports of optic neuropathy/neuritis, cutaneous lupus erythematosus, elevated triglycerides with pancreatitis. Fatigue, nausea and vomiting have been very commonly reported with tamoxifen use.

Table 8: Cumulative reports of Adverse Events from Clinical Studies (compiled from the PBRER provided)

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies					
	Total Up to 29-APR-2014				
System Organ Class Preferred Term*	Investiga-tional Product	Blinded	Study Procedure	Active Com-parator	Placebo/ No study Product
Infections and infestations	8	0	0	5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	52	0	0	7	1
Breast cancer	8	0	0	0	0
Endometrial cancer	5	0	0	0	0
Ovarian cancer	5	0	0	0	0
Uterine cancer	3	0	0	0	0
Uterine leiomyoma	1	0	0	0	0
Blood and lymphatic system disorders	14	0	0	27	3
Thrombocytopenia	4	0	0	12	2
Metabolism and nutrition disorders	4	0	0	7	0
Psychiatric disorders	7	0	0	2	0
Completed suicide	4	0	0	0	0
Nervous system disorders	23	0	0	7	3
Cerebrovascular accident	6	0	0	1	0
Cardiac disorders	14	0	0	11	0
Myocardial infarction, acute myocardial infarction	5	0	0	5	0
Vascular disorders	12	0	0	2	2

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies					
Deep vein thrombosis	3	0	0	0	2
Phlebitis, Phlebitis superficial, thrombophlebitis, thrombosis	6	0	0	0	0
Respiratory, thoracic and mediastinal disorders	22	0	0	13	4
Pulmonary embolism, Pulmonary infarction	11	0	0	1	0
Gastrointestinal disorders	16	0	0	13	3
Nausea, vomiting	6	0	0	5	3
Hepatobiliary disorders	19	0	0	1	0
Hepatic failure, Hepatitis fulminant	15	0	0	1	0
Renal and urinary disorders	4	0	0	2	0
Reproductive system and breast disorders	8	0	0	0	0
Endometrial hyperplasia, hypertrophy, polyp	3	0	0	0	0
Ovarian cyst	2	0	0	0	0
General disorders and administration site conditions	22	0	0	14	1
Concomitant disease progression	8	0	0	0	0
Death	11	0	0	0	0
Investigations	6	0	0	9	0
* Preferred term included if number of reports 5 or more or event of special interest (identified risk or common AE reported in the publications					

Table 9: Cumulative reports of Adverse Events from Spontaneous Reports (compiled from PBRER provided)

Spontaneous reports of Adverse Events during Tamoxifen Treatment, including regulatory authority and literature

Spontaneous reports of Adverse Events during Tamoxifen Treatment, including regulatory authority and literature			
		Cumulative total up to 29 April 2014	
System Organ Class* Preferred Term**	**Serious**	**Non-serious**	**Total**
Infections and infestations	**157**	**433**	**590**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2543**	**458**	**3001**
Breast cancer, breast cancer female	143	6	149
Breast cancer metastatic, breast cancer recurrent, contralateral breast cancer	169	24	194
Endometrial cancer, neoplasm, adenocarcinoma, metastatic, recurrent, Stage I or III	757	109	866
Endometrial sarcoma, stromal sarcoma	26	1	27
Female reproductive neoplasm	31	4	35
Ovarian cancer, ovarian cancer metastatic, stage IV, ovarian neoplasm	65	8	73
Sarcoma uterus	97	1	98
Uterine cancer, neoplasm	248	14	262
Uterine leiomyoma	120	101	221
Blood and lymphatic system disorders	**305**	**632**	**937**
Metabolism and nutrition disorders	**184**	**846**	**1030**
Psychiatric disorders	**179**	**1828**	**2007**
Anxiety	7	123	130
Depression	54	575	629
Insomnia	9	269	278
Nervous system disorders	**634**	**2411**	**3045**
Cerebrovascular accident	154	19	173
Eye disorders	**645**	**2193**	**2838**

Spontaneous reports of Adverse Events during Tamoxifen Treatment, including regulatory authority and literature			
Cataract	126	214	340
Cardiac disorders	**376**	**215**	**591**
Acute myocardial infarction, myocardial infarction	119	5	124
Vascular disorders	**680**	**2984**	**3664**
Deep vein thrombosis	268	112	380
Hot flush	39	2195	2234
Phlebitis, phlebitis deep or superficial, thrombophlebitis, thrombophlebitis superficial, thrombosis	169	278	447
Respiratory, thoracic and mediastinal disorders	**607**	**774**	**1381**
Pulmonary embolism	273	57	330
Gastrointestinal disorders	**377**	**2979**	**3356**
Nausea, vomiting	70	1089	1159
Hepatobiliary disorders	**372**	**535**	**907**
Hepatic failure	13	4	17
Hepatic function abnormal	17	79	96
Skin and subcutaneous tissue disorders	**307**	**4489**	**4796**
Alopecia	19	1044	1063
Hyperhidrosis	7	296	303
Night sweats	2	117	119
Rash	30	640	670
Musculoskeletal and connective tissue disorders	**364**	**2710**	**3074**
Arthralgia	67	588	655
Reproductive system and breast disorders	**1115**	**3954**	**5069**

Spontaneous reports of Adverse Events during Tamoxifen Treatment, including regulatory authority and literature			
Endometrial hyperplasia, hypertrophy	201	399	600
Endometriosis	38	27	65
Ovarian cyst	112	164	276
Uterine polyp	305	180	485
Vaginal discharge	15	472	487
Vaginal haemorrhage	85	512	597
General disorders and administration site conditions	**1869**	**3020**	**4889**
Death	1429	55	1484
Fatigue	31	519	550
Investigations	**276**	**3171**	**3447**
Hepatic enzyme increased	18	159	177
Liver function test abnormal	15	132	147
Weight increased	27	886	913
Weight decreased	11	144	155
* SOC included if number of reports greater than 500 **Preferred term included if cumulative total greater than 500 or of special interest (recognised risk, commonly reported AE in publications). Similar preferred terms have been grouped together where appropriate			

9.11. Evaluator's overall conclusions on clinical safety

The use of tamoxifen for risk reduction in women at increased risk of breast cancer is associated with both serious and non-serious adverse events.

Potentially life-threatening adverse events include venous thromboembolic events and uterine cancer:

- It was estimated in the Nelson 2013 meta-analysis that tamoxifen increased the risk for venous thromboembolic events (VTEs) by 4 to 7 events per 1000 women over 5 years. The risk of VTE with tamoxifen was higher in women aged 50 years or more compared to women aged less than 50 years. It was also found that factors such as recent surgery, immobility and lower limb fractures further increased the risk of VTE in women taking tamoxifen.
- It was estimated in the Nelson 2013 meta-analysis that tamoxifen increased risk for endometrial cancer by approximately 4 cases per 1000 women The risk of endometrial cancer with tamoxifen was only increased in women aged 50 years or more; the incidence of

endometrial cancer in women aged less than 50 years taking tamoxifen did not differ from the placebo group. The presence of a uterus also determined the risk of endometrial cancer.

Less serious adverse effects that were more common with tamoxifen included other gynaecological conditions and procedures, including hysterectomy, and cataracts. Symptoms such as hot flushes, night sweats, and vaginal discharge were very common in women taking tamoxifen. These symptoms, although not classified as serious, may affect a patient's quality of life and willingness to use or adhere to these medications.

10. First round benefit-risk assessment

10.1. First round assessment of benefits

The benefits of tamoxifen in the proposed usage are:

- Reduction in the incidence of potentially life-threatening invasive breast cancer in healthy women at increased risk of breast cancer

10.2. First round assessment of risks

The risks of tamoxifen in the proposed usage are:

- Increased risk of potentially life-threatening adverse events such as pulmonary embolism and uterine cancer
- Likely experience of the common side effects of fatigue, nausea and vomiting, hot flushes, night sweats, vaginal discharge and benign gynaecological conditions. These side effects are not typically classified as serious but may affect a woman's quality of life and willingness to continue use of tamoxifen
- Unclear risk of osteoporotic fractures in relation to tamoxifen use and menopausal status
- Tamoxifen should not be used in women who have a history of thromboembolic events (deep venous thrombosis, pulmonary embolus)

10.3. First round assessment of benefit-risk balance

The potential benefit of tamoxifen for the proposed usage is a reduction in the incidence of potentially life-threatening invasive breast cancer. Against this, are the potential life-threatening risks of endometrial cancer and thromboembolic disease and the discomfort and inconvenience of the common side effects of hot flushes, night sweats, vaginal discharge and benign gynaecological conditions.

Determining the benefit-risk balance of tamoxifen for the indication of the reduction of the risk of breast cancer in healthy women at increased risk of breast cancer is complex as the potential risks and benefits may vary considerably between individual women. The woman's personal risk of breast cancer will vary with age and other factors such as family history, parity and breast feeding. The risk of adverse events with tamoxifen will vary with the woman's age and menopausal status, whether the woman has a uterus and other factors.

Two of the publications provided in the dossier have attempted to address some of these complexities and provide an assessment of the risk-benefits. Fisher 2005 presented breast cancer cases prevented against VTE and endometrial cancer cases caused, according to age group, risk of breast cancer and race in the following graphs:

Figure 1: Benefits and risks associated with tamoxifen use for breast cancer risk reduction

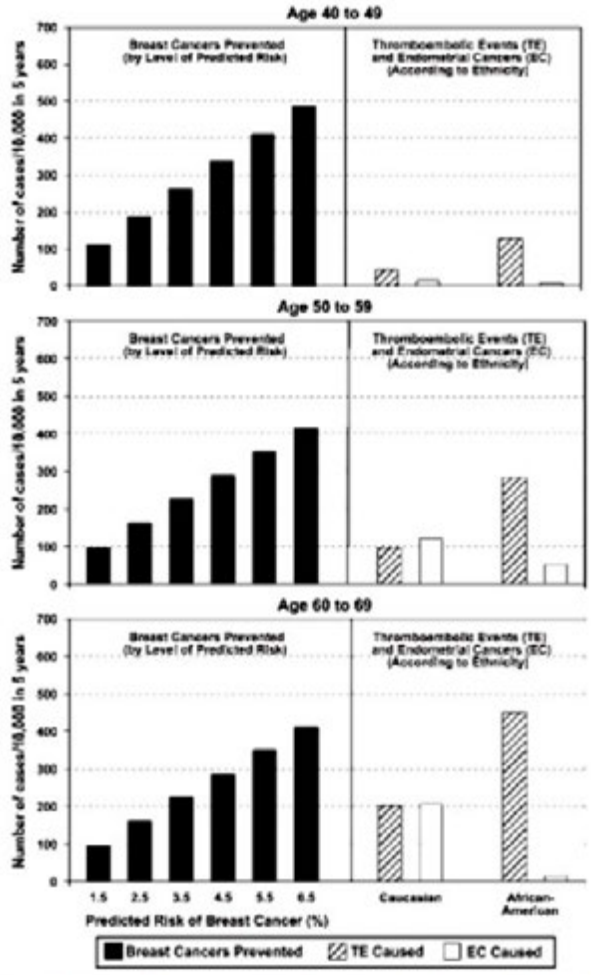
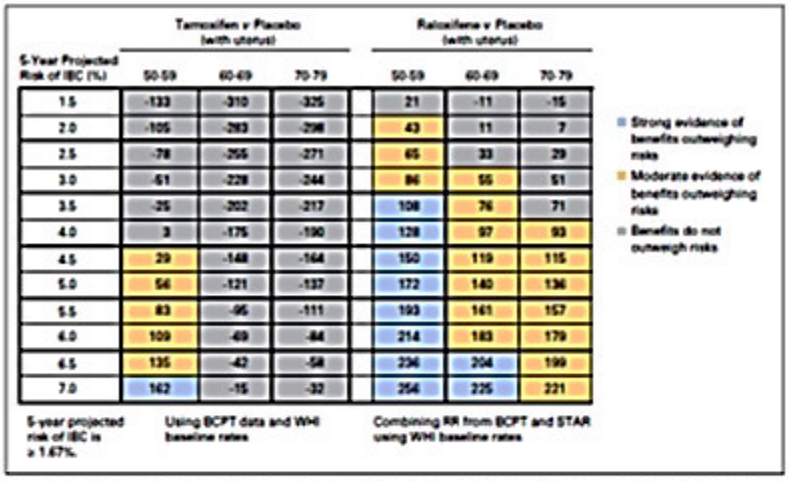


Fig. 4. Benefits and risks associated with tamoxifen use for breast cancer risk reduction. Numbers of breast cancers prevented by tamoxifen in cases per 10 000 women over 5 years by 10-year age group and by level of predicted risk (**left**). Numbers of thromboembolic events and endometrial cancers caused by tamoxifen in cases per 10 000 women over 5 years, by ethnicity (**right**).

Freedman 2011 used data from the NSABP P1 and STAR studies, together with surveys to determine background incidence rates, to develop a risk matrix for women with or without a uterus and according to the 5 year projected risk of breast cancer:

Table 9: Benefit/risk for tamoxifen and raloxifene chemoprevention by level of 5 year projected risk for invasive breast cancer for White non-Hispanic women with a uterus by age group



5-Year Projected Risk of IBC (%)	Tamoxifen v Placebo (with uterus) 50-59	60-69	70-79	Raloxifene v Placebo (with uterus) 50-59	60-69	70-79
1.5	-133	-310	-325	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-228	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	136
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

Fig 1. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic women with a uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > .9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events ($P < .6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

5-Year Projected Risk of IBC (%)	Tamoxifen v Placebo (without uterus) 50-59	60-69	70-79	Raloxifene v Placebo (without uterus) 50-59	60-69	70-79
1.5	3	-53	-93	27	2	-4
2.0	31	-26	-66	49	23	18
2.5	57	2	-39	71	45	40
3.0	84	29	-12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	342	201	262	237	232

Fig 2. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk of invasive breast cancer (IBC) for white non-Hispanic women without uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 114 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > 0.9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would also result in the prevention of 111 life-threatening events ($P < 0.9$; blue). Among 10,000 non-Hispanic white women without a uterus, age 70 to 79 years, and with a 5-year IBC risk of 3.0%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P \geq 0.6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 12 excess life-threatening events ($P < 0.6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

The woman's personal assessment of the risk and benefit, together with her own tolerance of the different risks, must also be considered. Nelson 2013 reported a study of women with elevated risk for the development of breast cancer: 12% of these women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided. Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining.

The judgement as to whether the use of 'preventative' tamoxifen is appropriate in a particular woman requires careful weighing up of these risks and benefits together with consideration of

how risk-averse the woman is regarding her personal risk of breast cancer or adverse effects. It is therefore essential that this is a shared decision making process and that the individual woman is provided with the necessary information with which to make an informed decision. This would most appropriately be achieved through discussion with a specialist with knowledge and experience in the management of breast and familial cancer. If the planned 5 years of treatment is to be completed by a healthy woman, it is necessary that the woman engage in the decision-making process and understands the relevance to her personal situation. For women who choose to commence risk reduction therapy with tamoxifen, careful advice must also be given regarding the need for review if symptoms/signs of thromboembolic events develop or abnormal gynaecological symptoms develop. The information provided in the PI and CMI must form an integral part of both the decision-making process and monitoring during therapy.

The benefit-risk balance of tamoxifen for the proposed usage is favourable provided the recommendations made in regard to the PI and CMI below are agreed to.

11. First round recommendation regarding authorisation

The evaluator recommends that tamoxifen be approved for the proposed usage, provided the suggestions made with regard to the PI and CMI are agreed to.

Approval of tamoxifen for this usage is consistent with the publically available recommendations of reputable groups such as the Australian federal government agency Cancer Australia, the national non-government organisation Cancer Council Australia, the professional body American Society of Clinical Oncology and the UK National Institute for Health and Care Excellence (NICE).

12. Clinical questions

12.1. Search Strategy and Results

Clinical Question Search Strategy and Results 1

There were 14 publications related to prevention in women who were at 'less than increased risk' of the development of breast cancer. Could the sponsor provide more information regarding these publications?

Clinical Question Search Strategy and Results 2

The 'Italian' study included 5408 healthy women who had undergone hysterectomy were randomly assigned in a double-blind manner to tamoxifen (20 mg daily) or placebo for 5 years with comparison of rates of breast cancer and other events in the two groups. Initial results of the trial were published in 1998[9] and long term results were published in 2007[10]. Patients were not recruited according to risk of breast cancer development and this is given as the reason for publications related to this study having been excluded for the assessment. The HOT study was included even though this study recruited post-menopausal women on HRT rather than women

[9] Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Rotmensz N et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998;352:93-7

[10] Umberto Veronesi, Patrick Maisonneuve, Nicole Rotmensz, Bernardo Bonanni, Peter Boyle, Giuseppe Viale, Alberto Costa, Virgilio Sacchini, Roberto Travaglini, Giuseppe D'Aiuto, Pasquale Oliviero, Francesco Lovison, Giacomo Gucciardo, Marco Rosselli del Turco, Maria Grazia Muraca, Maria Antonietta Pizzichetta, Serafino Conforti, and Andrea Decensi For the Italian Tamoxifen Study GroupTamoxifen for the Prevention of Breast Cancer: Late Results of the Italian Randomized Tamoxifen Prevention Trial Among Women With Hysterectomy JNCI J Natl Cancer Inst (2007) 99 (9): 727-737

at increased risk of breast cancer. The evaluator does not understand why the Italian Prevention Study was not included in the submission (particularly given the reference to it in the pivotal meta-analysis) and the HOT was. Could the sponsor please clarify this?

Clinical Question Search Strategy and Results 3

The publication *Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Randomized Study. J Natl Cancer Inst. 2001; 93(21):1615-23* has been included as a primary supporting publication for the assessment of safety. This publication is a follow-on of the initial report of health related quality of life in participants of the NSABP P1 trial*, Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659–69.* The latter publication has not been included in the sponsor's dossier. Can the sponsor explain why it was excluded?

Clinical Question Search Strategy and Results 4

Could the sponsor explain why Fallowfield 2001, which presents the results of a subgroup of women from the Royal Marsden and IBIS-1 studies who prospectively completed surveys of psychological well-being, is described as a meta-analysis rather than an ancillary study?

12.2. Pharmacodynamics

Nil

12.3. Efficacy

Clinical Question Efficacy 1

Cuzick 2013 used individual participant data from nine prevention trials comparing four selective oestrogen receptor modulators (SERMs; tamoxifen, raloxifene, arzoxifene, and lasofoxifene) with placebo, or in one study with tamoxifen (STAR), with the objective of assessing the effectiveness of all SERMs in the reduction of breast cancer. Of the included studies comparing tamoxifen to placebo, one study (the Italian Prevention study) did not have increased risk of breast cancer as an inclusion criterion. Could the sponsor confirm if the results presented from this publication in the assessment of efficacy are those from the publication that relate only to tamoxifen and not to the other SERMS?

Clinical Question Efficacy 2

In the Clinical Overview, the following discussion is provided regarding the effect of tamoxifen according to menopausal status:

> Menopausal status
>
> In the Cuzick 2013 meta-analysis, tamoxifen was the only drug shown to be effective for the primary prevention of breast cancer in premenopausal women. In the final report of IBIS-I, tamoxifen significantly reduced the risk of breast cancer in premenopausal women compared with placebo (RR 0.65, 95% CI 0.45 to 0.91). In postmenopausal women, there was no significant difference between the treatment groups (RR 0.79, 95% CI 0.59 to 1.06). Although this suggests that tamoxifen might be more effective at preventing breast cancer in premenopausal women, findings from the Royal Marsden trial found that tamoxifen significantly reduced the risk of breast cancer in premenopausal and postmenopausal women. No subgroup analyses of pre and postmenopausal women were reported in the NSABP P1 trial.

The evaluator was unable to confirm this in the cited publications. The evaluator found:

> The evaluator was unable to locate the discussion of the relative effect of tamoxifen in pre- and post-menopausal women in the Cuzick 2013 meta-analysis. In Cuzick 2015, the final report of the IBIS-1 trial, results were given according to the age group rather than menopausal status: women ≤ 50 years HR 0.62, 95% CI 0.48-0.79; women >50 years HR 0.78, 95% CI 0.63-0.97). In Powles 2007, a significant reduction in all breast cancer events was found in premenopausal women (14 v 28, HR 0.5, 95% CI 0.26-0.95, P 0.03) and a reduction that did not reach significance in post-menopausal women 9 versus 19, (HR 0.46, 95% CI 0.21-1.02, P0.06).

Could the sponsor account for these discrepancies with regard to the Cuzick 2013 meta-analysis and the Cuzick 2015 publication of the most recent report of the IBIS-1 trial or direct the evaluator to the location of the data in the cited publications?

Clinical Question Efficacy 3

Regarding *Family History*

The Clinical Overview states *'For those with a strong family history, data suggest that long-term therapy with tamoxifen can reduce the occurrence of invasive breast cancer by around 40% (AstraZeneca PBRER).'*

The evaluator found that:

> The PBRER states that 'For those with a strong family history, data suggest that long-term therapy with tamoxifen can reduce the occurrence of invasive breast cancer by around 40%.' [page 39(54) of the PBRER]. From the context, this appears to be based on the results of the NSABP P1 study as shown in Table 3 Fisher 2005. Of note is that multiple risk factors were required for eligibility in this trial for most participants. The analysis provided in Fisher 2005 presents risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer.

Could the sponsor confirm if this statement regarding the reduction in occurrence of invasive breast cancer of around 40% in the PBRER is based on the findings of the NSABP P1 study? If not, could the sponsor provide the source of the information and a more detailed evaluation of the effect of tamoxifen in woman with a 'strong family history' of breast cancer?

TGA Clinical Question Efficacy 4

Regarding BRCA1 and BRCA 2 mutations

No discussion of this subgroup is provided in the Efficacy Assessment. The evaluator found that:

> A retrospective cohort study of the NSABP P1 trial using data until unblinding in 1998 (King 2001) found that most breast cancers were BRCA 'wild type' (182/211 in the placebo arm and 87/109 in the tamoxifen arm). Of the 211 participants in the placebo arm who developed breast cancer, 3 were found to have the BRCA1 mutation and 8 the BRCA2 mutation. Of the 109 participants in the tamoxifen arm who developed breast cancer, 5 were found to have a BRCA1 mutation and 3 a BRCA2 mutation. A similar analysis of the Royal Marsden cohort at the time of the initial report in 1998 (Kote-Jarai 2007) found that only 4 (6%) of the 70 patients (DNA samples available for 62) who developed breast cancer were found to have BRCA 1 or BRCA 2 mutations (1 in *BRCA I,* 3 in *BRCA2).* Given the small numbers of patients with breast cancer who were also found to have these mutations, no conclusions can be drawn as to the efficacy of tamoxifen in this group.
>
> In Duffy 2002, results from a number of 'randomised' preventive or therapeutic trials using tamoxifen were combined with the published tumour surveys providing the oestrogen receptor status of tumours in women with BRCA1 and BRCA2 mutations and used in mathematical modelling to obtain estimates of the likely effect of tamoxifen administration in mutation carriers. The speculative results of this study were that 'any

> preventive benefit of tamoxifen in women positive for the high risk BRCA1 mutation is likely to be modest, but that a larger benefit of the order of a 25 – 35% reduction in incidence may be conferred in BRCA2 mutation carriers' with this due to the lesser effect of tamoxifen in prevention or treatment of ER negative cancers, which are more common in BRCA1 mutation carriers.

Does the sponsor agree that there is a lack of evidence with which to determine the effect of tamoxifen in this sub-group? Does the sponsor agree that a statement regarding this should be included in the PI and that this would most appropriately be included in the Precautions section?

Clinical Question Efficacy 5

The Assessment of Efficacy provided in the Clinical Overview does not discuss the lack of demonstrated efficacy on mortality. The evaluator found that:

> Each of the pivotal trials (IBIS-1, NSABP P1, and Royal Marsden) included mortality (breast cancer specific and overall) as a secondary outcome measure. The most recent publication for each trial (Cuzick 2015, Fisher 2005, and Powles 2007) reported no significant difference in overall mortality with tamoxifen compared to placebo.

Table 10: Mortality Results from NSABP P1, Royal Marsden, and IBIS-1 Trials

T= Tamoxifen and P=Placebo

	NSABP P1		Royal Marsden		IBIS-1	
	T	P	T	P	T	P
	n=6466	n=6498	1238	1233	n=3573	n=3566
Deaths, all cause - number (%)	57 (0.9)	71 (1.1)	54 (4.4)	54 (4.4)	182 (5.1)	166 (4.7)
OR, (95% CI)	RR 0.81 (0.56-1.16)		NA		OR 1.1, (0.88-1.37)	
Deaths, breast cancer specific - number (%)	3 (0.05)	6 (0.09)	12 (1.0)	9 (0.7)	31 (0.9)	26 (0.7)
OR, (95% CI)	NA		NA		NA	
Table constructed from Table 3 Powles 2007, Table 7 Cuzick 2015 and text Fisher 2005						

> The pivotal meta-analysis (Cuzick 2013) commented that '*No trial was designed to look at mortality as an endpoint, and no effect of any SERM was reported for all causes of death*' and that '*No effect on breast cancer death was reported in the tamoxifen trials'*. The Nelson 2013 systematic review also found that tamoxifen did not reduce breast cancer–specific mortality (RR 1.07, 95%CI 0.66-1.74) or all-cause mortality (RR 1.07, 95%CI 0.90-1.27).

A reduction in the incidence of breast cancer has not translated into a reduction in breast-cancer specific or all-cause mortality during follow-up of up to 20 years. Could the sponsor comment on this?

Clinical Question Efficacy 6

Quality of life was a secondary outcome measure in the NSABP P1 trial. This outcome was not reported in the main publications related to this trial. A publication of the analysis of the results for the first 36 months of follow-up was reported in

> Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999; 17:2659–69.

This publication was not included by the sponsor (see also Clinical Question Search Strategy and Results 3).

Could the sponsor provide a discussion of the effect of tamoxifen, when used for risk reduction, on quality of life?

Clinical Question Efficacy 7

Adherence with the treatment regimen will be an important factor in the proposed indication. Available information would indicate that adherence to the treatment regimen was low, although this measure, together with treatment discontinuations, was poorly described in the pivotal trials. In the Royal Marsden trial, 35.5% of women did not complete the planned 8 years of treatment (25.8% of the tamoxifen group and 14.3% of the placebo group, P=0.002). In Day 2001, it was reported that 3539 women in the NSABP P1 trial completed an 'Off therapy form' after discontinuing treatment with tamoxifen early and that '*The most frequent reasons for going off therapy were nonmedical in nature (1667 women [47.1%]), perceived toxic effects (921 women [26.0%]), and various protocol and nonprotocol medical conditions (841 women [23.8%])'* (page 1620). The meta-analysis Nelson 2013 found that (page 608): *In NSABP P-1, 41% of participants took 100% of study medication and 79% took at least 76% of study medication at 36 months. Forgetting was the primary reason for nonadherence for 62% of women at 36 months.* In a review of adherence and compliance, Nelson 2013 also found that (page 608): *A study of women with elevated risk scores reported that 12% of women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided (68). Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining. However, 90% of women stated that they would take a medication with the same benefit as tamoxifen if it had no side effects, and one half would take a medication with the same side effects as tamoxifen if it could eliminate the chance of getting breast cancer.*

Could the sponsor discuss likely take up of tamoxifen for the proposed indication and adherence to the 5 year regimen in the Australian population?

12.4. Safety

Clinical Question Safety 1

The Clinical Overview in the Assessment of Safety makes the statement in relation to fractures:

'*No significant differences in the incidence of fractures were observed in IBIS-I, NSABP P1, or the Cuzick 2013 meta-analysis. Thus, there was no evidence in the primary prevention trials to suggest that tamoxifen affects fracture risk in women who are at increased risk of breast cancer*'.

A differential effect of tamoxifen on bone density according to menopausal status was demonstrated in a sub-group of the Royal Marsden trial (Powles 1996). This found that in premenopausal women, the mean spinal and hip BMD for women on tamoxifen were significantly less than for women on placebo. In postmenopausal women, there was a significant increase in BMD at both the lumbar spine and the hip in the tamoxifen group and a small but not significant decrease in BMD at the lumbar spine and hip, so that there was a significant increase in BMD in the tamoxifen group compared to the placebo group. Presentation of results

regarding osteoporotic fractures was not broken down according to menopausal status in Cuzick 2013, IBIS-1 and NSABP P1. A differential effect according to menopausal status cannot therefore be excluded.

Could the sponsor please comment on the possible differential effect of tamoxifen on fracture risk according to menopausal state? The evaluator suggests that a statement regarding possible reduction in bone density in premenopausal women be included in the PRECAUTIONS section of the PI (see TGA Clinical Question PI 5) and in the CMI

13. Second round evaluation of clinical data submitted in response to questions

13.1. Clinical questions

13.1.1. Search Strategy and Results

13.1.1.1. Clinical Question Search Strategy and Results 1

Sponsor's response

Of the 14 publications related to breast cancer risk reduction which were placed in the category 'women at less than increased risk of breast cancer', 13 of the publications arose from the Italian trial which largely enrolled women at low to normal risk of breast cancer (Bonanni et al. 1999). The remaining publication in this group was a population-based case control study in women taking tamoxifen or raloxifene (DeMichele et al. 2008). This remaining publication should have been included under 'Unrelated indication' given that it included women who had previously had breast cancer. The main findings from the Italian trial are summarised below and abstracts for the 13 articles are included.

The Italian trial included women aged 35 to 70 years who had undergone a hysterectomy (to eliminate their risk of developing endometrial cancer while on tamoxifen). This trial was excluded from the submission because it did not assess breast cancer risk before enrolling women in the trial. Furthermore, when the 5408 women were stratified according to breast cancer risk, 87% of the women were found to be at low risk of developing hormone receptor positive (HR+) breast cancer (Table 2): 53% of women in the study had had both ovaries removed during their hysterectomy (which reduced their risk of developing HR+ breast cancer); 34% of women with at least 1 ovary were also classified as low risk; and only 13% of women were classified as 'high risk' for developing HR+ breast cancer. Furthermore, in this study, the definition of high risk was applied retrospectively and included women who were taller than 160 cm, had at least 1 intact ovary, were younger than 14 years at menarche, and had no full-term pregnancy before age 24 years.

Efficacy

In the most recent analysis conducted after 11 months of follow up, no significant difference in overall breast cancer incidence was observed between the tamoxifen and placebo groups (74 placebo versus 62 tamoxifen; risk ration (RR) 0.84, 95% confidence interval (CI) 0.60-1.17; Table 2; Veronesi et al. 2007). Similarly, in both the low risk categories in the Italian trial, the differences between the treatment groups were not significant. However, in the 'high risk' group defined above, significantly fewer women in the tamoxifen group developed breast cancer during the trial compared to the placebo group (24 placebo versus 6 tamoxifen; RR 0.24, 95% CI = 0.10 to 0.59). Thus, in the subpopulation of women defined as 'high risk' in the Italian trial, the results are consistent with the conclusions drawn from the pivotal trials in the original submission.

Table 11: Breast cancer incidence in the Italian trial

Class of risk	Placebo N = 2708 n (%)	Tamoxifen N = 2700 n (%)	Breast cancer incidence Placebo vs tamoxifen
Overall	2708	2700	74 vs 62; RR 0.84, 95% CI 0.60-1.17
Without ovaries	1458 (53.8%)	1406 (52.1%)	29 vs 24; RR 0.86, 95% CI 0.50-1.47
Low risk[a]	900 (33.2%)	942 (34.9%)	21 vs 32; RR 1.46, 95% CI 0.84-2.53
High risk[a]	350 (12.9%)	352 (13.0%)	24 vs 6; RR 0.24, 95% CI 0.10-0.59

[a] The high risk group was defined women who were taller than 160 cm, had at least 1 intact ovary, were younger than 14 years at menarche, and had no full-term pregnancy before age 24 years; the low risk group was defined as all remaining women in the study who had one intact ovary.
Data is from Tables 2 and 3 in Veronesi et al 2007.

Safety

The safety profile of tamoxifen in the Italian trial was similar to the pivotal trials included in this submission. During the 5 year treatment period of the Italian trial, significantly more vasomotor symptoms were reported, which was largely attributed to the increased incidence of hot flashes and vaginal discharge in the tamoxifen group (Table 3; Veronesi et al. 2007). The number of venous thromboembolic events (VTEs) during the 5 year treatment period was 28 for placebo and 44 for tamoxifen (HR 1.63, 95% CI 1.02-2.62). The increase in VTEs in the tamoxifen group was attributed solely to an increase in superficial phlebitis of the legs; all other VTEs were similar in the placebo and tamoxifen group (Decensi et al. 2005).

Table 12: Numbers and incidence rates of selected adverse events in the placebo and tamoxifen groups during treatment in the Italian trial

Adverse event	No. of events		Risk ratio (95% CI) Tamoxifen vs placebo
	Placebo	Tamoxifen	
Hot flashes [a]	446	635	1.78 (1.57 to 2.00)
Vaginal dryness [a]	269	295	1.14 (0.97 to 1.34)
Vaginal discharges [a]	173	505	3.44 (2.90 to 4.09)
Urinary disturbances	140	202	1.52 (1.23 to 1.89)
Headache	95	63	0.68 (0.50 to 0.94)
Cardiac arrhythmias/atrial fibrillation	21	35	1.73 (1.01 to 2.98)
Cerebrovascular events	7	12	1.78 (0.70 to 4.52)
Thromboembolic events	28	44	1.63 (1.02 to 2.62)

[a] Among women who were free of symptoms at baseline.

CI = confidence interval. Data is from Table 4 in Veronesi et al. 2007

No differences were observed in the overall rate of death (RR=0.95, 95% CI = 0.60 to 1.49) or death due to specific causes (Veronesi et al. 2007). Cancer and colorectal cancer were the most common causes of death and they were similar in the tamoxifen and placebo groups.

Evaluator's Comment

This is helpful.

13.1.1.2. Clinical Question Search Strategy and Results 2

Sponsor's response

In the Italian trial, the majority of the women were considered low to normal risk of developing breast cancer (Bonanni et al. 1999). Only 13% of the women were considered at high risk and this definition of high risk was applied retrospectively (see response to Clinical Question Search Strategy and Results 1 in Section 3.2) (Veronesi et al. 2007). Due to the low numbers of women at increased risk, and the high numbers of women at low risk, the benefit of tamoxifen therapy for breast cancer risk reduction in women at increased risk of breast cancer could not be determined in the Italian trial. On the other hand, in the HOT study, 72% of women had a 5-year Gail breast cancer risk ≥1 and 28% of these women had a risk of ≥ 1.5. In addition, the women were on HRT (an inclusion criteria), which further increases the risk of breast cancer (Chlebowski et al. 2003). Thus, most women in the HOT study were at increased risk of breast cancer.

Evaluator's comment

The evaluator accepts the rationale for including the HOT study and excluding the Italian study on the basis of the perceived differing risk of breast cancer in the participants of the two studies.

13.1.1.3. Clinical Question Search Strategy and Results 3

Sponsor's response

In the approved search strategy, the safety outcome measures were defined as 'any adverse events in the indication'. The sponsor did not consider health-related quality of life (QoL) an 'adverse event' and therefore Day et al. 1999 was not included. However, the sponsor does agree with the evaluator that QoL outcomes are relevant and important when weighing up the benefits and risks of tamoxifen, particularly when used for primary risk reduction. For this reason, we have added a paragraph on the QoL findings in the CLINICAL TRIALS section of the PI. The rationale for including the sentence in the PI and a summary of the findings from this study has been included in response to Clinical Question Efficacy 6.

Evaluator's comment

This is acceptable

13.1.2. Clinical Question Search Strategy and Results 4

Sponsor's response

Fallowfield et al. 2001 was categorised as a meta-analysis because data from two separate studies were pooled to assess psychosocial characteristics and changes in anxiety, mood, and sexual functioning. These data were included because this is one of the few studies to provide information on these outcomes. However, psychological characteristics were not the primary endpoints for these trials and the evaluator is correct that Fallowfield et al. 2001 may be considered as an ancillary pooled analysis.

Evaluator's comment

Fallowfield et al appeared to use a convenience sample of participants from the two studies to complete regular surveys that provided information regarding these psychosocial outcomes. The evaluator agrees that this was one of few studies to address these issues and that it was important to include this study

1.1.2. Pharmacodynamics

Nil

1.1.3. Efficacy

13.1.3. Clinical Question Efficacy 1

Sponsor's response

The sponsor can confirm that the results presented from the Cuzick 2013 meta-analysis are from Table 2, rows 5 to 8 (page 1829) which summarises the analysis of individual patient data from the Royal Marsden, IBIS-I, NSABP-P1 and Italian trials which were all tamoxifen trials (Cuzick et al. 2013). These data are presented in the Summary of Clinical Efficacy and in the PI. Results from the combined analysis of all SERMs have not been included in this submission.

Evaluator's Comment

This is acceptable

13.1.4. Clinical Question Efficacy 2

Sponsor's response

The sponsor thanks the evaluator for pointing out these errors. The first statement 'In the Cuzick 2013 meta-analysis, tamoxifen was the only drug shown to be effective for the primary prevention of breast cancer in premenopausal women' is incorrect. This statement is not a finding of the Cuzick 2013 meta-analysis, but is a statement made on page 1833 of the discussion: '*Only tamoxifen has been assessed in premenopausal women, in whom it is the only drug with proven effectiveness'* (Cuzick et al. 2013).

In IBIS-I, breast cancer incidence was reported separately for pre and postmenopausal women in the 96-month analysis (Cuzick et al. 2007) but not the final analysis (Cuzick et al. 2015). In the 96-month analysis, tamoxifen significantly reduced the risk of breast cancer in premenopausal women compared with placebo (placebo 88 events, tamoxifen, 58 events; RR0.67, 95% CI 0.47 to 0.95). In postmenopausal women, there was no significant difference between the treatment groups (placebo 107 events, tamoxifen 84 events; RR 0.77, 95% CI 0.57 to 1.04).

In the Royal Marsden trial, the evaluator correctly points out that a significant reduction in all breast cancer events was found in premenopausal women (tamoxifen 14 events versus placebo 28 events, hazard ratio [HR] 0.5, 95% CI 0.26-0.95. P 0.03) but not in postmenopausal women (tamoxifen 9 events versus placebo 19 events, HR 0.46, 95% CI 0.21-1.02, P0.06) (Powles et al. 2007). The lack of statistical significance in postmenopausal women in the Royal Marsden study, despite less than half of the events occurring in the tamoxifen versus placebo group, is explained by the few events that were reported overall and the lack of statistical power to detect a difference.

Evaluator's comment

This would suggest that any benefit of tamoxifen in post-menopausal women for primary breast cancer risk reduction has not been established. Given that this group is more at risk of adverse events, it may be appropriate to provide a comment regarding the use of tamoxifen for this purpose in post-menopausal women. The most recent proposed PI includes the following statement, in the Clinical Trials section, under the 'Effects of Age*: No age-related effects of tamoxifen on breast cancer incidence were reported in the primary risk reduction trials*.'

Change this to Effects of Age and Menopausal Status

No age-related effects of tamoxifen on breast cancer incidence were reported in the primary risk reduction trials. Analysis according to menopausal status was performed in the 96 month analysis of IBIS-1 and the Royal Marden study. These found that tamoxifen significantly reduced the risk of breast cancer in premenopausal women but not in post-menopausal women.

13.1.5. Clinical Question Efficacy 3

Sponsor's response

The sponsor confirms that the above statement was derived from Table 3 in Fisher et al. 2005. Specifically, they report that women with 2 first degree relatives had a 37% reduction in risk with tamoxifen and women with 3 first-degree relatives had a 51% reduction in risk. In the PBRER this was approximated to 40% (as substantially more women had 2 relatives than 3).

Evaluator's comment

Given that the analysis provided in Fisher 2005 presents risk factors individually, regardless of other co-existing risk factors, this interpretation of risk reduction according to the risk factor of family history can only be considered an approximation on a number of levels. It is appropriate that no specific reference is made to this in the PI.

13.1.6. Clinical Question Efficacy 4

Sponsor's response

The sponsor agrees with the evaluator that there is too little evidence to determine the effect on the incidence of breast cancer in women with the high risk mutations BRCA1 (breast cancer 1, early onset gene) and BRCA 2 (breast cancer 2, early onset gene). This is also true for various other potential subgroups that the evaluator has not suggested a specific notation about, for example women with mutations in other breast cancer predisposition genes, women with previous chest irradiation, or women with multiple cancer risk associated single-nucleotide polymorphisms. Other reasons for not including such a statement include:

- While the NSABP-P1 subgroup analysis does not clearly show that tamoxifen reduces breast cancer risk in BRCA1 or BRCA2 mutation carriers, it also does not provide any evidence to exclude an effect; the substudy was underpowered which is why the confidence intervals both for BRCA1 and BRCA2 are very wide (King et al. 2001). Including the suggested statement in the PI might therefore be misleading especially given new information is emerging all the time.
- Observational studies have shown that tamoxifen is associated with reduced contralateral breast cancer risk in both BRCA1 and BRCA2 mutation carriers in the secondary prevention setting (Phillips et al. 2013, Phillips et al. 2014).
- Mouse model and in vitro data are consistent with role of oestrogen in breast tumour initiation in BRCA mutation carriers (Phillips et al. 2014).
- Women who are at very high risk for breast cancer have few options available to them: in Australia only about 20% choose to undergo bilateral risk-reducing mastectomy and only 26% undergo risk-reducing oophorectomy before age 40 (when it may be expected to reduce breast cancer risk substantially) (Collins et al. 2013). Putting the proposed statement in the PI might dissuade health professionals from prescribing tamoxifen to women who refuse, or wish to postpone, risk-reducing surgery, leaving those women with no option to reduce their very high breast cancer risk.

Evaluator's Comment

The evaluator accepts that this is a difficult area and that specific notations regarding other risk groups as listed by the sponsor have not been suggested by the evaluator. However, the effect of tamoxifen as primary risk reduction for breast cancer was only discussed in relation to the sub-group of women with BRCA1 and BRCA2 mutations in the dossier provided. This reflects the status of these high risk mutations, with this also demonstrated by the statement in Phillips et al 2014 that '*The most important BC risk factors are age, family history, mammographic density, certain types of proliferative breast disease and having a mutation in genes such as BRCA1 or BRCA2.'* With regard to the other concerns raised by the sponsor:

- If new information emerges that demonstrates efficacy, or lack of efficacy, then the PI can be adjusted accordingly through standard processes
- The observational studies in secondary prevention in women with breast cancer and mouse studies may indicate some efficacy of tamoxifen in these settings, with all the caveats that pertain to observational studies and animal studies, but this is not generalisable to primary risk reduction in women at increased risk of breast cancer.
- The concern that inclusion of the statement may dissuade health professionals from prescribing tamoxifen to women with limited options presupposes that tamoxifen is efficacious in this setting. This has not been established.

The evaluator remains of the opinion that a statement regarding the lack of knowledge regarding the effect of tamoxifen in women with BRCA1 and BRCA2 mutations is appropriate with wording such as:

> *There is currently too little evidence to determine the effect on the incidence of breast cancer in women with the high risk mutations BRCA1 and BRCA 2. The effect of tamoxifen on the incidence of breast cancer following risk-reducing bilateral salpingo-oophorectomy in these women is also unknown*

13.1.7. Clinical Question Efficacy 5

Sponsor's response

As pointed out by the investigator, no significant differences in mortality were observed between the tamoxifen and placebo groups in any of the trials.

However, these trials cannot exclude an effect of tamoxifen on mortality because none of the trials were powered to find a difference in mortality between the groups. A detailed discussion on this topic as well as the proposed wording in the revised PI can be found in the response to Clinical Question PI 1 in Section 3.5 [beyond the scope of this AusPAR].

Evaluator's Comment

Noted.

13.1.8. Clinical Question Efficacy 6

Sponsor's response

Day et al. 1999 reported health-related QoL in women enrolled in the NSABP-1 trial during the first 36 months after randomisation. Of the 13,388 women in the NSAPB-1 trial, 11,064 were recruited to the trial.

The following self-reported questionnaires were used to assess QoL:

- The Centre for Epidemiological Studies – Depression Scale (CES-D, 20 items)
- The Medical Outcomes Study (MOS) 36-item Short Form Health Status Survey (SP-36, 36-items); results are split into the physical component summary (PCS) and mental component summary (MCS).
- The MOS sexual functioning scale (5 items)
- A symptom checklist (SCL 43 items)

Adherence declined over time in both groups but was similar in the tamoxifen and placebo group. The most common reason for stopping treatment was hot flashes (n=251) and these were more frequent in the tamoxifen group (n=184 women).

In the CES-D a score of ≥ 16 was considered clinically significant. Over the 36-month treatment period, the proportion of women with a score ≥ 16 was similar between the tamoxifen and

placebo groups. Similar results were seen with the MOS SF-36 mental health subscale. Thus, there was no sign that women on tamoxifen were more susceptible to depression.

In the SF-36 physical component summary, no significant differences were observed between the tamoxifen and placebo groups for women aged 35 to 49 or ≥ years. However, women aged 50 to 59 years had significantly lower PCS scores with tamoxifen versus placebo but the differences were very small (≤ 10% of a standard deviation). Thus, based on the SF-36, tamoxifen does not impact general physical health in women compared to placebo.

In the SCL, the number of reported symptoms was higher in the tamoxifen group than the placebo group for vasomotor symptoms, gynaecological symptoms, and sexual functioning symptoms. These findings are consistent with the known safety profile of tamoxifen and with the current PI. Tamoxifen also did not significantly increase the frequency of reported changes in body weight.

In the MOS sexual functioning scale, small but significant differences were seen between the treatment groups for the following items: Sexually active last six months (mean difference 0.78%, P = 0.031); Lack of sexual interest (mean difference 0.74%, P = 0.031); Difficulty becoming sexually aroused (mean difference 0.93%, P = 0.016); and Difficulty in having an orgasm (mean difference 1.24%, P = 0.016). However, no difference was seen for the item Unable to relax and enjoy sex (P = 0.453).

In a separately-reported analysis, women were prospectively assessed for depression risk and placed in a high-, medium-, or low-risk groups (Day et al. 2001). This study showed no differences in the proportion of women with depression between the tamoxifen and placebo groups, irrespective of baseline risk for depression.

Thus, based on the results of this QoL substudies from the NSABP trial, tamoxifen is well tolerated in healthy women. There was no sign that tamoxifen increased depression or weight gain, and the reported symptoms were consistent with the known safety profile of tamoxifen.

Given the importance of QoL data in assessing the benefits and risks of a treatment, particularly in a primary risk reduction setting, a summary of the QoL findings has been added to the Clinical trials section of the PI:

> '*In the health-related quality of life component of NSABP-1 trial, which included 11,064 of the 13,388 women enrolled in the trial, tamoxifen did not increase the rate of depression or mental health problems in general. Tamoxifen did not significantly increase the frequency of reported changes in body weight. Vasomotor and gynaecological symptoms were reported significantly more frequently in the tamoxifen group, consistent with the known safety profile of tamoxifen. Some sexual functioning symptoms were reported more frequently in the tamoxifen group, but the differences were very small (mean differences between the treatment groups ranged from 0.54% to 1.24%).*'

Evaluator's Comment

The evaluator thanks the sponsor for this analysis and agrees with the inclusion of the proposed summary of the QoL findings in the PI.

13.1.9. Clinical Question Efficacy 7

Sponsor's response

The sponsor anticipates that the uptake of tamoxifen for breast cancer risk reduction will be approximately 15%, based on two meta-analyses of uptake rates of primary risk-reducing medications (Ropka et al. 2010; Smith et al. 2015). The sponsor anticipates that adherence might be similar to that which was seen in the clinical trials.

Evaluator's Comment

The sponsor's cited references, each a meta-analysis of patient decisions about breast cancer chemoprevention, indicate that both uptake and adherence over five years are likely to be very low. No clear factors contributing to this were identified.

1.1.4. Safety

13.1.10. Clinical Question Safety 1

Sponsor's response

The evaluator correctly points out that the Royal Marsden trial showed a reduction in bone mineral density in premenopausal women in the tamoxifen group versus the placebo group (Powles et al. 1996). In postmenopausal women, tamoxifen has the opposite effect on bone mineral density. The implications of the reduced bone density in premenopausal women are not known. Fracture risk was not assessed in the Royal Marsden trial and the other pivotal trials did not find any significant differences in fracture risk between the tamoxifen and placebo groups. The Royal Marsden trial authors point out that their finding is consistent with mouse model data. They also state that the clinical significance of this reduced bone density is uncertain, and point out that it is reversible in other settings where bone density is reduced, for example, after withdrawal of medroxyprogesterone acetate or a luteinizing hormone-releasing hormone agonist.

Therefore, it is not clear whether there are any long-term implications of the reduced density in premenopausal women and it may be reversible when treatment is stopped. A statement regarding a possible reduction in bone density has been added to the PI.

Evaluator's Comment

This is acceptable. The evaluator notes the change in wording for proposed inclusion in the PI from 'reduce their risk of fracture' to 'maintain bone health'. This is acceptable.

14. Second round benefit-risk assessment

14.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tamoxifen in the proposed usage are unchanged from those identified in the First round evaluation.

14.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of tamoxifen in the proposed usage are unchanged from those identified in the First round evaluation.

14.3. Second round assessment of benefit-risk balance

The benefit-risk balance of tamoxifen is favourable given the proposed usage, provided the changes recommended are adopted.

15. Second round recommendation regarding authorisation

The evaluator recommends that tamoxifen be approved for the proposed usage, provided the suggestions made with regard to the PI and CMI are agreed to.

15.1. Indications

The evaluator agrees with the change in wording from 'prevention' to 'reduction of breast cancer risk' and removal of the reference to validated algorithms. However, the evaluator considers that the following advice be retained:

> *Treatment should be initiated by a specialist with expertise in managing breast cancer or familial cancer*

16. References

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17. Description of Individual Publications

IBIS – 1 Description of Individual Publications

The International Breast Cancer Intervention Study (IBIS-I) (clinicaltrials.gov - NCT00002644)		
Trial description	Double-blind placebo-controlled randomised trial of tamoxifen, 20 mg/day for 5 years, in 7152 women aged 35–70 years, who were at increased risk of breast cancer. The primary outcome measure was the frequency of breast cancer (including ductal carcinoma in situ). Analyses were by intention to treat. Predefined subgroups were oestrogen receptor status of the cancer, use of hormonal replacement therapy, and age (<50, ≥50 years) Secondary endpoints were other cancers, thromboembolic events, cardiovascular events, and cause-specific mortality.	
Related Publications		
Key Publication (s)	**Relationship to Trial**	**Page**
Cuzick 2002	First publication of results (median follow-up 50 months after randomisation)	72
Cuzick 2007	Long term results – 10 year follow up (median follow-up 96 months after randomization)	81

The International Breast Cancer Intervention Study (IBIS-I) (clinicaltrials.gov - NCT00002644)		
Cuzick 2015	Extended Long term results - 20 year follow-up (median follow up 16 years)	85
Related Publications**		
Efficacy/safety		90
Sestak 2012b	Retrospective, case control, nested, sub-group analysis of the effect of the CYP2D6 phenotype on the development of ER-positive invasive breast cancer	
Safety		91
Duggan 2003	Case control, nested analysis to investigate the association between acquired and inherited risk factors for VTE	91
Sestak 2012a	Retrospective subgroup analysis of the IBIS-1 population to assess the effect of tamoxifen on weight gain in breast cancer prevention	93
Palva 2013	To investigate the effects of 5-years of tamoxifen use on endometrium and gynaecological symptoms in the IBIS-1 population (?total or subgroup)	94
Sestak 2006	Retrospective analysis of the IBIS-1 population to investigate the influence of HRT on tamoxifen-induced vasomotor symptoms	95
*Trial acronyms refer to the trials described above ** A list of citations is provided in Section 19, starting on page68 of this report		
Comments: • A detailed description of the trial method is provided in the description of the first publication. This is supplemented with information from subsequent publications where appropriate (and identified as such). The description of the trial method is not repeated for the subsequent publications. A brief description of each publication is provided with results described in appropriate details. • All figures and Tables are copied from the relevant publication (with original captions) unless otherwise specified. • Both safety and efficacy results are provided in the publication description The evaluator's opinion of the publication results is provided following the publication description. It can be identified by Calibri font and shading		

IBIS – 1 Key Publications (Efficacy and Safety)

Cuzick 2002

Publication Identifier	**Cuzick 2002, Efficacy and Safety, Primary Supportive**
Citation	**Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet. 2002;360(9336):817-24.**
Relationship to trial	First publication of results of the IBIS - 1 trial with 5 year follow-up (median 50 months from randomisation)
Documented	The following statement is provided: *Approval of the local ethics committee from each centre was*

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive
GCP or ethics approval	*obtained*. The trial was done under the auspices of the UK Coordinating Committee for Cancer Research (now part of the National Cancer Research Network) in the UK and the Australia New Zealand Breast Cancer Trials Group in Australia and New Zealand.
Conflict of Interest	Of the authors, M Baum, J Cuzick and J Forbes have served as occasional consultants and advisory board members to AstraZeneca and are principal investigators for trials for which their institutions receive funding from AstraZeneca.
Funding source(s)	The IBIS Trial was supported in the UK by Cancer Research UK. In Australia it was supported by the National Health and Medical Research Council grants awarded to the ANZ Breast Cancer Trials Group, University of Newcastle The following statement is provided: *The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The manufacturers (AstraZeneca) supplied tamoxifen and matching placebo without charge and provided technical advice, but were not involved in the conduct or analysis of the trial*.
Study design	multinational double-blind placebo-controlled randomised trial
Study Location	UK, Australia, New Zealand, and some European countries (from the 2015 publication: Finland, Spain, Switzerland, Belgium, and Ireland)
Study Dates	Recruitment occurred between April 1992 and March 2001; the cut-off date of follow-up for the analysis was Jan 1 2002.
Study treatment	Participants were randomly assigned (1:1) to receive either oral tamoxifen or oral placebo every day for 5 years in the absence of breast cancer development or pregnancy. Participants were followed every 6 months for 5 years (with mammography was done every 12–18 months); then annually (by annual questionnaire or clinical visit) for up to 5 years.
Study population	Women aged 35 to 70 years with an increased risk of breast cancer; 60% were from the UK, 37% from Australia or New Zealand, and 3% from the rest of Europe
Key selection criteria	Eligible women had to have risk factors for breast cancer indicating at least a two-fold relative risk if they were aged 45 to 70 years, a four-fold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to 39 years Further detail (from 2007 publication): • Women were eligible from age 45 years if they had 1) a mother or sister diagnosed with breast cancer before the age of 50 years, 2) two first- or second-degree relatives with breast cancer at any age, or 3) a first-degree relative with breast cancer at any age, and either were nulliparous or had a previous hyperplastic benign lesion • Women were eligible from the age of 40 years if they had 1) atypical ductal or lobular hyperplasia, 2) a first-degree relative with bilateral breast cancer at any age, or 3) two first- or second-degree relatives with breast cancer, one of whom was diagnosed before age 50 years • Women were eligible from the age of 35 years if they had either 1) lobular carcinoma in situ or 2) two first-degree relatives with breast cancer, both diagnosed before the age of 50 years • any women with an estimated 10-year risk of 5% or more, based on a complex model, were also eligible as risk equivalent after approval by the study chairman All women had a baseline mammogram within the previous 12 months or at the time of randomisation to exclude pre-existing breast cancer

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive
	Women with a history of thromboembolic disease or current use of anticoagulants or a life expectancy judged to be less than 10 year or women who were pregnant or wished to become pregnant were excluded
Concurrent medications	Hormone replacement therapy for menopausal symptoms allowed at lowest effective dose; no anticoagulants
Study Location	UK, Australia, New Zealand, and some European countries. Participants: 60% were from the UK, 37% from Australia or New Zealand, and 3% from the rest of Europe.
Study Dates	April 1992 to March 2001. In January 2002, the data monitoring committee decided the results were sufficiently mature for publication: the cut-off date of follow-up for the analysis was Jan 1 2002.
Outcome measure(s)	Frequency of breast cancer (including ductal carcinoma in situ). Cause specific mortality Compliance was measured by pill counts at each 6-month follow-up visit.
Safety measure(s)	Deaths, endometrial cancer, other cancers, venous thromboembolic events, cardiovascular events Adverse events: Details of any side-effects were collected at every visit, both as predefined items and free text and coded according to the NHS Read codes. Symptoms, diagnoses, and procedures were each recorded separately. Comment: From the 2007 publication, the predefined illness categories were myocardial infarction, other cardiovascular events, thromboembolic diseases, gynaecologic problems, visual disturbances, fractures, osteoporosis, and any non-breast cancer. The pre-defined side effects were: nausea, vomiting, hot flushes, headaches, vaginal discharge, vaginal dryness, and vaginal bleeding. Each was recorded as mild, moderate, or severe.
Randomisation	Randomisation was done centrally by telephone or fax, stratified by centre and balanced in blocks of eight. The lists were then randomly permuted again in blocks of six to ten (chosen randomly) to ensure that the last member of each block was not predictable
Blinding	Both investigators and patients remain blinded to treatment allocation. Endpoints and deaths were externally reviewed and coded with masking of treatment allocation. Comment: From the 2007 publication, the codes for 284 women were broken before they completed the 5 years of active treatment. The circumstances under which this occurred is not described in either publication
Statistical analysis	With and enrolment of 7000, the trial was powered to detect a 40% compliance adjusted reduction in the rate of breast cancer including ductal carcinoma in situ. For 90% power, 164 events would be required. Analyses were mainly based on comparison of proportions by odds ratios, and Fisher's exact values were used where appropriate. Major comparisons were expressed as odds ratios, with hazard ratios used for rare events. All p values are two-sided and confidence intervals were based on a normal approximation. Analyses were by intention to treat, after exclusion of the 13 women found to have breast cancer at baseline.

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive

Participant Flow

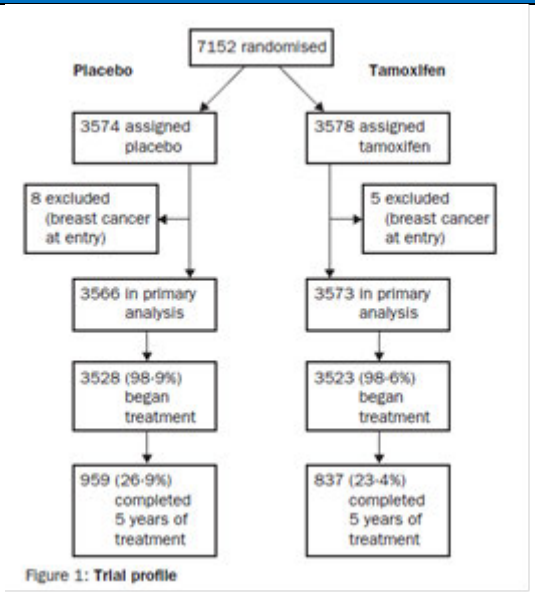


Figure 1: **Trial profile**

Of the women who had a baseline mammogram at the time of randomisation, 13 were found to have a pre-existing breast cancer and did not continue in the trial. These patients were excluded from the intention to treat analysis.

Comment: it is not clear if these 13 women were included in the ITT population in subsequent publications.

At the time of data lock, 25% of women had completed a full 5 years of treatment (959 [26·9%] placebo *vs* 837 [23·4%] tamoxifen) and a further 47% were still on treatment (1760 [49·4%] *vs* 1574 [44·0%]). Full compliance to 5 years was estimated to be 64% in the tamoxifen group and 74% in the placebo group (p<0·001).

Comment: A total of 2029 women are not accounted for in the participant flow provided. This number includes:

- women described as "in the primary analysis" but who did not begin treatment (58 in the placebo group and 50 in the tamoxifen group)
- 809 of the 3528 women who commenced treatment with placebo and who had not completed 5 years of treatment (959) or were still in treatment at data lock (1760)
- 1112 of the 3523 women who commenced treatment with tamoxifen and who had not completed 5 years of treatment (837) or were still in treatment at data lock (1574)

The article provides no breakdown/description of these 2029 women

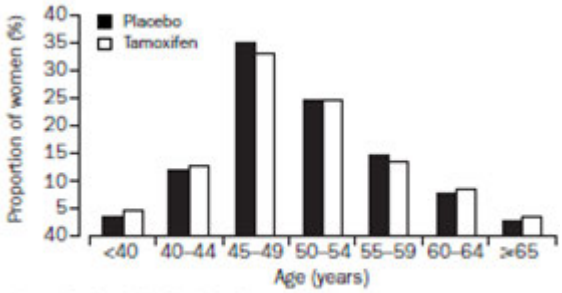
From the 2007 study, 2574/3566 [72%] women in the placebo group and 2287/3573 [63.9%] women in the tamoxifen group completed 5 years of treatment.

Baseline Characteristics of Participants

	Placebo (n=3566)	Tamoxifen (n=3573)
Demography		
Mean (SD) age, years	50·8 (6·7)	50·7 (7·0)
Postmenopausal	1740 (48·8%)	1761 (49·3%)
HRT use		
Before entry	1443 (40·5%)	1469 (41·1%)
During trial	1399 (39·2%)	1445 (40·4%)
Ever	1783 (50·0%)	1849 (51·7%)
Anthropometry		
Mean (SD) height, cm	162·9 (6·4)	162·8 (6·6)
Mean (SD) weight, kg	71·4 (14·0)	71·7 (14·5)
Mean (SD) body-mass index, kg/m²	26·9 (5·1)	27·0 (5·3)
Hysterectomy		
All	1283 (36·0%)	1232 (34·5%)
With both ovaries retained	737 (20·7%)	711 (19·9%)
One ovary removed	207 (5·8%)	229 (6·4%)
Both ovaries removed	327 (9·2%)	281 (7·9%)

Data are number of women unless otherwise stated.

Table 2: **Baseline characteristics and HRT use**

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive
Age Distribution	 Figure 3: **Age distribution of participants**
Distribution of Risk Factor(s) for the development of Breast Cancer	**Risk factor** / **Placebo (n=3566)** / **Tamoxifen (n=3573)** First-degree relative who developed breast cancer at or before age 50: 1744 (48·9%) / 1689 (47·3%) First-degree relative with bilateral breast cancer*: 601 (16·9%) / 579 (16·2%) Two or more first-degree or second-degree relatives with breast cancer†: 2206 (61·9%) / 2204 (61·7%) Lobular carcinoma in situ: 44 (1·2%) / 44 (1·2%) Atypical hyperplasia: 104 (2·9%) / 97 (2·7%) Nulliparous and a first-degree relative who developed breast cancer: 325 (9·1%) / 314 (8·8%) Benign biopsy and first-degree relative who developed breast cancer: 132 (3·7%) / 123 (3·4%) Risk equivalent‡: 143 (4·0%) / 177 (5·0%) All criteria permit entry from age 45 years. Atypical hyperplasia permits entry from age 40 and lobular carcinoma in situ from age 35. Total number adds up to 148% of total entry because some women met several entry criteria. *Eligible from age 40 if relative had cancer before age 50 and at age 35 if relative's cancer was diagnosed before age 40. †Eligible from age 40 if both relatives developed breast cancer before age 50 and from age 35 if both relatives were first degree and developed breast cancer before age 50. ‡Risk-equivalent women were those with a strong family history, not fitting specific categories, but judged to be at higher risk than the minimum eligibility category by the study chairman. Table 1: **Entry criteria and distribution by treatment group** The yearly frequency of breast cancer in the absence of treatment was projected to be 7·50 per 1000; the actual frequency in the placebo group was 6·74 per 1000, which did not differ significantly from the projected frequency.
	The cut-off date of follow-up for the analysis was Jan 1, 2002. Median follow-up was 50 months (IQR 32–67). Full compliance to 5 years was estimated to be 64% in the tamoxifen group and 74% in the placebo group (p<0·001).
Efficacy Results	**Occurrence of Breast Cancer** After median follow-up of 50 months (IQR 32–67), 69 breast cancers had been diagnosed in 3578 women in the tamoxifen group and 101 in 3566 in the placebo group (risk reduction 32% [95% CI 8–50]; p=0·013).

Breast Cancer Characteristics by Treatment Allocation

(derived from publication table 3)

	Placebo Group	Tamoxifen Group	Odds Ratio, 95% CI
Total	101	69	0.68, 0.50-0.92
Invasiveness			
Invasive	85	64	0.75, 0.54-1.04
DCIS	16	5	0.31, 0.12-0.82
Unknown	0	1	
Invasive Cancers			

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive

ER status,			
ER +	63	44	0.69, 0.47-1.02
ER -	36	31	1.00, 0.53-1.87
Unknown	1	2	
Size (cm)			
<=1	51	39	0.72, 0.42-1.22
>1-2	78	44	0.69, 0.42-1.15
>2			0.59, 0.27-1.26
Unknown	1	2	

- Noninvasive breast cancer: tamoxifen vs placebo (5 vs 16; HR 0.31, 95% CI 0.12-0.82).
- ER-positive breast cancer: fewer events for tamoxifen vs placebo but the difference was not significant: (44 vs 63; HR 0.69, 95% CI 0.47-1.02).
- ER-negative breast cancer: tamoxifen vs placebo (19 vs 19; HR 1.00, 95% CI 0.53-1.87).

Of the invasive cancers, 69% were node negative, 72% were oestrogen-receptor (ER) positive, and 78% were 2 cm or less in diameter. Nodal status, size, and grade were similar in both study groups. Age and use of HRT did not significantly affect the risk reduction. There was no evidence that the degree of protection changed over the 5 years of treatment (see figure below).

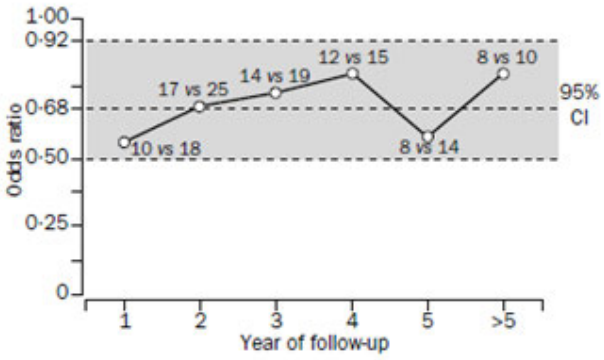


Figure 4: **Risk reduction with tamoxifen by year of follow-up**
Numbers on curve are the number of cancers in the tamoxifen group versus the number in the placebo group.

Mortality

There was a significant excess of deaths from all causes in the tamoxifen group (25 *vs* 11, p=0·028). Four deaths from breast cancer have been reported (two in each study group).

Increases are seen for cancers other than breast cancer, pulmonary embolisms, other vascular causes, and cardiac deaths.

Specific causes of death according to treatment allocation (derived from publication Table 7)		
Cause of Death	**Placebo (N=3566)**	**Tamoxifen (N= 3573)**

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive

Total	11	25
Breast cancer	2	2
Endometrial cancer	0	0
Colorectal cancer	1	4
Lung cancer	0	0
Ovarian cancer	2	0
Other cancer	1	4
Myocardial infarction	0	2
Other cardiac	0	3
DVT/PE	2	3
Stroke or CVA or SAH	1	2
Other	2	5

DVT = deep venous thrombosis, PE = pulmonary embolus, CVA = cerebrovascular accident, SAH = subarachnoid haemorrhage

Comment: This finding of increased mortality in the tamoxifen arm was described as unexpected and not in keeping with the other prevention trials (NSABP-P1 and the Italian trial). It was attributed by the authors to thromboembolic disease

Safety Results

Comment:

Discontinuations

No discussion of discontinuations is provided in this or subsequent follow-up reports. A total of

2029 women (28%) are not accounted for in the participant flow figure provided – it is not known if these women discontinued from the trial or if they were lost to follow up.

The related publication Sestak 2006 provides the information that higher discontinuation rates were seen in the tamoxifen group in the first 18 months.

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive

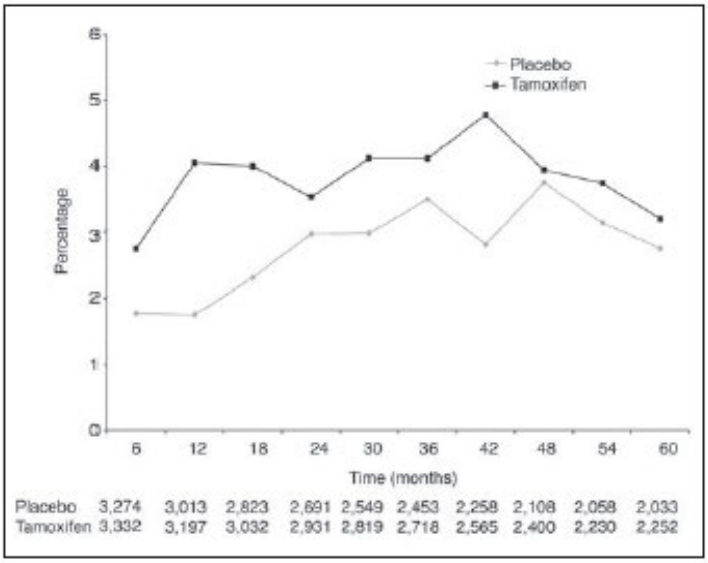


Fig 2. Dropouts according to treatment arm and follow-up time.

An analysis of a small sub-group in the Pavla 2013 publication found that the most common reason for discontinuation in the tamoxifen group was vasomotor symptoms.

Deaths:

See above

Endometrial cancer:

A non-significant increase in endometrial cancer was found in the tamoxifen group (11 *vs* five in the placebo group; odds ratio 2·20 [95% CI 0·80–6·06], p=0·2). Most of these cancers were in women who were older than 50 years at randomisation (ten tamoxifen group *vs* three placebo group), and all the women affected were postmenopausal at diagnosis. All but one of these cancers (a low-grade sarcoma in the placebo group) were adenocarcinomas, and all but one were FIGO stage I (i.e., localised tumours). There was no apparent relationship between endometrial cancer and HRT: 10 of the women with endometrial cancers had never used HRT (seven *vs* three), only four had used it during the trial (two *vs* two), and two in the tamoxifen group had used it before the trial The rate of endometrial cancer in the placebo group (34 per 100 000 woman-years) was similar to population rates for the UK and Australia.

Cancers other than Endometrial:

Other cancers were equally distributed between the two study groups (39 in each group), and no cancer differed significantly in frequency between the tamoxifen and placebo groups (colorectal nine *vs* six; stomach one *vs* three; liver none *vs* two; pancreas one *vs* none; lung three *vs* none; larynx one *vs* none; melanoma eight *vs* seven; bladder or kidney two *vs* three; ovary six in each group; endocrine two *vs* seven; meningioma two in each group; haematological or lymphatic two *vs* three; and two primary unknown cancers in the tamoxifen group).

Thromboembolic events:

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive

Event	Number of cases		p
	Placebo	Tamoxifen	
Venous thromboembolism (excluding superficial thrombophlebitis)			
All thromboembolism	17	43	0·001
Occurring within 3 months of leg surgery or fracture	5	20	0·004
Spontaneous	12	23	0·09
Pulmonary embolism	10	13	0·68
Deep-vein thrombosis	5	24	0·0005
Thrombosis (other)	2	6	0·29
Thrombophlebitis	9	27	0·004

Excerpt from publication Table 4 Thromboembolic, cerebrovascular and cardiac events according to treatment

Venous thromboembolic events were significantly increased with tamoxifen (43 *vs* 17; odds ratio 2·5 [1·5–4·4], p=0·001); 25 (42%) of these events occurred within 3 months of major surgery or after long-duration immobility with 20/25 in the tamoxifen group (p=0·004).

There were no differences in the numbers of cerebrovascular accidents, myocardial infarctions, or other vascular events. A more detailed analysis of factors affecting vascular events was published separately (Duggan 2003).

Adverse Events:

The major groupings that showed significant differences were vasomotor and gynaecological reports (see detail in tables below), which were about 21% higher in the tamoxifen than the placebo group, and breast complaints, which were 22% lower.

	Number of events (%)		p
	Placebo (n=3566)	Tamoxifen (n=3573)	
Side-effect			
Gynaecological or vasomotor	2414 (67·7%)	2922 (81·8%)	<0·0001
Headaches and migraines	1067 (29·9%)	997 (27·9%)	0·13
All fractures	127 (3·6%)	116 (3·3%)	0·52
Osteoporotic fractures (hip, spine, wrist, or forearm)	40 (1·1%)	45 (1·3%)	0·66
Breast complaints	675 (18·9%)	525 (14·7%)	<0·0001
Nail changes	96 (2·7%)	148 (4·1%)	0·001
Eye (excluding cataracts)	376 (10·5%)	373 (10·4%)	0·94
Cataracts	37 (1·0%)	38 (1·0%)	1·00

Table 5: **Side-effects reported at any time and of any severity, according to allocated treatment**

	Number of events (%)				p
	Premenopausal		Postmenopausal		
	Placebo (n=1826)	Tamoxifen (n=1810)	Placebo (n=1740)	Tamoxifen (n=1763)	
Procedures					
Hysteroscopy	107 (5·9%)	136 (7·5%)	31 (1·8%)	92 (5·2%)	<0·0001
Pelvic ultrasonography	89 (4·9%)	136 (7·5%)	43 (2·5%)	73 (4·1%)	<0·0001
Dilation and curettage	76 (4·2%)	106 (5·9%)	18 (1·0%)	72 (4·1%)	<0·0001
Hysterectomy	76 (4·2%)	118 (6·5%)	28 (1·6%)	36 (2·0%)	0·002
Oophorectomy	53 (2·9%)	76 (4·2%)	14 (0·8%)	27 (1·5%)	0·006
Symptoms					
Vasomotor symptoms	988 (54·1%)	1233 (68·0%)	849 (48·8%)	1219 (69·0%)	<0·0001
Vaginal discharge	266 (14·6%)	517 (28·6%)	237 (13·6%)	509 (28·9%)	<0·0001
Vaginal dryness	329 (18·0%)	379 (20·9%)	394 (22·6%)	403 (22·9%)	0·10
Abnormal bleeding	565 (30·9%)	669 (36·9%)	113 (6·5%)	173 (9·8%)	<0·0001
Endometrial polyps	43 (2·4%)	69 (3·8%)	22 (1·3%)	61 (3·5%)	<0·0001
Uterine fibroids	71 (3·9%)	84 (4·6%)	11 (0·6%)	22 (1·2%)	0·09
Amenorrhoea	77 (4·2%)	171 (9·4%)	..	..	<0·0001
Thrush/candida	36 (1·9%)	103 (5·7%)	28 (1·6%)	84 (4·8%)	<0·0001
Prolapse	36 (1·9%)	33 (1·8%)	45 (2·6%)	52 (2·9%)	0·81
Ovarian cysts and lumps	33 (1·8%)	86 (4·8%)	9 (0·5%)	15 (0·9%)	<0·0001
Endometriosis	16 (0·9%)	14 (0·8%)	5 (0·3%)	6 (0·3%)	0·88

p values are for premenopausal and postmenopausal women combined.

Table 6: **Gynaecological procedures and gynaecological and vasomotor symptoms in premenopausal and postmenopausal women (defined at randomisation) according to allocated treatment**

Publication Identifier	Cuzick 2002, Efficacy and Safety, Primary Supportive
Missing data	2029 women are not accounted for. It is not known whether these women discontinued from the study or if they were lost to follow-up
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. The study appears to have been well run with minimisation of potential bias. The major efficacy finding was of a significant reduction in all breast cancer frequency, but this did not reach significance for invasive breast cancer. Tamoxifen use was, however, associated with a significant increase in mortality during the follow-up period. Of note is that 28% of study participants are not accounted for in this report. Subsequent reports indicate that discontinuation was more common in the tamoxifen group. This publication contains results that are generalisable to the Australian population given that it included approximately 2500 Australian women.

Cuzick 2007

Publication identifier	Cuzick 2007, Efficacy and Safety, Primary Supportive
Citation	**Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, et al. Long-term results of tamoxifen prophylaxis for breast cancer - 96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99(4):272-82**
Study description	This publication provided long-term results for the IBIS-1 trial with 10 year follow up (median follow-up 96 months after randomization). The trial description is provided above under the 2002 publication.
Study Dates	Recruitment occurred between April 1992 and March 2001. The cutoff date for this analysis was April 1 2006: follow-up accrued until the development of breast cancer, death, or the cutoff date.
Study Follow-up Method	Women who completed their 5 years of active treatment were followed by an annual mailed questionnaire for women in the United Kingdom (60% of women) and Europe (3%) or annual clinic visit for women in Australia and New Zealand (37%). In addition, in the United Kingdom, the central IBIS office was notified on a quarterly basis of all cancers and deaths in trial participants using data obtained from the mandatory U.K. national registration system.
Blinding	Both investigators and patients were blinded to treatment allocation. Treatment allocation had been disclosed for 777 (10.9%) women who did not develop breast cancer. Of these, the codes for 493 (63.4%) women were broken after they completed the 5 years of active treatment. According to the publication "*In many cases, the code was broken by prearrangement with the local clinician to provide unblinding at year 6".*
Efficacy Measures	Incidence of breast cancer. Mortality
Safety measures	Deaths and side effects. Occurrence of side effects was collected differently in the UK/Europe and Australia and New Zealand. In UK/Europe, long term follow up was by an annual mailed questionnaire with a list of predefined side effects together with a free-text field. The list was less detailed than that used in the active treatment and first follow-up period. In Australia and New Zealand, the same detailed list was used in both the first and second follow-up periods, with the questions asked directly during the clinic visit

<table>
<tr><td>Statistical analysis</td><td>Analysis was by intention to treat. Incidence rates for breast cancer and major side effects were calculated by dividing the number of observed events by the number of woman years of follow-up for each group and/or period.

Relative risks were computed as the ratios of incidence rates. Confidence intervals and P values are based on exact distributions, assuming that the events followed independent Poisson distributions in the two groups. Interactions between treatment and subgroups were based on likelihood ratio tests for an added interaction term. All P values are two-sided, and confidence intervals are at the 95% level. No adjustments were made for covariates.</td></tr>
<tr><td>Participant follow up</td><td>There were 3566 women in the placebo group and 3573 in the tamoxifen group for the primary analysis. Of these, 2574 women [72%] in the placebo group and 2287 [63.9%] women in the tamoxifen group completed the full 5 years of treatment.

Follow-up was by posted questionnaire in the UK and Europe – the response rate was 85.9% in the tamoxifen group and 84.6% in the placebo group. All major side effects or endpoints reported on questionnaires were verifi ed from medical records

Follow up was by regular clinic visits in Australia and New Zealand – compliance rates with this were not provided.

Comment: Details regarding follow-up was only provided as “woman years” with total of 57 128 woman years of follow-up (28 573 in the placebo group and 28 555 in the tamoxifen group) having been accrued. The number of women in each group participating in long term follow-up was not provided in this publication. The 2015 Extended Long term Follow up publication notes: Most women (6639 [93%] of 7154) have had more than 10 years of follow-up</td></tr>
<tr><td>Baseline characteristics</td><td>As above</td></tr>
<tr><td>Efficacy Results</td><td>Occurrence of Breast Cancer

337 breast cancers (invasive and DCIS combined) were reported: 142/3573 (3.97%) in the tamoxifen group versus 195/3566 (5.4%) in the placebo group. The characteristics of the diagnosed breast cancers are shown below (see also Table 2 of the publication for more details)
<table>
<tr><th colspan="4">Breast Cancer Characteristics by Treatment Allocation
(derived from publication Table 2)</th></tr>
<tr><th></th><th>Placebo Group</th><th>Tamoxifen Group</th><th>Relative Risk, 95% CI</th></tr>
<tr><td>Total</td><td>196</td><td>142</td><td>0.73, 0.58-0.91</td></tr>
<tr><td>Invasiveness</td><td></td><td></td><td></td></tr>
<tr><td>Invasive</td><td>168</td><td>124</td><td>0.74, 0.58-0.94</td></tr>
<tr><td>DCIS</td><td>27</td><td>17</td><td>0.63, 0.32-1.20</td></tr>
<tr><td>Unknown</td><td>0</td><td>1</td><td></td></tr>
<tr><td>Invasive Cancers</td><td></td><td></td><td></td></tr>
<tr><td>ER status</td><td></td><td></td><td></td></tr>
<tr><td>ER +</td><td>132</td><td>87</td><td>0.66, 0.50-0.87</td></tr>
<tr><td>ER -</td><td>36</td><td>31</td><td>1.00, 0.61-1.65</td></tr>
</table></td></tr>
</table>

Unknown	1	2	
Size (cm)			
<=1	51	39	0.77, 0.49-1.18
>1-2	78	44	0.56, 0.38-0.83
>2			1.03, 0.64-1.65
Unknown	1	2	

The annual incidence rate was 6.82 per 1000 woman-years in the placebo group and 4.97 per 1000 woman-years in the tamoxifen group. Cumulative incidence is shown in the figure below.

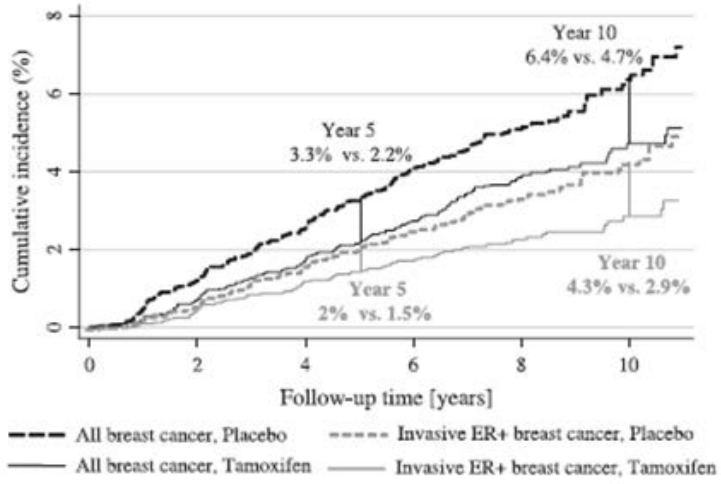


Fig. 1. Cumulative incidence rates for all breast cancers and invasive estrogen receptor (ER)–positive breast cancers according to treatment arm.

Comment: the numbers of women continuing in follow-up at the different time-points were not provided.

HRT

Among women who never used HRT or who used it only before the trial, there was a statistically significant reduction in ER-positive breast cancers in the tamoxifen arm compared with the placebo arm regardless of type of HRT (for all breast cancers, 76 versus 126 cases, RR = 0.62, 95% CI = 0.46 to 0.83; for ER-positive cancers, 37 versus 77 cases, RR = 0.49, 95% CI = 0.32 to 0.74). However, for women who used HRT at some stage during the trial, no clear effect of tamoxifen was seen, either overall (66 versus 69 cases, RR = 0.92, 95 % CI = 0.65 to 1.31) or for ER-positive tumors (40 versus 43 cases, RR = 0.89, 95% CI = 0.57 to 1.41).

Mortality:

Table 4. Specific causes of death by treatment arm*

Cause of death	Placebo (N = 3575)	Tamoxifen (N = 3579)
Total	55	65
Breast cancer	13	11
Endometrial cancer	0	1
Colon cancer	5	4
Lung cancer	6	5
Ovarian cancer	4	2
Other cancer	6	13
Myocardial infarction	0	4
Other cardiac	2	2
DVT/PE	2	3
Stroke or CVA	1	1
Other	16	19

* DVT = deep-vein thrombosis; PE = pulmonary embolism; CVA = cerebrovascular accident.

The number of deaths from any cause was non – statistically significantly higher in the tamoxifen group than in the placebo group (65 versus 55 deaths, RR = 1.18, 95% CI = 0.81 to 1.73). The difference between the two groups in deaths from any cause is smaller than it was in the original report (see Cuzick 2002 above).

Safety Results

Deaths: see above

Endometrial cancer:

There were 17 cases of endometrial cancer reported in the tamoxifen group and 11 in the placebo group (RR = 1.55, 95% CI = 0.68 to 3.65). Most of the endometrial cancers were adenocarcinomas (5/11 in the placebo group and 14/17 in the tamoxifen group); FIGO stage 1 (placebo: 9/11, tamoxifen 14/17) and occurred in women aged 50 years of age or more (placebo: 9/11, tamoxifen: 16/17). There were 5 cases of endometroid carcinoma, 2 sarcomas and one clear cell carcinoma (see publication table 5 for details).

Cancers other than Endometrial:

These were not described in this publication

Thromboembolic events:

Thromboembolic events were statistically significantly higher in the tamoxifen group than in the placebo group (117 versus 68 events, RR = 1.72, 95% CI = 1.27 to 2.36). The incidence rates were 4.10 per 1000 woman-years in the tamoxifen group and 2.38 per 1000 woman-years in the placebo group

	Entire period		
Side effect	Placebo	Tamoxifen	RR (95% CI)
All VTE	68 (2.38)	117 (4.10)	1.72 (1.27 to 2.36)
DVT/PE	37 (1.29)	68 (2.38)	1.84 (1.21 to 2.82)
Superficial thrombophlebitis	8 (0.28)	23 (0.81)	2.88 (1.24 to 7.44)
Other thrombosis	23 (0.81)	26 (0.91)	1.13 (0.62 to 2.08)
All cerebrovascular	34 (1.19)	32 (1.12)	0.94 (0.56 to 1.57)
Stroke/CVA	12 (0.42)	15 (0.53)	1.25 (0.55 to 2.93)
TIA	22 (0.77)	17 (0.60)	0.77 (0.39 to 1.52)
All cardiac	123 (4.30)	122 (4.27)	0.99 (0.77 to 1.29)
Myocardial infarction	15 (0.53)	9 (0.32)	0.60 (0.23 to 1.46)
Angina	51 (1.78)	60 (2.10)	1.18 (0.80 to 1.74)
Other cardiac	57 (1.99)	53 (1.86)	0.93 (0.63 to 1.38)

Excerpt from publication Table 6 Thromboembolic, cerebrovascular and cardiac events

Comparison of the active treatment phase to the follow-up phase found that the excess of thromboembolic events was found only in the active treatment phase.

Adverse Events:

	Overall, statistically significantly more women in the tamoxifen group than in the placebo group reported gynaecologic or vasomotor side effects. The increase was observed only during the active treatment phase (RR = 1.20, 95% CI = 1.16 to 1.25) and not in the subsequent period (RR = 1.06, 95% CI = 0.99 to 1.12).

Table 7. Side effects and relative risk of having an event according to treatment arm and follow-up time*

	Entire period			During active treatment†			After active treatment‡		
Side effect	Placebo (N = 3575)	Tamoxifen (N = 3579)	RR (95% CI)	Placebo (N = 3575)	Tamoxifen (N = 3579)	RR (95% CI)	Placebo (N = 3489)	Tamoxifen (N = 3449)	RR (95% CI)
Gynecologic/ vasomotor	2922 (81.7)	3151 (88.0)	1.08 (1.06 to 1.10)	1983 (55.5)	2389 (66.8)	1.20 (1.16 to 1.25)	1438 (41.2)	1508 (43.7)	1.06 (0.99 to 1.12)
Headaches	1261 (35.3)	1169 (32.7)	0.93 (0.87 to 0.99)	1030 (28.8)	878 (24.5)	0.85 (0.79 to 0.92)	343 (9.8)	386 (11.2)	1.14 (0.99 to 1.31)
All breast complaints	903 (25.3)	693 (19.4)	0.77 (0.70 to 0.84)	833 (23.3)	612 (17.1)	0.73 (0.67 to 0.81)	676 (19.4)	554 (16.1)	0.83 (0.75 to 0.92)
Multiple breast cysts	156 (4.4)	63 (1.8)	0.40 (0.30 to 0.54)	100 (2.8)	29 (0.8)	0.29 (0.19 to 0.44)	56 (1.6)	34 (0.9)	0.61 (0.40 to 0.94)
All fractures	235 (6.6)	240 (6.7)	1.02 (0.86 to 1.21)	142 (3.9)	121 (3.4)	0.85 (0.67 to 1.08)	93 (2.67)	119 (3.5)	1.29 (0.99 to 1.69)
Osteoporotic site fracture§	76 (2.1)	91 (2.5)	1.19 (0.89 to 1.62)	44 (1.2)	45 (1.3)	1.02 (0.68 to 1.54)	32 (0.9)	46 (1.3)	1.44 (0.92 to 2.25)
Eye complaints (excluding cataracts)	934 (26.1)	947 (26.6)	1.01 (0.94 to 1.09)	896 (25.1)	901 (25.2)	1.00 (0.93 to 1.09)	597 (17.1)	622 (18.0)	1.05 (0.95 to 1.17)
Cataracts	54 (1.5)	67 (1.9)	1.24 (0.87 to 1.77)	34 (0.9)	29 (0.8)	0.85 (0.52 to 1.40)	20 (0.6)	38 (1.1)	1.92 (1.12 to 3.29)

* Data are given as number of events, with percentage of the group in parentheses. Risk ratios (RRs) are based on the number of women who ever reported the side effect in the given period. CI = confidence interval.

† Side effect evaluation based on clinic-administered questionnaire.

‡ Side effect evaluation based on postal questionnaire or clinic visit. Denominator is all women alive and without breast cancer at year 5.

§ Fractures of the hip, spine, wrist, or forearm.

Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. As with the 2002 publication, the study appears to have been well run with minimisation of potential bias. However, the number of women who participated in the follow-up is not apparent in the publication. The main efficacy result was of a significant reduction in the occurrence of breast cancer with this reaching significance for the sub-groups of invasive breast cancer and ER+ breast cancer but not for ER- breast cancer. This result did not appear to be affected by concomitant use of HRT. Mortality was increased in the tamoxifen arm but the difference was not statistically significant, unlike the initial report. There was a significant increase in thromboembolic events in the tamoxifen arm but these appeared to occur only during treatment. The results are generalisable to the Australian population given that it included approximately 2500 Australian women.

Cuzick 2015

Publication identifier	**Cuzick 2015, Efficacy and Safety, Primary Supportive**
Citation	Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancerprevention trial. Lancet Oncol. 2015;16(1):67-75.
Study description	Extended long term results of the IBIS-1 trial with 20 year follow-up (median follow up 16 years)
Study Dates	Recruitment occurred between April 1992 and March 2001; the cut-off date of follow-up for the analysis was May 1, 2014
Study Follow-up Method	By telephone at 6-monthly intervals. In the UK, cancers and deaths are also reported to the IBIS-I central office by the Office for National Statistics. In the non-UK centres annual clinic visits, or hospital notes were used to collect these data Adverse events were collected by annual postal questionnaires

<table>
<tr><th>Publication identifier</th><th>Cuzick 2015, Efficacy and Safety, Primary Supportive</th></tr>
<tr><td>Blinding</td><td>The following statement is provided: Treatment allocation still remains largely masked for investigators and participating women who have not developed breast or any other cancer (2702 [75·5%] of those assigned to tamoxifen vs 2646 [74·0%] of those who received placebo)</td></tr>
<tr><td>Efficacy Measures</td><td>occurrence of any type of breast cancer (including ductal carcinoma in situ); occurrence of invasive oestrogen receptor-positive breast cancer, all-cause mortality</td></tr>
<tr><td>Safety measures</td><td>Adverse events – only major thromboembolic, cerebrovascular, and cardiac events continued to be collected</td></tr>
<tr><td>Statistical analysis</td><td>All analyses were by intention to treat (analysis population: 3579 tamoxifen; 3575 placebo). Efficacy endpoints were based on HRs from Cox proportional hazard models with corresponding 95% CIs. Survival curves were estimated using the Kaplan-Meier method. secondary endpoints were compared using logistic regression. Adverse events were compared using Fisher's exact tests. All p values were two-sided.</td></tr>
<tr><td>Follow-up and Response rates</td><td>The following statement is provided: Most women (6639 [93%] of 7154) have had more than 10 years of follow-up, and the cumulative number of women-years of follow-up are 69 074 before 10 years and 40 969 thereafter</td></tr>
<tr><td>Baseline characteristics</td><td>As above (Cuzick 2002)</td></tr>
<tr><td>Efficacy Results</td><td>Efficacy:
A total of 601 breast cancers were reported : 251 [7·0%] in 3579 women in the tamoxifen group vs 350 [9·8%] of 3575 in the placebo group;
<table>
<tr><th colspan="4">Breast Cancer Characteristics by Treatment Allocation
(derived from publication Table 1)</th></tr>
<tr><th></th><th>Placebo Group</th><th>Tamoxifen Group</th><th>Hazard ratio, 95% CI</th></tr>
<tr><td>Total</td><td>350</td><td>251</td><td>0.71, 0.60-0.83</td></tr>
<tr><td>Invasiveness</td><td></td><td></td><td></td></tr>
<tr><td>Invasive</td><td>289</td><td>214</td><td>0.73, 0.61-0.87</td></tr>
<tr><td>DCIS</td><td>53</td><td>35</td><td>0.65, 0.43-1.00</td></tr>
<tr><td>Unknown</td><td>8</td><td>2</td><td></td></tr>
<tr><td>Invasive Cancers</td><td></td><td></td><td></td></tr>
<tr><td>ER status</td><td></td><td></td><td></td></tr>
<tr><td>ER +</td><td>238</td><td>160</td><td>0.66, 0.54-0.81</td></tr>
<tr><td>ER -</td><td>47</td><td>50</td><td>1.05, 0.71-1.57</td></tr>
<tr><td>Unknown</td><td>65</td><td>41</td><td></td></tr>
</table></td></tr>
</table>

Publication identifier	Cuzick 2015, Efficacy and Safety, Primary Supportive

Size (cm)			
<=1	82	61	0.73, 0.53-1.02
>1-2	123	80	0.64, 0.49-0.85
>2	84	73	0.86, 0.63-1.17
Unknown	61	37	

The preventive effects of tamoxifen did not differ according to tumour size, nodal status, or grade. There was no significant difference between women aged 50 years or younger than in older women throughout the follow-up periods. No interactions were recorded with other demographic factors

HRT

Women who had menopausal hormone therapy during the 5 years of active treatment had significantly less benefit from tamoxifen than those who did not This effect was larger for women who developed invasive oestrogen receptor-positive cancers (users of menopausal hormone therapy HR 0·87 [95% C 0·64–1·19] *vs* non users 0·55 [0·42–0·72]; p=0·03).

The reduction in the incidence of breast cancer in the tamoxifen group extended throughout the duration of follow-up – see figure below.

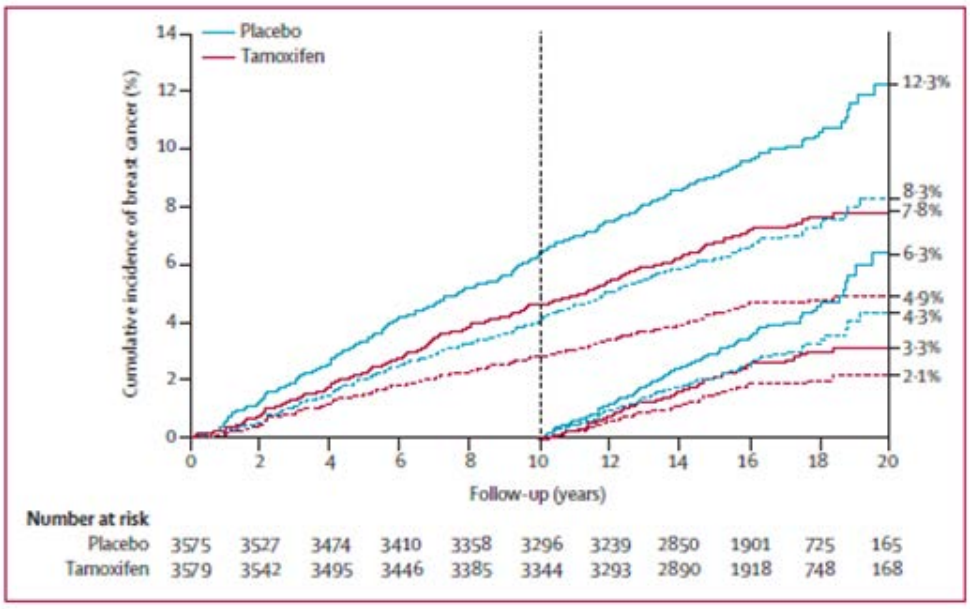


Figure 1: **Cumulative incidence of breast cancers over time**
All breast cancers (solid lines) and invasive oestrogen receptor-positive breast cancers (dashed lines), according to treatment group and duration of follow-up.

Mortality:

A total of 348 deaths were reported: 182 [5·1%] of 3579 women in the tamoxifen group and 166 [4·6%] of 3575 women in the placebo group. There was no significant difference in mortality between the two groups (OR 1·10 [95% CI 0·88–1·37], p=0·4).

Specific causes of death according to treatment allocation (derived from publication Table 7)

Publication identifier	Cuzick 2015, Efficacy and Safety, Primary Supportive

Cause of Death	Placebo (N=3566)	Tamoxifen (N= 3573)
Total	166	182
Breast cancer	26	31
Endometrial cancer	NR	NR
Other cancer	78	88
Cardiac	14	12
DVT/PE	3	4
Stroke or CVA or SAH	12	10
Other	33	37

DVT = deep venous thrombosis, PE = pulmonary embolus, CVA = cerebrovascular accident, SAH = subarachnoid haemorrhage

Evaluation according to follow-up periods

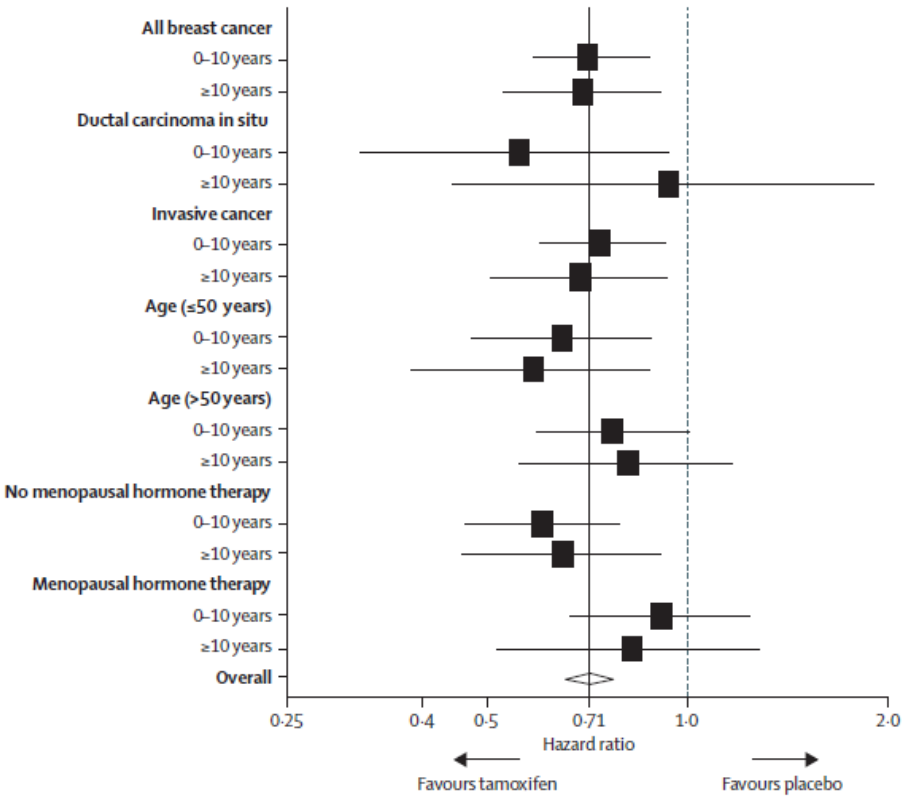
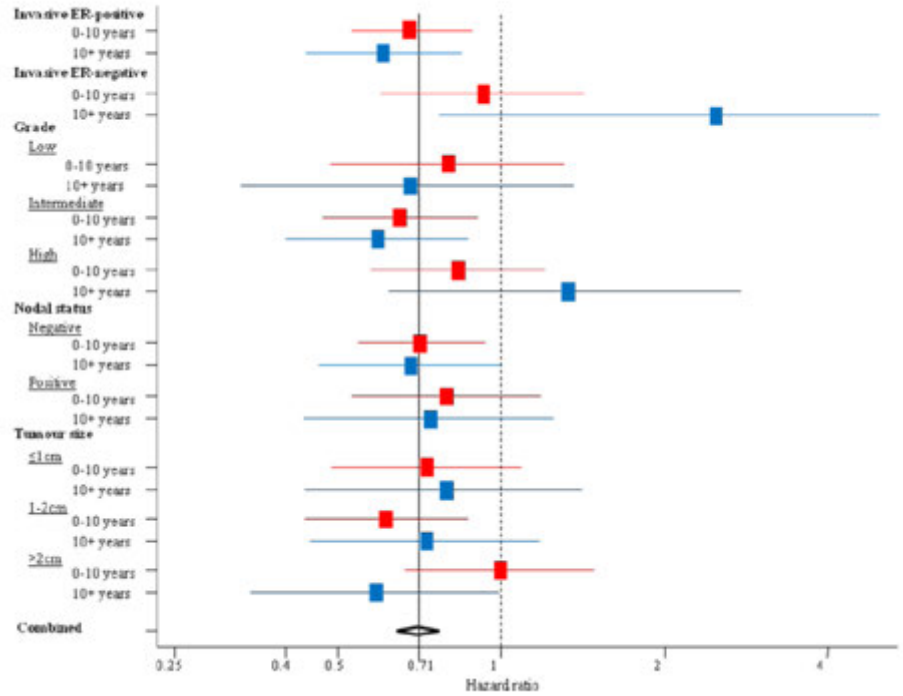


Figure 3: Forest plot for subgroup analyses according to follow-up periods (0–10 years *vs* ≥10 years)
Horizontal lines are 95% CIs.

Publication identifier	Cuzick 2015, Efficacy and Safety, Primary Supportive
	Supplementary Figure 1: Forest plot for invasive breast cancer characteristics according to follow-up period (red: 0-10 years, blue: 10+ years). 
Safety Results	**Deaths:** see above **Endometrial cancer:** There was a non-significant increase in the number of endometrial cancers in the tamoxifen group than the placebo group (29 v 20, p=0.19). The main excess was confined to the first 5 years of active treatment (15 v 4) with no subsequent significant difference **Cancers other than Endometrial:** Other gynaecological cancers were distributed similarly between the two treatment groups. Significantly fewer gastrointestinal cancers occurred in women receiving tamoxifen than in those receiving placebo (42 in the tamoxifen group *vs* 63 in the placebo group; OR 0·66 [95% CI 0·44–0·99], p=0·038). Non-melanoma skin cancers were significantly increased in the tamoxifen group, whereas there was a similar incidence of melanoma skin cancers between the two treatment groups. More cases of lung cancer were reported with tamoxifen (32 cases) than with placebo(24 cases), although this difference was not significant **Thromboembolic events:** There was a significantly higher incidence of deep vein thrombosis an dsuperficial thrombophlebitis in women receiving tamoxifen than those receiving placebo. However, the increased risk of DVT was only during the first 10 years of follow-up (46 [1·3%] in the tamoxifen group *vs* 25 [0·7%] in the placebo group; OR 1·87 [95% CI 1·11–3·18], p=0·011). More women in the tamoxifen arm had PEs but this did not reach significance. No significant differences between treatment groups were seen for major cardiovascular events - see table below

Publication identifier	Cuzick 2015, Efficacy and Safety, Primary Supportive
	Supplementary Table 3: Thromboembolic, cardiovascular, and cerebrovascular events according to treatment allocation. *DVT=Deep vein thrombosis, PE=Pulmonary embolism, CVA=Cerebrovascular accident, TIA = Transient ischaemic attack

	Placebo	Tamoxifen	OR (95% CI)
Thromboembolic events			
DVT	29	50	1·73 (1·07-2·85)
PE	22	30	1·37 (0·76-2·49)
Superficial thrombophlebitis	11	24	2·19 (1·03-4·95)
All	**62**	**104**	**1·70 (1·22-2·37)**
Cardiovascular events			
Myocardial infarction	17	13	0·76 (0·34-1·67)
Angina	51	60	1·18 (0·80-1·75)
All	**153**	**141**	**0·92 (0·72-1·17)**
Cerebrovascular events			
Stroke/CVA	28	30	1·07 (0·62-1·86)
TIA	40	27	0·67 (0·40-1·12)
All	**74**	**62**	**0·83 (0·58-1·19)**

Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. As with the 2002 publication, the study appears to have been well run with minimisation of potential bias, although it was stated that blinding was not maintained for approximately 25% of women in each arm who continued in follow-up. A clear account of the numbers of women continuing in follow-up was not provided, although it was stated that "*6639 [93%] of 7154) have had more than 10 years of follow-up*". This update confirms the main efficacy findings of the 2007 report with a significant reduction in the occurrence of breast cancer with this also reaching significance for the sub-groups of invasive breast cancer and ER+ breast cancer, but not for ER- breast cancer. Unlike earlier reports, this result did appear to be affected by concomitant use of HRT: women taking HRT had significantly less benefit from tamoxifen compared to those who did not. Mortality was slightly increased in the tamoxifen arm but the difference was not statistically significant, unlike the initial report. There was a non-significant increase in the number of endometrial cancers in the tamoxifen arm. There was a significant increase in thromboembolic events in the tamoxifen arm but these appeared to occur only during treatment. The results are generalisable to the Australian population given that it included approximately 2500 Australian women.

IBIS – 1 Related Publications (Efficacy and Safety)

Sestak 2012b

Publication identifier	Sestak 2012b, Efficacy and Safety, Secondary Supportive
Citation	Sestak I, Kealy R, Nikoloff M, Fontecha M, Forbes JF, Howell A, et al. 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. Br J Cancer. 2012;107(2):230-3.
Study description	Retrospective, case control, nested, analysis in tamoxifen-treated women from the IBIS-1 trial to assess of the effect of the CYP2D6 phenotype on the development of ER-positive invasive breast cancer and endocrine symptoms. The objective was to explore the premise that women with specific alterations in the CYP2D6 enzyme, which correlate with reduced enzyme activity and lower endoxifen levels (may have less benefit from tamoxifen treatment and fewer hot flushes than women

Publication identifier	Sestak 2012b, Efficacy and Safety, Secondary Supportive
	with a normal enzyme activity. Tamoxifen is metabolised through the cytochrome P450 (CYP) 2D6 pathway to 4-hydroxy-tamoxifen and endoxifen - these metabolites are believed to be more potent anti-oestrogens than tamoxifen itself.
Funding source, Conflicts of interest	Funding source not described, No statements regarding potential conflict(s) of interest provided
Study Dates	The first 5 years of the IBIS-1 trial
Study Method	Women allocated to tamoxifen who had an oestrogen receptor (ER) positive tumour at any time during the first 5 years of follow-up (from randomisation) were included. Women on tamoxifen who did not develop an ER + or ER – cancer were used as case controls Purified DNA from whole-blood samples collected at baseline was analysed and used to classify women into three phenotypic categories, ranked from low to high level of enzymatic function: poor metaboliser, intermediate metaboliser and extensive metaboliser. During the IBIS-1 trial, specific questions about hot flushes were asked at each 6-month follow-up visit, with all reported side effects reported graded at the time. The reporting of these symptoms (all severities) at the first 6-month follow-up visit was used as the measure of symptom occurrence. Cases were matched according to personal breast cancer risk, age and follow-up time with controls who also received tamoxifen but did not develop breast cancer. For a total of 54 cases and 215 controls, Cytochrome P450 (CYP) 2D6-predicted phenotypes were analysed.
Blinding	Laboratory performing the DNA analysis was blind to case-control status and all clinical factors
Results	9 women (16.6%) who developed ER+ invasive breast cancer had a 2D6 poor or intermed1ate metaboliser phenotype compared with 45 (20.6%) controls. Adjusted matched logistic regression revealed no significant difference between cases and controls for extensive *vs* intermediate metabollser phenotype (OR= 0.81 (0.30-2.23). *P* = 0.7) or extensive *vs* poor metaboliser phenotype (OR= 1.02 (0.31-3.32). *P* = 0.9). Controls in the tamox,fen group with a poor metaboliser phenotype developed nonsigrnficantly fewer hot flushes compared with those with an extensive metaboliser phenotype (OR= 0.40 (0.12-1.31)). but those with the intermediate phenotype developed non-significantly more hot flushes (OR- 1.38 (0.58-3.29)) in an unadjusted analysis.
Conclusion	Data from the preventive IBIS-I study did not support an association between the CYP2D6 phenotype and breast cancer outcome or the development of endocrine symptoms in tamoxifen-treated women
Allocation by sponsor and Evaluator assessment	This was described as a "primary supportive publication" with no NHMRC level of evidence by the sponsor. It may be more appropriate to describe it as a "secondary supportive publication" as this retrospective sub-group analysis adds little information of relevance.

IBIS – 1 Related Publications (Safety)

Duggan 2003

Publication identifier	Duggan 2003, Safety, Secondary Supportive
Citation	Duggan C, Marriott K, Edwards R, Cuzick J. Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. J Clin Oncol. 2003;21(19):3588-93.

Publication identifier	Duggan 2003, Safety, Secondary Supportive
Study description	Retrospective nested case-control study design to investigate the role of tamoxifen and acquired risk factors in the risk of developing a VTE (and arterial occlusion)
Funding source, Conflicts of interest	Funding source not described, Statements regarding potential conflict(s) of interest provided: *Acted as a consultant within the last 2 years: Jack Cuzick, AstraZeneca. Received more than $2,000 a year from a company for either of the last 2 years: Jack Cuzick, AstraZeneca*.
Study Dates	The first 5 years of the IBIS-1 trial (from randomisation)
Study Method	96 women with a VTE were identified from the IBIS-I trial. Two sets of controls were selected, with two control women for each patient in each set: 1.for the investigation of acquired risk factors - matched only on age 2. for the investigation of inherited risk factors (factor V Leiden or prothrombin G20210A mutations) - matched on age, body mass index, smoking history, and hormone replacement therapy use but also restricted to women who had a blood sample available for DNA extraction and testing for factor V Leiden and prothrombin G20210A mutations Venous thromboembolic events were defined as major events, in order of severity, as pulmonary embolus, DVT, retinal thrombosis and the minor event of superficial thrombophlebitis. Data was also collected on cerebrovascular events (defined as transient ischemic attack, stroke, cerebral aneurysm, or subarachnoid haemorrhage), and myocardial infarctions. Information about acquired risk factors for VTE (body mass index, hormone replacement therapy use, and smoking status) was collected at baseline. Information about recent surgical procedures, immobilization, and fractures to the lower extremities was recorded during the IBIS-I follow-up period (first 5 years from randomisation). Surgery and fractures were restricted to those events occurring within 3 months prior to diagnosis of a VTE.
Results	96 VTEs were observed during the IBIS-1 trial, including 57 major events (32 DVT, 23 pulmonary emboli, two retinal thrombi), and 39 superficial thrombophlebitises. Tamoxifen was associated with a significantly increased risk of developing a major VTE (odds ratio [OR], 2.1; 95% CI, 1.1 to 4.1). Women who had surgery, immobilization, or fracture in the previous month had a greatly increased risk of developing a major VTE (OR, 4.7; 95% CI, 2.2 to 10.1). Prothrombin and factor V Leiden mutations were found only in the control group. Being overweight, smoking, or taking hormone replacement therapy was not associated with VTE, but the CIs were wide 33 cerebrovascular events were observed in IBIS-I, including 24 cerebrovascular accidents or strokes and nine transient ischemic attacks. Seventeen of these occurred in the placebo arm and 16 occurred in the tamoxifen arm. None of the women who had a cerebrovascular event carried either the factor V Leiden or the prothrombin G20210A mutation. Similarly, none of the 10 women who developed a myocardial infarction (five in the tamoxifen arm and five in the placebo arm) were carriers of these mutations. Neither tamoxifen, body mass index, use of hormone replacement therapy, nor smoking status were associated with the incidence of either cerebrovascular events or myocardial infarctions in the IBIS-I cohort. The risk of developing a VTE associated with tamoxifen reported in this article differs from that in the main report (Cuzick 2002). This is mainly due the reclassification, after review of the events, of six reports of major VTE in the original report into three major events (all controls) and three superficial events (all cases)
Conclusion	Tamoxifen was associated with an increased risk of VTE but not cerebrovascular events or myocardial infarction. Hypercoagulability factor mutations were not associated with thrombosis.
Allocation by	This was described as a “secondary supportive publication” with NHMRC level of evidence III-2 by the

Publication identifier	Duggan 2003, Safety, Secondary Supportive
sponsor and Evaluator assessment	sponsor. This is appropriate. This retrospective sub-group analysis provides additional information regarding the risk of VTE with tamoxifen used for breast cancer prevention in women at increased risk of breast cancer. The article provides this advice: *Where possible, tamoxifen should be discontinued 1 month before major surgery and administration should not resume until mobility has been achieved*

Sestak 2012a

Publication identifier	Sestak 2012a, Safety, Secondary Supportive
Citation	Sestak I, Harvie M, Howell A, Forbes JF, Dowsett M, Cuzick J. Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Res Treat. 2012; 134(2):727-34.
Study description	The objective of this study was 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 (AT AC)) trial and to placebo in the International Breast cancer Intervention Study (IBIS-II) in the preventive setting. The authors also investigated weight change in the IBIS-I study. The results of the analysis of the IBIS=I group only are described below. This was a retrospective analysis including only post-menopausal women from the IBIS-1 trial.
Funding source, Conflicts of interest	The following statements are provided: *Acknowledgments This analysis was supported by the Cancer Research UK and Astra Zeneca* *Conflict of interest Jack Cuzick received research funding from AstraZeneca. John F. Forbes received honoraria from AstraZeneca and Novanis. Mitch Dowsett received consultancy fees, honoraria. research funding and expert testimony from AstraZeneca*.
Study Dates	The first 5 years of the IBIS-1 trial
Study Method	All postmenopausal women (placebo N = 1922; tamoxifen N = 1936) are included in the analysis. Comparison of weight at baseline, 12 months and 60 months was made: • baseline weight measurements were available for 1,898 (98.0 %) in the tamoxifen group and for 1,885 (98.1 %) in the placebo group • 1,369 (70.7 %) of women in the tamoxifen group and 1,396 (72.6 %) of women in the placebo group had a baseline and 12 month weight measurement • 606 (31.3 %) of women in the tamoxifen group and 648 (33.7 %) women in the placebo group had a baseline, 12 and 60 month weight measurement Weight change categories were defined as: weight loss (losing more than 2 kg). stable weight (weight change between -2 kg and +2 kg), weight gain (gaining between 2 kg and 5 kg) and significant weight gain (more than 5 kg). Potential risk factors for weight gain of more than 5 kg were analysed (age, HRT use, smoking status at entry)
Results	Over the entire treatment period (baseline to 60 month), 35 % of postmenopausal women kept their weight stable and 19 % either lost more 2 kg or gained more than 5 kg. Mean weight at baseline, 12 and 60 months of follow-up was comparable between treatment groups. With regard to the potential risk factors for weight gain, only age was a significant factor, with women under the age of 60 years significantly more likely to gain more than 5 kg of weight compared to their counterparts
Conclusion	Mean weight at baseline, and changes at 12 and 60 months of follow-up were not significantly different between the tamoxifen and placebo groups

Publication identifier	Sestak 2012a, Safety, Secondary Supportive
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor and is appropriate. This retrospective sub-group analysis provides additional information regarding the potential effect of weight gain with tamoxifen use.

Palva 2013

Publication identifier	Palva 2013, Safety, Secondary Supportive
Citation	Palva T, Ranta H, Koivisto A-M, Pylkkanen L, Cuzick J, Holli K. A double-blind placebo-controlled study to evaluate endometrial safety and gynaecological symptoms in women treated for up to 5 years with tamoxifen or placebo - a substudy for IBIS I Breast Cancer Prevention Trial. Eur J Cancer. 2013;49(1):45-51.
Study description	Retrospective analysis of a sub-group of the IBIS-1 cohort – 96 women in Finland who participated in the IBIS-1 trial and who had an intact uterus at trial entry and who consented to participate in this sub-study - to investigate the effects of 5-years of tamoxifen use on endometrium and gynaecological symptoms.
Ethics approval	The following statement was provided: *The study protocol was approved by the Pirkanmaa Hospital District Ethics Committee*
Funding source, Conflicts of interest	Funding source not described, The following statement regarding potential conflict(s) of interest was provided: *There are no conflicts of interest for any of the authors*.
Study Dates	The first 5 years of the IBIS-1 trial and then follow-up to July 2009
Study Method	The subjects were followed-up clinically from randomisation up to 6 years, or until premature discontinuation due to withdrawal of consent, breast cancer or other reason, such as hysterectomy. For occurrence of gynaecological malignancies, the subjects were followed-up to at least 9 years (9-14 years). Gynaecological follow-up was by trans-vaginal ultrasound were performed at baseline at 2.5 and *5* years and at the 6 years follow-up visit and endometrial biopsies at baseline, at 2.5 and 5 years. Outcomes included endometrial thickness, endometrial biopsies, serious adverse events, gynaecological complaints and referrals to hospital, and gynaecological cancers. The information on gynaecological cancers diagnosed in the study subjects after completion of the IBIS-1 trial (up to 21st July 2009) were retrieved from the Finnish Cancer Registry (FCR) database, by linking the study database with the FCR database
Blinding	As described in Cuzick 2002
Results	Of the 96 included women, 45 were treated with tamoxifen and 51 with placebo. Women in the tamoxifen group were significantly more likely to discontinue the study compared to the placebo group (20/45, 44% compared to 11/51, 22%, p=0.017). The most common reason for discontinuation in the tamoxifen group was vasomotor symptoms (10/20). The median time for discontinuation in the tamoxifen group was 15 months (range 2-60months) compared to 30 months (range 14-44) in the placebo group. Median endometrial thickness in postmenopausal women was significantly increased at 5 years in the tamoxifen group (4.3mm compared to 2.0mm, p=0.011), but there was no difference between the groups within one year after discontinuation of the treatment. During the treatment period, the

Publication identifier	Palva 2013, Safety, Secondary Supportive
	number of extra gynaecological visits, the number of hospital referrals per patient and the frequency of endometrial curettage were significantly higher in the tamoxifen group. The difference in the curettage rate between the groups was more marked for premenopausal women (RR= 4.22, 95% CT) 1.09-23.86).No significant findings were observed in the endometrial biopsies. For example, the endometrial biopsies of those three women subsequently diagnosed with endometrial cancers, did not show any premalignant or otherwise suspicious changes prior to cancer diagnosis. There was 1 hysterectomy during the follow-up in the tamoxifen group and 4 in the placebo group – the reason for the hysterectomy were myomas in all but one case. There were 4 gynaecological malignancies diagnosed, all in the tamoxifen group – 2 endometrial cancer, one ovarian cancer and one endometrial carcinosarcoma.
Conclusion	The discontinuation rate in the tamoxifen group was comparatively high, occurred early and was mainly due to side effects. Even though there were significantly more non-serious gynaecological events during the tamoxifen treatment. routine gynaecological follow-up cannot be recommended
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This retrospective sub-group analysis is limited by the small number of participants. It provides some information regarding the rate and reason of discontinuations from the IBIS-1 trial (this information is not provided in the main reports) and adds some information regarding endometrial thickening during tamoxifen use. It also documents a significant increase in the need for referral and invasive procedures in the tamoxifen group, with 27% of women in the tamoxifen group having endometrial curettage compared to 10% in the placebo group.

Sestak 2006

Publication identifier	Sestak 2006, Safety, Secondary Supportive
Citation	Sestak I, Kealy R, Edwards R, Forbes J, Cuzick J. Influence of hormone replacement therapy on tamoxifen-induced vasomotor symptoms. J Clin Oncol. 2006;24(24):3991-6.
Study description	Retrospective analysis of the IBIS-1 population to investigate the influence of HRT on tamoxifen-induced vasomotor symptoms
Ethics approval	The following statement was provided: *The study protocol was approved by the Pirkanmaa Hospital District Ethics Committee*
Funding source, Conflicts of interest	The following statements were provided: *Supported by Cancer Research UK, Oncosuisse Switzerland, and by National Health and Medical Research Council Grants* *The authors indicated no potential conflicts of interest*
Study Dates	The first 5 years of the IBIS-1 trial – follow-up extended to a median of 84 months
Study Method	All women recruited to the IBIS-1 trial were included in this analysis. Use of HRT was permitted during the trial, but women had to experience menopausal symptoms. Women were defined as postmenopausal if they had experienced 12 consecutive months of amenorrhea or if they were aged 50 years or older and had had a hysterectomy alone or in combination with an oophorectomy. Specific questions about hot flushes were asked at each 6-month follow-up visit but not at baseline, at which time only details of any menopausal symptoms were requested. Hot flushes were defined as

Publication identifier	Sestak 2006, Safety, Secondary Supportive
	mild, moderate, or severe. Information about use of HRT was collected both at baseline and at each follow-up visit. HRT groups were initially categorized as never users (never used HRT before trial), baseline users, and ex-users (used HRT at one point before the trial). Women were defined as baseline users if they had used HRT at any time 6 months before random assignment. Women were considered ex-users if they previously used HRT but stopped 6 months before random assignment. Details of HRT use during the trial were collected at each follow-up visit. Women were considered continuing users of HRT during a follow-up period if they took HRT for at least 1 month between follow-up visits.
Blinding	As for IBIS-1 see Cuzick 2002
Results	95.4% of the 7154 women had completed active treatment at data-lock for the analysis (median follow-up of 84 months). There were 3855 postmenopausal women, 40.1% were baseline users of HRT at entry, 22.6% were ex-users, and 37% had never taken HRT before joining the study. Women in the tamoxifen group reported more hot flushes than women in the placebo group (2,527 women, 70.6%, on tamoxifen v 2,040 women, 57.1%, on placebo; OR, 1.83; 95% CI, 1.64 to 2.04). Night sweats and menstrual irregularities were also significantly increased in the tamoxifen group. Hot flushes continued in a majority of the tamoxifen-treated women and were unaffected by HRT use during that period (66.7% v 73.7% in HRT nonusers and users, respectively; P=0.8). For women in the placebo arm, continuing use of HRT reduced the number of reports of hot flushes. For women who developed hot flushes in the first 6 months and who were not taking HRT at entry, HRT only showed efficacy in the placebo group. No difference between oestrogen-only and oestrogen-progestin HRT preparations was seen according to treatment arm.
Conclusion	HRT use at entry or during the trial was not effective in alleviating hot flushes for women in the tamoxifen arm
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor and is appropriate. This analysis provides some additional detail above that in the main report (Cuzick 2002) and provides some information regarding discontinuations from the IBIS-1 trial.

NSABP P1 – Description of individual publications

The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial clinicaltrials.gov identifier NCT00000529		
Trial description	Double-blind placebo-controlled randomised trial in the USA of women aged 35 years or older with an increased risk of breast cancer. To be eligible, women had to be either 60 years of age or older, or between 35 and 59 years of age with a history of lobular carcinoma in situ or a five-year predicted risk of breast cancer of at least 1.66% based on the Gail algorithm. All women had a mammogram within 180 days before randomisation to exclude pre-existing breast cancer. Recruitment of subjects was from 1992 to 1997. The trial was unblended in 1998 after the initial analysis. Participants in the placebo group were given the opportunity either to receive a 5-year course of tamoxifen or to be randomized to the Study of Tamoxifen and Raloxifene (STAR) trial	
Related Publications		
Key Publication (s)	**Relationship to Trial**	**Page**

The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP P1) trial clinicaltrials.gov identifier NCT00000529		
Fisher 1998	First publication of results (median follow-up 54.6 months after randomisation)	98
Related Publications**		
Efficacy		
Fisher 2005	Long term results – 7 year open follow up (mean follow-up 74 months after randomisation)	109
King 2001	Comparison of incidence of breast cancer in women with BRAC1 and BRAC2 mutations	115
Shen 2008	Effect of tamoxifen on time to diagnosis of breast cancer	117
Safety		
Reis 2001	Comparison of ischaemic cardiac events in women with or without prior CHD	117
Day 2001	Comparison of depressive symptoms	119
Cushman2001	Sub group (100) comparison of antithrombin, protein C antigen, and total protein S concentrations	123
Cushman 2003	Sub-group (100) comparison of total cholesterol, triglyceride levels, fibrinogen, factor VIIc, prothrombin fragments 1-2 and C-reactive protein concentrations	121
Abramson 2002	Screening for hypercoagulable abnormalities in 24/155 cases who developed VTE or stroke	124
Abramson 2006	Assess relationship between risk of VTE and Factor V Leiden and prothrombin mutations in 76/81 cases.	125
Chalas 2005	Comparison of benign gynaecological conditions	125

*Trial acronyms refer to the trials described above

** A list of citations is provided in Section 19, starting on page68 of this report

Comments:

- A detailed description of the trial method is provided in the description of the first publication. This is supplemented with information from subsequent publications where appropriate (and identified as such). The description of the trial method is not repeated for the subsequent publications. A brief description of each publication is provided with results described in appropriate details.
- All figures and Tables are copied from the relevant publication (with original captions) unless otherwise specified.
- Both safety and efficacy results are provided in the publication description
- The evaluator's opinion of the publication results is provided following the publication description. It can be identified by Calibri font and shading

NSABP P1 - Key Publications (Efficacy and Safety)

Fisher 1998

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive
Citation	Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-88.
Relationship to trial	First report
Documented GCP or ethics approval	The following statements were provided: "*All investigations conducted were approved by review boards at each institution and were in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Each of the 131 clinical centers had on-site auditing to monitor and assess data quality*"
Conflict of Interest	No statement provided
Funding source(s)	The following statement is provided: "*This investigation was supported by Public Health Service grants U10-CA-37377 and U10-CA-69974 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services*"
Study design	Double-blind placebo-controlled randomised trial
Study Location	USA and Canada
Study Dates	Randomisation occurred between June 1992 – September 1997. It was ceased in 1997 after an adequate number to meet the primary study objective (demonstration of a reduction in the incidence of breast cacner) had been recruited. Data cutoff date was March 31 1998.
Study treatment	Placebo or 20 mg/day tamoxifen for 5 years Frequency of review, method of review and data collected at review is not described except for self-reported symptoms and quality of life: At each follow-up visit, participants completed a 43-item checklist regarding possible tamoxifen-related, non-life-threatening side effects including hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhoea, and weight change. A self-administered depression scale developed by the Center for Epidemiological Studies (CES-D) was used to estimate the relation of tamoxifen to the occurrence of depressive symptoms. Also self-reported at each visit were data from the Medical Outcomes Study Short Form 36 (MOSSF-36) and the Medical Outcomes Study (MOS) Sexual Functioning Scale
Study population	Women at increased risk for breast cancer in the United States and Canada
Key selection criteria	Women at increased risk for breast cancer because they were 60 years of age or older or were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66% (as determined by Gail's algorithm), or had a history of lobular carcinoma in situ AND had a life expectancy of at least 10 years; had no evidence of breast cancer (as shown by a breast examination and a mammogram within 180 days before randomisation); had normal white blood cell and platelet counts and normal hepatic and renal function tests; were not pregnant and had no plans

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive
	to become pregnant while on protocol therapy; were accessible for follow-up; were not on HRT or OCP; had no history of VTE; and (1994-1997 only)had undergone an endometrial sampling before randomization if they had a uterus
Gail's Algorithm	This is a multivariate logistic regression model in which combinations of risk factors were used to estimate the probability of occurrence of breast cancer (invasive and non-invasive) over time. The variables included in the model were age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. This model was adapted in this trial such that it was intended to predict the risk of invasive breast cancer
Concurrent medications	Use of HRT and OCP was not allowed
Outcome measure(s)	Incidence of breast cancer, incidence of invasive breast cancer, incidence of non-invasive breast cancer, deaths due to breast cancer; quality of life. The primary outcome measure was the incidence of breast cancer
Safety measure(s)	Incidence of endometrial cancer, incidence of invasive cancer other than breast and endometrial, ischaemic heart disease, fractures (hip, spine and Colle's), vascular events (stroke, transient ischaemic attack, pulmonary embolism, deep vein thrombosis), cataracts Occurrence of tamoxifen-related non-life-threatening side effects (hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhoea, and weight gain or loss)
Randomisation	Randomisation of participants in a double-blind fashion was performed centrally. Participants were stratified by age (35–49 years, 50–59 years, ù60 years), race (black, white, other), history of LCIS (yes, no), and breast cancer RR (<2.5, 2.5–3.9, ù4.0). To avoid imbalances in treatment assignment within a clinical centre, an adaptive randomisation scheme (biased-coin method of Efron) was used.
Blinding	Blinding of participants and investigators was maintained until April 1 1998, when all investigators were provided with lists identifying treatment assignment for each participant.
Statistical analysis	All analyses were based on assigned treatment at the time of randomisation. All randomly assigned participants with follow-up were included in the analyses. Average annual event rates for the study end points were calculated for each treatment group by the number of observed events divided by the number of observed event-specific person-years of follow-up. Calculation of P values (two-sided) for tests of differences between the treatment groups and CIs for RR assumed a Poisson distribution of events.
Participant Flow	A total of 98108 women were screened and 57641 were eligible according to breast cancer risk. Of these, 14453 agreed to be medically evaluated and 13954 met all eligibility requirements. 13388/13954 (96%) eligible women were recruited to the trial and randomised. 13175 women were included in the efficacy analysis: one participant was excluded due to the discovery that she had invasive breast cancer instead of the originally reported noninvasive lesion (LCIS) on mammographic and pathologic examination; 212 participants were excluded as there was no follow-up reported for these women.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 1. Summary of screening, accrual, and follow-up information for the study

Screening, accrual, and follow-up information	Placebo	Tamoxifen	Total
Breast cancer risk assessments	—	—	98 018
Women meeting risk eligibility requirement	—	—	57 641
Medical eligibility assessments	—	—	14 453
Women meeting both risk and medical eligibility requirements	—	—	13 954
Women randomly assigned	6707	6681	13 388
Not at risk for breast cancer*	0	1	1
Without follow-up	108	104	212
Included in analysis	6599	6576	13 175
Average follow-up time, mo	47.7	47.7	47.7
Median follow-up time, mo	54.6	54.5	54.6
% followed for >36 mo	74.0	73.7	73.9
% followed for >48 mo	66.7	67.0	67.0
% followed for >60 mo	37.1	36.4	36.8
Person-years of follow-up†	26 247	26 154	52 401

The median follow-up time was 54.6 months

NSABP P1 - Participant flow including discontinuations and withdrawal of consent			
	Placebo	**Tamoxifen**	**Total**
Randomised	6707	6681	13388
No follow-up	108	104	212
Included in analysis	6599	6576	13175
Withdrew consent*	475 (7.2%)	473 (7.2%)	948 (7.2%)
Discontinued treatment*	1300 (19.7%)	1583 (23.7%)	2845 (21.6%)
Complete follow-up	92.4%	92.3%	
* Calculated from percentages provided in publication			

Baseline Character-istics of Participants	See table below.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 2. Participant characteristics at time of randomization for women included in the analyses

Characteristic	Placebo No.	Placebo %	Tamoxifen No.	Tamoxifen %
Age, y				
35–39	185	2.8	159	2.4
40–49	2411	36.5	2422	36.8
50–59	2017	30.6	2031	30.9
60–69	1590	24.1	1571	23.9
⩾70	396	6.0	393	6.0
Race				
White	6359	96.4	6347	96.5
Black	111	1.7	109	1.7
Other	129	2.0	120	1.8
No. of first-degree relatives with breast cancer				
0	1595	24.2	1540	23.4
1	3731	56.5	3754	57.1
2	1092	16.5	1069	16.3
⩾3	181	2.7	213	3.2
Prior hysterectomy				
No	4194	63.6	4097	62.3
Yes	2405	36.4	2479	37.7
History of lobular carcinoma *in situ*				
No	6188	93.8	6161	93.7
Yes	411	6.2	415	6.3
History of atypical hyperplasia in the breast				
No	5985	90.7	5997	91.2
Yes	614	9.3	579	8.8
5-y predicted breast cancer risk, %				
⩽2.00	1660	25.2	1636	24.9
2.01–3.00	2031	30.8	2057	31.3
3.01–5.00	1791	27.1	1714	26.1
⩾5.01	1117	16.9	1169	17.8
Total	6599	100.0	6576	100.0

Comment: given the low recruitment of black women, this population is generalisable to the Australian population

Age Distribution	See above table
Distribution of Risk Factor(s) for the development of Breast Cancer	Approximately one-quarter of the women had a 5-year predicted breast cancer risk of 2.00% or less, almost 58% had a 5-year risk of between 2.01% and 5.00%, and 17% had a 5-year risk of more than 5.00%. – see table above Re family history: Almost one fourth (23.8%) of the participants had no first degree relatives with breast cancer. More than one half (56.8%) had one first-degree relative with breast cancer, 16.4% had two, and 3.0% had three or more
Efficacy Results	A total of 368 invasive and noninvasive breast cancers occurred among the 13 175 participants; 244 of these occurred in the placebo group and 124 in the tamoxifen group. **Invasive breast cancer:** There were 175 cases in the placebo group compared to 89 in the tamoxifen group (P<.00001). The cumulative incidence through 69 months was 43.4 per 1000 women and 22.0 per 1000 women in the two groups, respectively, showing a reduction in risk of 49% in the tamoxifen group. The reduction in events of invasive breast cancer was sustained across the duration of the trial – see figures below.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

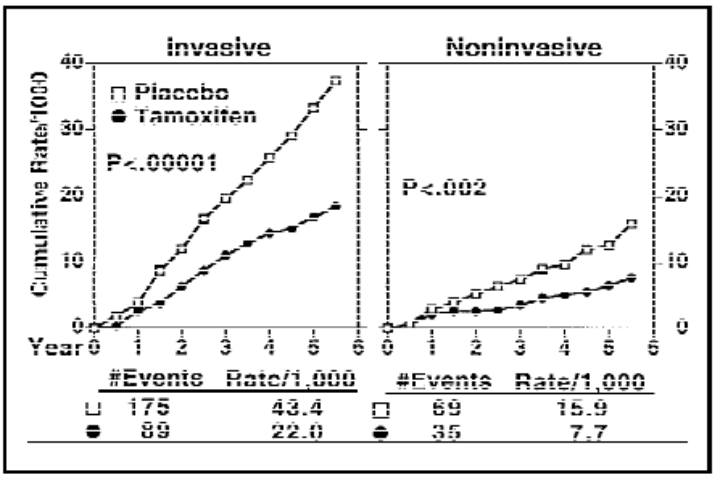


Fig. 2. Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen. The *P* values are two-sided.

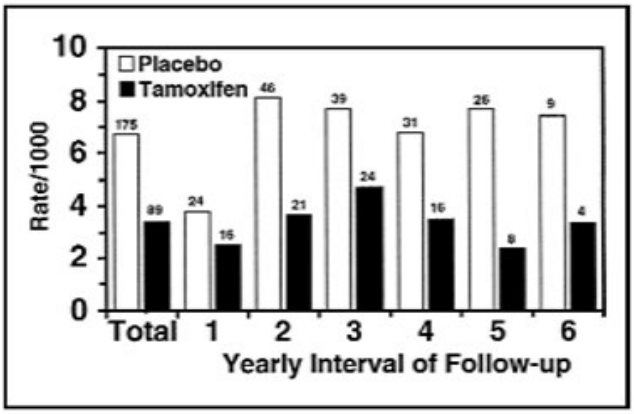


Fig. 3. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by yearly interval of follow-up. Numbers above the bars indicate numbers of events.

The rate of invasive breast cancer was reduced in all subgroups, although this was not significant in all groups (see table below).

Table 3. Average annual rates for invasive breast cancer by age, history of lobular carcinoma *in situ* (LCIS), history of atypical hyperplasia, 5-year predicted breast cancer risk, and number of first-degree relatives with breast cancer

Patient characteristic	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
All women	175	89	6.76	3.43	0.51	0.39–0.66
Age, y						
<49	68	38	6.70	3.77	0.56	0.37–0.85
50–59	50	25	6.28	3.10	0.49	0.29–0.81
≥60	57	26	7.33	3.33	0.45	0.27–0.74
History of LCIS						
No	157	81	6.41	3.30	0.51	0.39–0.68
Yes	18	8	12.99	5.69	0.44	0.16–1.06
History of atypical hyperplasia						
No	152	86	6.44	3.61	0.56	0.42–0.73
Yes	23	3	10.11	1.43	0.14	0.03–0.47
5-y predicted breast cancer risk, %						
≤2.00	35	13	5.54	2.06	0.37	0.18–0.72
2.01–3.00	42	29	5.18	3.51	0.68	0.41–1.11
3.01–5.00	43	27	5.88	3.88	0.66	0.39–1.09
≥5.01	55	20	13.28	4.52	0.34	0.19–0.58
No. of first-degree relatives with breast cancer						
0	38	17	6.45	2.97	0.46	0.24–0.84
1	90	46	6.00	3.03	0.51	0.35–0.73
2	37	20	8.68	4.75	0.55	0.30–0.97
≥3	10	6	13.72	7.02	0.51	0.15–1.55

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Comment: From the Foreign product information for Soltamox (tamoxifen as available in the USA) as provided by the sponsor- *For most participants, multiple risk factors would have been required for eligibility. This table presents risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer*

There was no evidence of a significant difference in the rates of ER-negative invasive breast cancer (1.20 per 1000 women in the placebo group and 1.46 per 1000 women in the tamoxifen group; RR 4 1.22; 95% CI 4 0.74–2.03) – see figure below

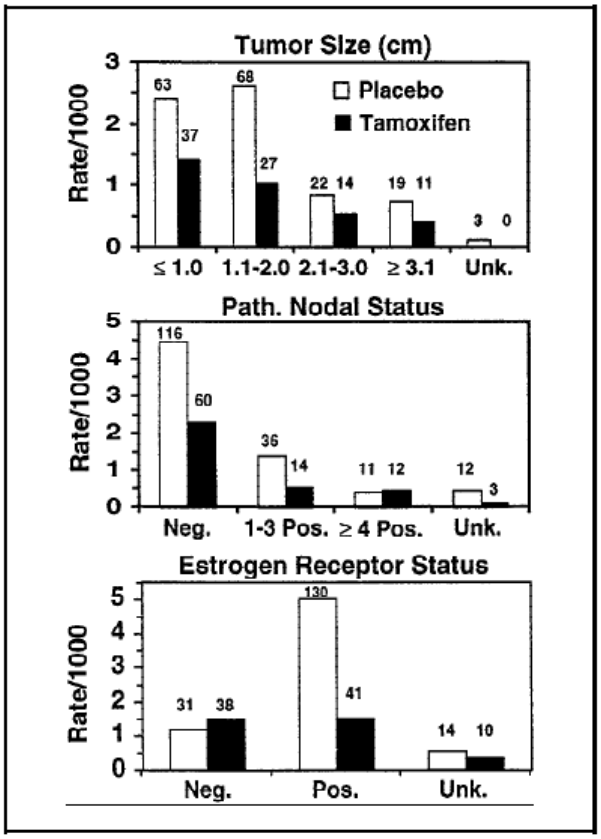


Fig. 4. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by tumor size, lymph node status, and estrogen receptor status. Numbers above the bars indicate numbers of events. UNK. = unknown; Path. = pathologic; Neg. = negative; Pos. = positive.

Non-invasive breast cancer:

There were 69 cases in women receiving placebo and 35 in those receiving tamoxifen (P<.002). The cumulative incidence through 69 months was 15.9 per 1000 women versus 7.7 per 1000 women in the tamoxifen group (see figure above). The average annual rate of noninvasive breast cancer per 1000 women was 2.68 in the placebo group compared with 1.35 in the tamoxifen group (RR of 0.50, 95% CI 4 0.33–0.77).

Deaths due to breast cancer:

Nine deaths were attributed to breast cancer: 6 in the group that received placebo and 3 in the tamoxifen group.

Quality of life:

Hot flashes and vaginal discharge were more common in the tamoxifen group. Similar proportions of women in each group had a CES-D score higher than 16.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 10. Distribution of participants in the placebo and tamoxifen groups by highest level of hot flashes, vaginal discharge, and depression reported*

Symptom	% of participants	
	Placebo (n = 6498)	Tamoxifen (n = 6466)
Hot flashes, bothersome		
No	31.4	19.4
Slightly	18.2	14.1
Moderately	21.7	21.8
Quite a bit	18.6	28.1
Extremely	10.1	17.6
Vaginal discharge, bothersome		
No	65.2	44.8
Slightly	21.8	26.2
Moderately	8.5	16.6
Quite a bit	3.3	9.3
Extremely	1.2	3.1
Depression (CES-D)†		
0–15	65.4	65.4
16–22	16.1	15.6
23–29	9.5	10.1
30–36	5.4	5.1
≥37	3.6	3.7

*The quality-of-life questionnaire that was used was a self-reporting instrument. Some participants opted not to complete the questionnaires. Thus, information is not available for 101 women in the placebo group and 110 in the tamoxifen group.

†CES-D refers to a self-administered depression scale developed by the Center for Epidemiological Studies *(36)*.

Further details regarding the findings regarding quality of life were presented in subsequent publications:

- *Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999;17:2659–69* that has not been included in the dossier (Clinical Question)
- Day 2001

Safety Results

Discontinuations –

Comment: Only the following information regarding premature discontinuation of treatment was provided: *The proportion of women who stopped their therapy was greater in the tamoxifen group, i.e., 19.7% in the placebo group versus 23.7% in the tamoxifen group*

Other information is available in other publications.

From the Soltamox PI:

As of Jan 1998, 27% of women randomized to placebo (1,782) and 24% of women randomized to tamoxifen (1,596) had completed 5 years of therapy.

From the related publication Day 2001 that compared the incidence of depressive symptoms in the study cohort:

An Off Therapy Form (OTF) was completed when participants discontinued from the trial. Of the 11 064 participants in the Day 2001 publication, an OTF was collected for 3539 women. Of these, 1679 were receiving placebo and 1860 were receiving tamoxifen. The most frequent reasons for going off therapy were nonmedical in nature (1667 women [47.1%]), perceived toxic effects (921 women [26.0%]), and various protocol and nonprotocol medical conditions (841 women [23.8%]) – see also table below from Day 2001.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 5. Reasons cited for going off treatment by depression risk* and treatment group

	Low risk		Medium risk		High risk		
Reasons cited for going off treatment	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Overall
Depression (No. of participants)	20	27	21	24	9	9	110
Other reasons (No. of participants)	1130	1275	416	431	83	94	3429
Depression as % of all off-treatment reasons	1.7	2.1	4.8	5.3	9.8	8.7	3.1

*Depression risk groups were assigned on the basis of the participants' responses to three medical history questions: 1) history of depression, 2) use of antidepressant medication, and 3) persistent mood disturbance (dysphoria). Each positive answer was worth 1 point. Participants with a score of 0 were assigned to the low-risk group, those with a score of 1–2 to the medium-risk group, and those with a score of 3 to the high-risk group.

Endometrial cancer:

There were a total of 51 reports of endometrial cancer: 36 in the tamoxifen group and 15 in the placebo group. Overall, participants who received tamoxifen had a 2.53 times greater risk of developing an invasive endometrial cancer (95% CI =1.35–4.97); the risk was 4 times greater in women aged over 50 years – see table below.

Table 4. Average annual rates of invasive and *in situ* endometrial cancer

	No. of events		Rate per 1000 women*			
Type of event	Placebo	Tamoxifen	Placebo	Tamoxifen	Risk ratio	95% confidence interval
Invasive cancer	15	36	0.91	2.30	2.53	1.35–4.97
Age, y						
<49	8	9	1.09	1.32	1.21	0.41–3.60
≥50	7	27	0.76	3.05	4.01	1.70–10.90
In situ cancer	3	1	0.18	0.06	0.35	0.01–4.38

*Women at risk; nonhysterectomized.

The increase in risk commenced early in the follow-up period and continued throughout – see figure below

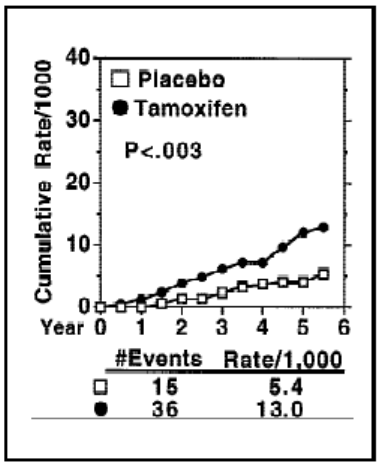


Fig. 5. Cumulative rates of invasive endometrial cancer occurring in participants receiving placebo or tamoxifen. The *P* value is two-sided.

Almost all of the endometrial cancers were assessed as FIGO stage 1(i.e., localised tumours): 14/15 in the placebo group and 36/36 in the tamoxifen group.

Invasive cancer other than breast and endometrial:

There were 97 cases of invasive cancer (not including breast or endometrial) in each group (RR

4 1.00; 95% CI 4 0.75–1.35). The distribution of these shows no disproportionate number of events at any site – see table below.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 5. Distribution of invasive cancers other than breast and uterine (endometrial) cancer

Primary cancer site*	No. of cancers	
	Placebo	Tamoxifen
Mouth, pharynx, larynx	2	3
Stomach	2	1
Gallbladder	1	0
Pancreas	7	4
Retroperitoneum	1	0
Colon	9	11
Rectum	3	4
Liver	0	0
Lung, trachea, bronchus	17	20
Lymphatic, hematopoietic systems	11	14
Ovary/fallopian tube	11	10
Other genital	4	4
Urinary bladder	1	3
Kidney	3	2
Connective tissue	2	1
Skin	9	11
Nervous system	3	1
Thyroid gland	5	4
Unknown	6	4
Total	97	97
Average annual rate per 1000 women	3.72	3.73
Risk ratio (95% confidence interval)	1.00 (0.75–1.35)	

*International Classification of Diseases code 9 *(68)*.

Ischaemic heart disease:

The number of participants who had an ischaemic cardiac event was 62 in the placebo group and 71 in the tamoxifen group. There was no significant change in risk with tamoxifen use – see table below.

Table 6. Average annual rates of ischemic heart disease

Type of event	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Myocardial infarction*	28	31	1.07	1.19	1.11	0.65–1.92
Fatal	8	7	0.30	0.27	0.88	0.27–2.77
Nonfatal	20	24	0.76	0.92	1.20	0.64–2.30
Severe angina†	14	13	0.53	0.50	0.93	0.40–2.14
Acute ischemic syndrome‡	20	27	0.77	1.03	1.36	0.78–2.55
Total	62	71	2.37	2.73	1.15	0.81–1.64

*International Classification of Diseases codes 410–414 *(68)*.
†Requiring angioplasty or coronary artery bypass graft.
‡New Q-wave on electrocardiogram without angina or elevation of serum enzymes or angina requiring hospitalization without surgery.

Fractures:

A total of 955 women experienced bone fractures, 483 and 472 in the placebo and tamoxifen groups. Fewer osteoporotic fracture events (combined hip, spine, and lower radius) occurred in women who received tamoxifen than in those who received placebo: 111 women in the tamoxifen group experienced fractures at one or more of these sites, as compared with 137 women in the placebo group, although this did not reach significance – see table below.

Table 7. Annual rates for fracture events among participants

Site of fracture	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Hip	22	12	0.84	0.46	0.55	0.25–1.15
Spine	31	23	1.18	0.88	0.74	0.41–1.32
Radius, Colles'	23	14	0.88	0.54	0.61	0.29–1.23
Other lower radius*	63	66	2.41	2.54	1.05	0.73–1.51
Total	137†	111‡	5.28	4.29	0.81	0.63–1.05
<49 y of age at entry	23	20	2.24	1.98	0.88	0.46–1.68
≥50 y of age at entry	114	91	7.27	5.76	0.79	0.60–1.05

*Excludes women who had a Colles' fracture.
†One woman had a hip fracture and a Colles' fracture, and one woman had a hip fracture and another lower radial fracture.
‡One woman had a hip fracture and a Colles' fracture, one woman had a hip fracture and a spine fracture, and two women had hip fractures and other lower radial fractures.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Vascular events (stroke, transient ischaemic attack, pulmonary embolism, deep vein thrombosis):

The numbers of events according to treatment group are shown in the table below. Strokes, DVT and PEs occurred more frequently in the tamoxifen group. This reached significance for DVTs and PEs..

Table 8. Average annual rates of vascular-related events by age at study entry

	No. of events		Rate per 1000 women			
Type of event by age at entry	Placebo	Tamoxifen	Placebo	Tamoxifen	Risk ratio	95% confidence interval
Stroke*	24	38	0.92	1.45	1.59	0.93–2.77
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	20	35	1.26	2.20	1.75	0.98–3.20
Transient ischemic attack	25	19	0.96	0.73	0.76	0.40–1.44
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	21	16	1.32	1.01	0.76	0.37–1.53
Pulmonary embolism†	6	18	0.23	0.69	3.01	1.15–9.27
≤49 y old	1	2	0.10	0.20	2.03	0.11–119.62
≥50 y old	5	16	0.31	1.00	3.19	1.12–11.15
Deep vein thrombosis‡	22	35	0.84	1.34	1.60	0.91–2.86
≤49 y old	8	11	0.78	1.08	1.39	0.51–3.99
≥50 y old	14	24	0.88	1.51	1.71	0.85–3.58

*Seven cases were fatal (three in the placebo group and four in the tamoxifen group).
†Three cases in the tamoxifen group were fatal.
‡All but three cases in each group required hospitalization.

Of the strokes, 14/24 that occurred in the placebo group and 21/38 of the strokes in the tamoxifen were reported as being the result of vascular occlusion.

Cataracts:

Two thirds of the way through the trial, the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC) reported an excess risk of cataracts and cataract surgery among women in the tamoxifen group. This was through self-reporting of cataract development and cataract surgery by participants. Information regarding cataract surgery was then verified by examination of medical records. The rate of cataract development among women who were cataract-free at the time of randomisation was 21.72 per 1000 women in the placebo group and 24.82 per 1000 women in the tamoxifen group (RR 1.14, 95% CI 4 1.01–1.29). The rate of undergoing cataract surgery was 3.00 per 1000 in the placebo and 4.72 per 1000 women in the amoxifen group (RR 1.57; 95% CI 1.16–2.14).

Occurrence of tamoxifen-related non-life-threatening side effects :

The only symptomatic differences noted between the placebo and tamoxifen groups were related to hot flashes and vaginal discharge, both of which occurred more often in the latter group – see table below.

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive

Table 10. Distribution of participants in the placebo and tamoxifen groups by highest level of hot flashes, vaginal discharge, and depression reported*

Symptom	% of participants	
	Placebo (n = 6498)	Tamoxifen (n = 6466)
Hot flashes, bothersome		
No	31.4	19.4
Slightly	18.2	14.1
Moderately	21.7	21.8
Quite a bit	18.6	28.1
Extremely	10.1	17.6
Vaginal discharge, bothersome		
No	65.2	44.8
Slightly	21.8	26.2
Moderately	8.5	16.6
Quite a bit	3.3	9.3
Extremely	1.2	3.1
Depression (CES-D)†		
0–15	65.4	65.4
16–22	16.1	15.6
23–29	9.5	10.1
30–36	5.4	5.1
⩾37	3.6	3.7

*The quality-of-life questionnaire that was used was a self-reporting instrument. Some participants opted not to complete the questionnaires. Thus, information is not available for 101 women in the placebo group and 110 in the tamoxifen group.

†CES-D refers to a self-administered depression scale developed by the Center for Epidemiological Studies *(36)*.

Deaths:

Seventy-one deaths occurred among participants in the placebo group and 57 occurred among women in the tamoxifen group (RR=0.81; 95% CI=0.56–1.16). See table below for the distribution of causes of death.

Table 11. Distribution of causes of death

Cause	No. of deaths	
	Placebo	Tamoxifen
Cancer	42	23
Brain	3	1
Breast	6	3
Colon	1	1
Uterus (endometrium)	1	0
Lung	11	8
Ovary	1	2
Lymphatic system	4	2
Pancreas	6	2
Extrahepatic bile duct	1	0
Kidney	2	0
Melanoma	0	1
Thyroid gland	1	0
Primary site unknown	5	3
Cardiac and vascular disease	15	22
Heart disease (ischemic and other)	12	13
Stroke	3	4
Pulmonary embolus	0	3
Arterial disease	0	2
Other	14	12
Amyotrophic lateral sclerosis	2	0
Automobile accident	2	1
Miscellaneous (11 different causes)	6	7
Unknown	4	4
Total deaths	71	57
Average annual rate per 1000 women	2.71	2.17
Risk ratio (95% confidence interval)	0.81 (0.56–1.16)	

Missing data	A breakdown of women who discontinued from the trial was not provided

Publication Identifier	Fisher 1998, Efficacy and Safety, Primary Supportive
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. The study appears to have been well run with potential bias minimised. Of note, however, is that only 24% of women completed 5 years of treatment with tamoxifen. The major efficacy finding was of a statistically and clinically significant reduction in oestrogen receptor positive breast cancer. This did not translate into a reduction in mortality during the follow-up period. There was a significant increase in the occurrence of endometrial cancer and cataracts in the tamoxifen group. Other adverse events of concern, including thromboembolic disease , were not significantly increased in the tamoxifen group.

Fisher 2005

Publication Identifier	Fisher 2005, Efficacy and Safety, Primary Supportive
Citation	Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652-62.
Relationship to trial	7 year follow-up results (average 74 months)
Documented GCP or ethics approval	No statement(s) provided.
Conflict of Interest	No statement(s) provided
Funding source(s)	The following statement was provided: *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*
Study design	The original protocol for the P-1 study included follow-up for 7 years after randomisation. After the trial was unblended, the protocol was amended to continue follow-up, beyond 7 years, but only for those women who had been randomly assigned to the tamoxifen group. The following rationale for unblinding was provided: *In 1998, when an overall 49% reduction in the risk of breast cancer (P <.001) was observed, the independent data monitoring committee that regularly reviewed the P-1 data decided that the primary aim of the trial had been attained beyond all reasonable doubt. The committee recommended, therefore, that the study be unblinded, the findings be disclosed, and participants be informed of whether or not they had received placebo so that they could decide whether to take tamoxifen to reduce their risk of breast cancer*. Comment: The method of follow-up, before and after unblinding, was not described
Study Location	USA and Canada
Study Dates	Randomisation occurred between June 1992 – September 1997. Data lock date for this publication was March 31, 2005
Study treatment	Follow-up for 7 years post-randomisation, including the initial 5 years of treatment with tamoxifen/placebo.
Study	As above – Fisher 1998

population	
Key selection criteria	As above – Fisher 1998
Concurrent medications	HRT and OCP not allowed during 5 years of treatment
Outcome measure(s)	Incidence of invasive breast cancer, incidence of non-invasive breast cancer
Safety measure(s)	Incidence of endometrial cancer, incidence of invasive cancer other than breast and endometrial, ischaemic heart disease, fractures (hip, spine and Colle's), vascular events (stroke, transient ischaemic attack, pulmonary embolism, deep vein thrombosis), cataracts Occurrence of tamoxifen-related non-life-threatening side effects (hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhea, and weight gain or loss)
Randomisation	As above – Fisher 1998
Blinding	Blinding of participants and investigators was maintained until April 1 1998, when all investigators were provided with lists identifying treatment assignment for each participant. Women in the tamoxifen group who wished to do so continued to receive that drug for a total of 5 years. Participants in the placebo group were given the opportunity either to receive a 5-year course of tamoxifen or to be randomized to the Study of Tamoxifen and Raloxifene (STAR) trial. Almost 32% of the women in the placebo group accepted one of those alternatives. Other women in the placebo group received tamoxifen or raloxifene by prescription, although the precise number of women who did so is unknown..
Statistical analysis	All randomly assigned participants who were at risk and for whom follow-up data were obtained were included. All analyses were based on the assignment of women at the time of their randomisation. Because follow-up data were not collected for participants in the placebo group after 7 years, analyses only included data up to 7 years. Incidence rates for the study end points were calculated for each group by dividing the number of observed events by the number of observed event-specific person-years of follow-up. Two-sided P values for tests of differences between the groups for the rates of invasive breast cancer, non-invasive breast cancer, and invasive endometrial cancer were determined by use of the exact method. Event rates in the two groups were also compared by use of risk ratios (RRs) and 95% confidence intervals (CIs).
Participant Flow	After unblinding of the study in March 1998, many women decided to withdraw from the study, with this disproportionately affecting the placebo group. As a result, the amount of information available for the two groups for the period between the sixth and seventh years of follow-up was substantially different (4931 completed 7 years in the tamoxifen group compared to 4379) - see table below.

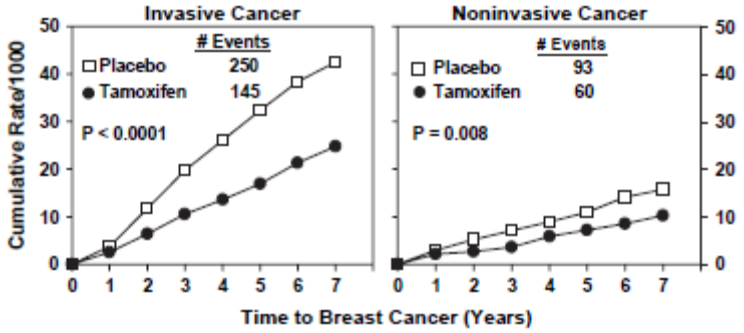
	Table 1. Women included in the analyses and number followed up through 5, 6, and 7 years | Accrual and follow-up status | Placebo | Tamoxifen | Total | |---|---|---|---| | Accrual | | | | | Women randomly assigned | 6707 | 6681 | 13 388 | | Not at risk* | 0 | 1 | 1 | | Without follow-up | 97 | 83 | 180 | | Included in analysis | 6610 | 6597 | 13 207 | | Follow-up time (y) | | | | | ≥5 | 5550 | 5602 | 11 152 | | ≥6 | 5285 | 5372 | 10 657 | | ≥7 | 4379 | 4931 | 9310 | | Average follow-up time (mo) | 73.8 | 74.3 | 74.0 | | Total person-years of follow-up included in this analysis† | 40 648 | 40 844 | 81 492 | *History of invasive breast cancer prior to randomization. †Follow-up was censored at 7 years (see text for details). Comment: In the initial report of the NSABP P1 results (Fisher 1998) , follow-up was not available for 212 women. According to this publication "*it has since been obtained for 32 of those women*" with this included in the 2005 publication.
Baseline Character-istics of Participants	See above – Fisher 1998
Efficacy Results	<u>Invasive Breast Cancer</u> The cumulative rate of invasive breast cancer was reduced from 42.5 per 1000 women in the placebo group to 24.8 per 1000 women in the tamoxifen group (P <.001) with a risk ratio of 0.57 (95% CI = 0.46 to 0.70) – see figure below  **Fig. 2.** Cumulative rates per 1000 women of invasive and noninvasive breast cancers in NSABP P-1 participants by treatment group. The risk of invasive breast cancer was reduced in the tamoxifen group for all subgroups, as defined by age, history of LCIS, history of atypical hyperplasia, or level of predicted risk of breast cancer –see table below.

Table 3. Events and incidence rates of invasive breast cancer in the placebo and tamoxifen groups by selected participant characteristics*

Characteristic	No. of events		Rate per 1000 women				
	Placebo	Tamoxifen	Placebo	Tamoxifen	Difference†	RR‡	95% CI
All women	250	145	6.29	3.59	2.70	0.57	0.46 to 0.70
Age at Entry (y)							
<49	98	63	6.32	4.04	2.28	0.64	0.46 to 0.89
50–59	72	42	5.87	3.33	2.54	0.57	0.38 to 0.84
≥60	80	40	6.68	3.30	3.38	0.49	0.33 to 0.73
History of LCIS							
No	221	129	5.93	3.41	2.52	0.58	0.46 to 0.72
Yes	29	16	11.70	6.27	5.43	0.54	0.27 to 1.02
History of AH							
No	212	136	5.87	3.69	2.18	0.63	0.50 to 0.78
Yes	38	9	10.42	2.55	7.87	0.25	0.10 to 0.52
5-y predicted breast cancer risk (%)§							
<2.00	58	40	4.77	3.18	1.59	0.67	0.43 to 1.01
2.01–3.00	67	41	6.13	3.88	2.25	0.63	0.42 to 0.95
3.01–5.00	45	27	4.51	2.70	1.81	0.60	0.36 to 0.99
≥5.01	80	37	11.98	5.15	6.83	0.43	0.28 to 0.64
No. of first-degree relatives with breast cancer							
0	62	33	6.47	3.48	2.99	0.54	0.34 to 0.83
1	124	73	5.52	3.16	2.36	0.57	0.42 to 0.77
2	52	32	7.84	4.91	2.93	0.63	0.39 to 0.99
≥3	12	7	11.24	5.48	5.76	0.49	0.16 to 1.34

*LCIS = lobular carcinoma in situ; AH = atypical hyperplasia; RR = risk ratio; CI = confidence interval.
†Rate in the placebo group minus rate in the tamoxifen group.
‡Risk ratio for women in the tamoxifen group relative to women in the placebo group.
§Determined with the Gail model (11).

Tamoxifen administration resulted in a 62% reduction in the rate of ER-positive invasive breast cancer but did not reduce the rate of ER-negative breast cancer – see table below

Table 4. Events and incidence rates of invasive cancer in the placebo and tamoxifen groups by selected tumor characteristics

Characteristic	No. of events (%)		Rate per 1000 women				
	Placebo	Tamoxifen	Placebo	Tamoxifen	Difference*	RR†	95% CI
Tumor size (cm)							
≤1.0	90 (36.0)	56 (38.6)	2.26	1.39	0.87	0.61	0.43 to 0.87
1.1–3.0	130 (52.0)	75 (51.7)	3.27	1.86	1.41	0.57	0.42 to 0.76
≥3.1	25 (10.0)	13 (9.0)	0.63	0.32	0.31	0.51	0.24 to 1.04
Unknown	5 (2.0)	1 (0.7)	0.13	0.02	0.11	0.20	0.01 to 1.76
Pathologic nodal status							
Negative	162 (64.8)	91 (62.8)	4.08	2.26	1.82	0.55	0.42 to 0.72
Positive	70 (28.0)	48 (33.1)	1.76	1.19	0.57	0.68	0.46 to 0.99
Unknown	18 (7.2)	6 (4.1)	0.45	0.15	0.30	0.33	0.11 to 0.86
Estrogen receptor status							
Negative	42 (16.8)	56 (38.6)	1.06	1.39	−0.33	1.31	0.86 to 2.01
Positive	182 (72.8)	70 (48.3)	4.58	1.74	2.84	0.38	0.28 to 0.50
Unknown	26 (10.4)	19 (13.1)	0.65	0.47	0.18	0.72	0.38 to 1.35

*Rate in the placebo group minus rate in the tamoxifen group.
†Risk ratio for women in the tamoxifen group relative to women in the placebo group. RR = risk ratio; CI = confidence interval.

The annual rates of invasive breast cancer were relatively stable through the 7 years of follow up in the tamoxifen group. The placebo group showed a more variable annual rate – higher in the years 2 to 6 and then declining to a rate similar to the tamoxifen group.

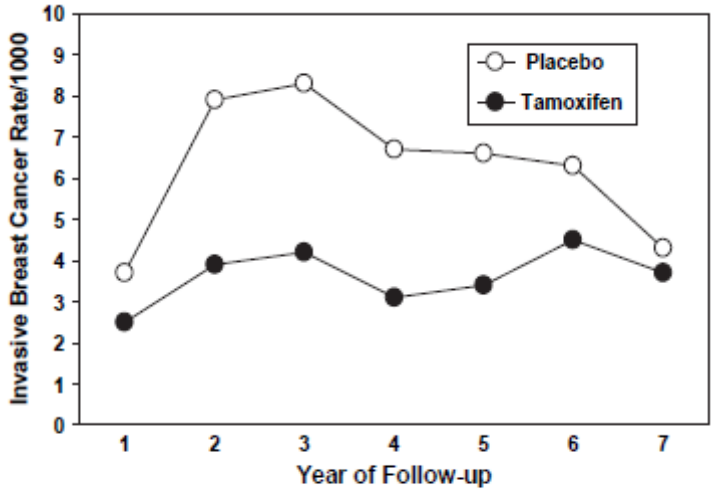


Fig. 3. Annual rates of invasive breast cancer per 1000 women by year of follow-up and treatment group in NSABP P-1.

Comment: there were 552 fewer women continuing in follow-up between the years 6 and 7 in the

placebo group

Non-invasive breast cancer

The cumulative rate of noninvasive breast cancer (ductal carcinoma in situ [DCIS] and LCIS) was lower in the tamoxifen group: 10.2 per 1000 women compared to 15.8 per 1000 women in the placebo group (P 0.008, RR 0.63 with 95% CI = 0.45 to 0.89)

Deaths due to breast cancer:

There were 11 deaths due to breast cancer in the placebo group and 12 such deaths in the tamoxifen group.

Safety Results

Discontinuations

Comment: No discussion/description provided apart from it being noted that there was a disproportionate discontinuation rate in the placebo group in the final years of follow-up (after announcement of the early results) resulting in the proportion of women in the placebo group who completed 7 years of follow-up being 8.5% less

Deaths

Death rates were similar in the two groups (RR = 1.10, 95% CI = 0.85 to 1.43). No cause-specific category of death exhibited a statistically significant difference between the groups. The most frequent cause of death was lung cancer, with 17 such deaths occurring in each group – see table below.

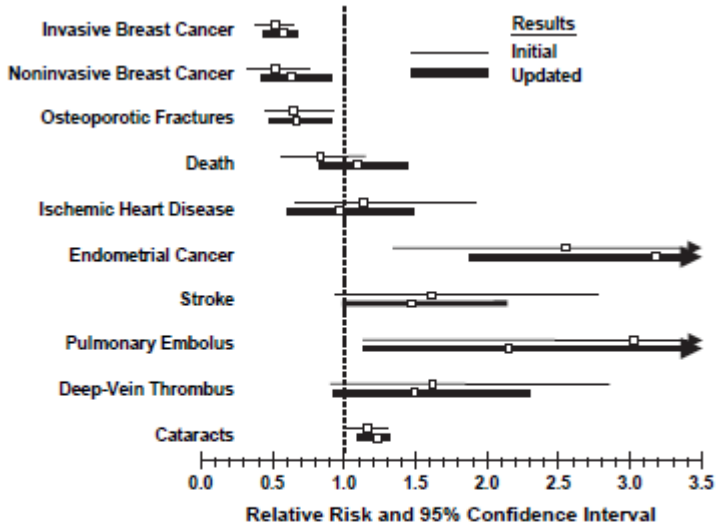
Table 10. Deaths in the placebo and tamoxifen groups

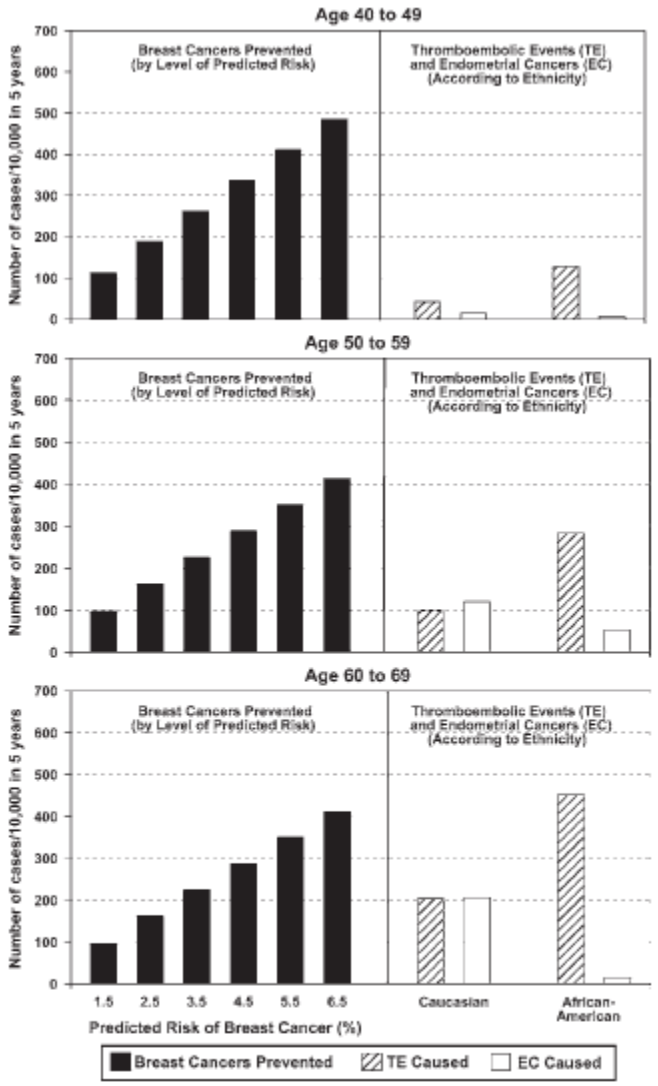
Cause of death	Placebo	Tamoxifen
Cancer		
Bladder	0	1
Brain	5	2
Breast	11	12
Colon	2	2
Gallbladder and extrahepatic bile duct	4	0
Kidney	3	2
Lung	17	17
Lymphatic and hematopoietic	8	5
Melanoma	0	1
Ovary	3	7
Pancreas	9	4
Stomach	1	1
Thyroid gland	1	0
Uterus	1	0
Primary site unknown	6	3
Cardiac and vascular disease		
Disorder of arteries	0	1
Ischemic heart disease	11	11
Other heart disease	7	12
Pulmonary embolism	1	3
Stroke	3	9
Other		
Auto accident	2	1
Other disease of the digestive system	3	1
Kidney/urinary tract	2	2
Other lung disease	0	3
Septicemia and other infection	1	2
Miscellaneous	6	7
Unknown	7	17
Total No. of deaths	114	126
Incidence rate per 1000 women	2.80	3.08
RR (95% CI)*	1.10 (0.85 to 1.43)	

*RR = risk ratio; CI = confidence interval.

Endometrial cancer

There were 70 cases of endometrial cancer (17 in the placebo group and 53 in the tamoxifen group). Overall, women who received tamoxifen had a statistically significantly increased risk of invasive endometrial cancer (RR = 3.28, 95% CI = 1.87 to 6.03). The risk was not increased in women aged 49

	years or younger (RR = 1.42, 95% CI = 0.55 to 3.81), but there was a statistically significant increase in risk in women aged 50 years or older (RR = 5.33, 95% CI = 2.47 to 13.17). The cumulative rate of invasive endometrial cancer through 7 years of follow-up was 4.68 per 1000 women in the placebo group and 15.64 per 1000 women in the tamoxifen group, respectively (P <.001). Of the 70 cases, 67 cases (15 in the placebo group and 52 in the tamoxifen group) were International Federation of Gynecology and Obstetrics (FIGO) stage I. In addition to these cases of endometrial cancer, there were four cases of uterine sarcoma, one in the placebo group and three in the tamoxifen group **Invasive cancer other than breast or endometrial** There were 155 cancers at 18 sites other than the breast and endometrium among women who received placebo and 178 cancers at 21 other sites among those who received tamoxifen. None of the differences by site was statistically significant. **Thromboembolic events** (strokes, TIAs, PE, DVT) The incidence rate of stroke was 0.05% greater in the tamoxifen group than in the placebo group but the increase was not statistically significant (RR = 1.42, 95% CI = 0.97 to 2.08). The risk of transient ischemic attacks was similar in both groups (RR = 0.91, 95% CI = 0.54 to 1.52). The incidence of pulmonary embolism was statistically significantly greater in the tamoxifen group than in the placebo group: RR = 2.15, 95% CI = 1.08 to 4.51); for DVT . **Ischaemic heart disease** Risk ratios comparing tamoxifen with placebo for fatal and nonfatal myocardial infarctions, severe angina, and acute ischemic syndrome ranged from 0.94 (95% CI = 0.55 to 1.58) to 1.12 (95% CI = 0.68 to 1.86). Overall, the risk ratio for ischemic heart disease was 1.03 (95% CI = 0.79 to 1.36). **Fractures** The rate of hip, spine, and radius (Colles') fractures was reduced in the tamoxifen group (RR 0.68, 95% CI = 0.51 to 0.92). Most fractures (89%) occurred in women aged 50 years or older. In this age group, fractures in the tamoxifen group was reduced fractures by 29% (RR 0.71, 95% CI = 0.52 to 0.97).
Comparison to 1998 results	A comparison to the earlier report (Fisher 1998) was provided – see figure below  **Fig. 1.** Comparison of relative risks (with 95% confidence intervals) of benefits and undesirable effects of tamoxifen from the initial and updated results of NSABP P-1.
Risk-benefit	A discussion of the possible net benefit of tamoxifen is provided. This compares the reduction in the

assessment	incidence of breast cancer with the increase in the major risks of PE and endometrial cancer – see figure below  **Fig. 4.** Benefits and risks associated with tamoxifen use for breast cancer risk reduction. Numbers of breast cancers prevented by tamoxifen in cases per 10 000 women over 5 years by 10-year age group and by level of predicted risk (**left**). Numbers of thromboembolic events and endometrial cancers caused by tamoxifen in cases per 10 000 women over 5 years, by ethnicity (**right**).
Missing data	
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. Given that this was an open follow-up phase of the original randomised controlled double blinded trial it may be more correctly categorised as Level III and as a secondary supportive publication. Interpretation of results of this follow-up study is limited due to potential bias and confounding of the long-term results resulting from unblinding and disproportionate discontinuations in the placebo group following the announcement of the "positive result" in the initial publication.

NSABP P1 Related Publications (Efficacy and Safety)

King 2001

Publication identifier	**King 2001, Efficacy, Secondary Supportive**

Publication identifier	King 2001, Efficacy, Secondary Supportive
Citation	King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, Wickerman L et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286(18):2251-6.
Study description	Retrospective cohort study To evaluate the effect of tamoxifen on incidence of breast cancer among cancer-free women with inherited BRCA1 or BRCA2 mutations
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *Tamoxifen was supplied by AstraZeneca Pharmaceuticals LP. Dr Wickerham is a member of the speaker's bureau for AstraZeneca* *Funding/Support This work was supported by National Institutes of Health grant U10 CA37377 to the NSABP Operations Center with a subaward (U10CA69974) to the University of Washington and the NSABP Biostatistics Center*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was performed after 1998
Study Method	All cases of invasive breast cancer occurring in participants of the NSABP P1 trial prior to un-blinding in 1998 and for whom a peripheral blood sample was available for retrospective DNA testing were included. DNA testing for all mutations definitely predisposing to breast cancer was performed with these defined as protein terminating mutations anywhere in *BRCA1* and in exons 2 through 26 of *BRCA2,* and missense mutations in the canonical cysteine residues of the *BRCA1* ring finger. Comparison was made of women who developed breast cancer according to the mutation status and whether the woman was randomised to placebo or tamoxifen.
Blinding	As above
Results	DNA testing was possible for 288 of 320 women who developed breast cancer: 19 (6.6%) women carried inherited, disease predisposing mutations of which 8 involved BRCA1 and 11 BRCA2.

Table 3. Study Participants Who Developed Breast Cancer

	Placebo	Tamoxifen	Risk Ratio (95% Confidence Interval)
BRCA1 mutation	3	5	1.67 (0.32-10.70)
BRCA2 mutation	8	3	0.38 (0.06-1.56)
Wild type	182	87	0.48 (0.37-0.61)
All participants*	211	109	0.52 (0.41-0.65)

*Includes 288 genotyped cases and 32 cases without DNA available.

Table 4. Estrogen-Receptor (ER) Status of Tumors*

	ER-Positive		ER-Negative	
	Placebo	Tamoxifen	Placebo	Tamoxifen
BRCA1 mutation	0	1	3	3
BRCA2 mutation	4	2	2	1
Wild type	132	41	32	36

*ER status unknown for 1 *BRCA1* tumor, 2 *BRCA2* tumors, and 28 wild-type tumors

Conclusion	There was a trend for tamoxifen to be associated with a lower incidence of breast cancer in women with BRCA2 mutations but not women with BRCA1 mutations.
Allocation by sponsor and	This was described as a "secondary supportive publication" with NHMRC level of evidence III-2 by the

Publication identifier	King 2001, Efficacy, Secondary Supportive
Evaluator assessment	sponsor. This is appropriate. Interpretation of this retrospective sub-group analysis is limited by the very small number of women who developed breast cancer and who were found to have BRCA1 or BRCA2 mutations.

Shen 2008

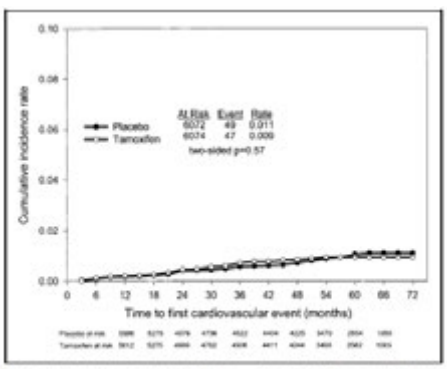
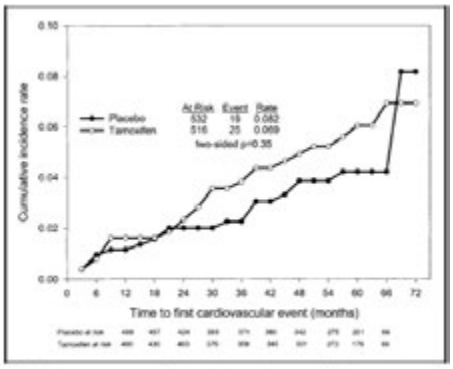
Publication identifier	Shen 2008, Efficacy, Secondary Supportive
Citation	Shen Y, Costantino JP, Qin J. Tamoxifen chemoprevention treatment and time to first diagnosis of estrogen receptor-negative breast cancer. J Natl Cancer Inst. 2008;100(20):1448-53.
Study description	Subset analysis of women who participated in the NSABP P1 trial and who developed invasive breast cancer
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *This study was reviewed and approved by NSABP Operations Center and the Institutional Review Board of the M. D. Anderson Cancer Center*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2008
Study Method	Analysis was according to time to diagnosis, oestrogen receptor status of the cancer, and randomisation to tamoxifen or placebo. At the time of this analysis, a total of 265 invasive breast cancers had been diagnosed (176 in the placebo arm and 89 in the tamoxifen arm). Among the 265 invasive breast cancers, 174 were ER positive, 69 were ER negative, and 22 had unknown ER status.
Blinding	As above
Results	Times to diagnosis of ER-positive tumours were similar in both tamoxifen and placebo treatment groups. Times to diagnosis of ER-negative tumors differed between treatment groups, with a median time of 36 months in the placebo group and 24 months in the tamoxifen group
Conclusion	Although chemoprevention with tamoxifen does not reduce the incidence of ER-negative breast cancer, it appears to have advanced the detection of ER-negative tumors by approximately 1 year.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with no NHMRC level of evidence by the sponsor. This sub-group analysis adds little information of relevance. Interpretation of the results is limited by the relatively small number of ER-negative breast cancers diagnosed

NSABP P1 Related Publications (Safety)

Reis 2001

Publication identifier	Reis 2001, Safety, Pivotal
Citation	Reis SE, Costantino JP, Wickerham DL, Tan-Chiu E, Wang J, Kavanah M. Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial Investigators. J Natl Cancer Inst.

Publication identifier	Reis 2001, Safety, Pivotal
	2001;93(1):16-21.
Study description	Retrospective cohort analysis to evaluate the cardiovascular effects of tamoxifen in women with and without pre-existing clinical coronary heart disease (CHD) who were enrolled in the NSABP P1 trial. Evaluation of the cardiovascular effects of tamoxifen was a secondary goal of the study, which was designed *a priori* to collect information on baseline cardiac status and cardiovascular events during follow-up.
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *Supported by Public Health Service grants U10CA37377 and U10CA69974 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services* *M. Kavanah and D. L. Wickerham are members of the speaker's bureau of Astra Zeneca, the manufacturer of tamoxifen.*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2001 with data up until the un-blinding of the trial (in 1998) included
Study Method	The 13 388 women enrolled in the trial were divided into those with and without a self-reported history of clinical CHD, defined as myocardial infarction or angina prior to randomisation. Medical records for subjects with suspected cardiovascular events during the trial were assessed by investigators who were blinded to treatment assignment. Primary cardiovascular events included fatal myocardial infarction, Q-wave and non-Q wave myocardial infarction. Secondary cardiovascular events included unstable angina (angina requiring hospitalization) and severe angina (angina requiring revascularization). All subjects were included in the analysis using the intent-to-treat principle. Comparisons of baseline characteristics between treatment groups were made. Average annual were calculated by dividing the observed number of events by the observed event-specific number of person-years of follow-up. Event rates between groups were by determining the risk ratio (RR) in which the rate in the tamoxifen group was divided by the rate in the placebo group. The 95% confidence intervals (CIs) for the RR were determined assuming that the events followed a Poisson distribution. Two-tailed *P* values <.05 or 95% CIs that did not include 1.0 were considered to be statistically significant
Blinding	As above
Results	Cardiovascular follow-up was available for 13 194 women, 1048 (7.9%) of whom had prior clinical CHD. The median follow-up was 57 months and mean follow-up was 49 months. There was no significant difference between the groups with regard to the baseline characteristics of BMI, race, systolic and diastolic blood pressure, cholesterol level, history of hypertension or diabetes or heart failure or TIA, use of aspirin or lipid lowering agents. There was a total of 140 cardiac events identified – 72 in the tamoxifen group and 68 in the placebo group, RR 1.06, 95% CI 0.75 to 1.49. There were also no statistically significant differences evident for any of the specific types of cardiovascular event – see table below. **Table 2.** Cardiovascular event rates for women in the Breast Cancer Prevention Trial Placebo (n = 6604) / Tamoxifen (n = 6590) Events / Rate* / Events / Rate* / Risk ratio† / 95% confidence interval Total myocardial infarction 30 1.11 32 1.19 1.07 0.63 to 1.82 Fatal myocardial infarction 8 0.30 7 0.26 0.88 0.27 to 2.76 Nonfatal myocardial infarction 22 0.82 25 0.93 1.14 0.62 to 2.12 Unstable angina 23 0.86 26 0.97 1.13 0.62 to 2.08 Severe angina 15 0.56 14 0.52 0.93 0.42 to 2.07 Total cardiovascular events 68 2.53 72 2.69 1.06 0.75 to 1.49 *Rate per 1000 person-years. †Risk ratio for tamoxifen compared with placebo users. Comparison of women with or without CHD showed a higher rate of cardiac events in the women

Publication identifier	Reis 2001, Safety, Pivotal
	with prior history of CHD. However, there is no significant difference between the treatment groups – see table below. **Table 3.** Cardiovascular event rates among women in the Breast Cancer Prevention Trial stratified by those with and without a baseline history of coronary heart disease (CHD) Placebo / Tamoxifen CHD history status and type of event — Events — Rate* — Events — Rate* — Risk ratio† — 95% confidence interval Women with baseline history of CHD (n = 1048) Total myocardial infarction — 9 — 4.27 — 6 — 2.97 — 0.69 — 0.20 to 2.18 Fatal myocardial infarction — 4 — 1.90 — 0 — 0 — 0.00 — 0 to 1.58 Nonfatal myocardial infarction — 5 — 2.37 — 6 — 2.97 — 1.25 — 0.32 to 5.18 Unstable angina — 7 — 3.37 — 15 — 7.61 — 2.26 — 0.87 to 6.55 Severe angina — 3 — 1.43 — 4 — 1.98 — 1.39 — 0.23 to 9.47 Total cardiovascular events — 19 — 9.14 — 25 — 12.68 — 1.39 — 0.73 to 2.67 Women without baseline history of CHD (n = 12146) Total myocardial infarction — 21 — 0.85 — 26 — 1.05 — 1.23 — 0.67 to 2.31 Fatal myocardial infarction — 4 — 0.16 — 7 — 0.28 — 1.75 — 0.44 to 8.13 Nonfatal myocardial infarction — 17 — 0.69 — 19 — 0.76 — 1.11 — 0.55 to 2.28 Unstable angina — 16 — 0.65 — 11 — 0.44 — 0.69 — 0.29 to 1.57 Severe angina — 12 — 0.48 — 10 — 0.40 — 0.83 — 0.32 to 2.10 Total cardiovascular events — 49 — 1.98 — 47 — 1.89 — 0.96 — 0.63 to 1.46 *Rate per 1000 person-years. †Risk ratio for tamoxifen compared with placebo users. Cumulative incidence curves for combined cardiovascular events were constructed. These show a progressive increase in events over time but no relationship to treatment (tamoxifen v placebo) for the two groups (with or without history of CHD) see figures below.   Comment: there were 133 events identified in the initial report of ischaemic cardiac events in Fisher 2008 where the average follow-up was around 48 months.
Conclusion	*A postulated cardio-protective effect of tamoxifen was not confirmed by this study.*
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" with NHMRC level of evidence II by the sponsor. Given that this is a retrospective analysis with grouping into cardiovascular risk groups by self-reporting of cardiac events, has median follow-up less than the planned treatment duration of tamoxifen and was not powered to demonstrate a difference in cardiac events between the two groups, it is arguable that it may be better characterised as primary supportive. The publication provides an additional analysis of the ischaemic cardiac events reported in the NSABP P1 and, within the limitations described, does not show either a protective effect or an increased risk of ischaemic cardiac events with tamoxifen for women with or without a history of CHD.

Day 2001

Publication identifier	Day 2001, Safety, Primary Supportive
Citation	Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Randomized Study. J Natl Cancer

Publication identifier	Day 2001, Safety, Primary Supportive
	Inst. 2001;93(21):1615-23.
Study description	Randomised, double blind, placebo controlled trial to investigate the effects of tamoxifen on women at different levels of risk for depression. Assessment of depressive symptoms was through completion of the Center for Epidemiological Studies—Depression (CES-D) questionnaire by participants
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *Supported by Public Health Service grant NCI-U10CA37377/69974 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; by career development award DAMD17–97–1-7058 from the Department of Defense (to R. Day); and in part by an American Cancer Society Clinical Research Professorship (to P. A. Ganz).* *All investigations conducted in the P-1 study were approved by review boards at each institution and were in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2001
Study Method	Women participating in the NSABP P1 trial were prospectively assessed for depression risk on the basis of medical history items collected at the baseline examination and placed in a high-, medium-, or low-risk group. Every 6 months, for a total of 36 months, the participants were assessed for depressive symptoms by completing the Center for Epidemiological Studies—Depression (CES-D) questionnaire. Scores of 16 or higher were indicative of an episode of affective distress. Differences between the risk groups and treatment arms were analysed by logistic regression. Participants in the trial who discontinued were asked about their primary reason for going off treatment, and their responses were recorded on an Off Therapy Form (OTF) that included "depression" as one of 10 specific response categories.
Blinding	As above
Results	11 064/13388 women enrolled in the NSABP P1 trial were included in this analysis. Baseline assessment of depressive risk and sociodemographic variables Women in the higher risk depression groups were more likely to score 16 or higher on the CES-D. Within each depression risk group, there was no difference in the proportion of women scoring 16 or higher by treatment assignment (tamoxifen versus placebo) (odds ratio =0.98; 95% CI = 0.93 to 1.02).

Publication identifier	Day 2001, Safety, Primary Supportive

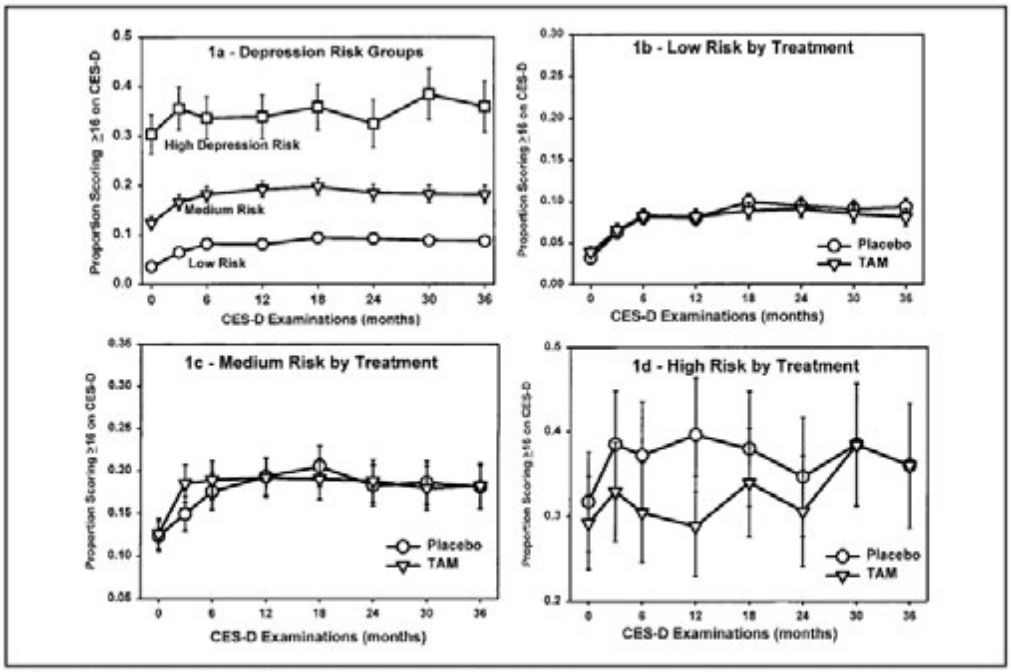


Fig. 1. Proportion of participants in the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Study scoring 16 or higher on the Center for Epidemiological Studies—Depression (CES-D) Scale with 95% confidence intervals by depression risk groups (low, medium, or high) (a) and by depression risk group and treatment assignment (placebo versus tamoxifen [TAM]) (b–d). Depression risk groups were assigned on the basis of the participants' responses to three medical history questions: 1) history of depression, 2) use of antidepressant medication, and 3) persistent mood disturbance (dysphoria). Each positive answer was worth 1 point. Participants with a score of 0 were assigned to the low-risk group, those with a score of 1–2 to the medium-risk group, and those with a score of 3 to the high-risk group.

An analysis of the missing data was performed. Logistic regression analysis by depression risk, controlling for sequential examination, indicates that, compared with placebo treatment, tamoxifen treatment was associated with higher proportions of missing data in the low-risk group (OR 1.11; 95% CI 1.06 to 1.16; *P*<.001) and the medium-risk group (OR 1.12; 95% CI 1.04 to 1.21; *P*<.001) but not in the high-risk group (OR 0.99; 95% CI 0.84 to 1.16; *P* = 0.91).

Of the 11 064 participants in this cohort, an OTF was collected for 3539 (80.8%) of 4382 women who missed at least one CES-D examination. Only 110 (3.1%) of these 3539 women reported that depression was the primary reason for their going off therapy.

Conclusion	As above
Allocation by sponsor and Evaluator assessment	This publication was described as a "primary supporting publication" with NHMRC level of evidence II by the sponsor. This seems appropriate. However, the publication does not describe why only 11064 of the 13388 trial participants were included, the assessment of depressive risk was through self-reporting and it covers only the first three of five years of tamoxifen treatment. Despite this, the publication provides some information regarding discontinuations from the NSABP P1 trial that has not been available elsewhere and suggests that depressive symptoms are not related to tamoxifen when used as prevention in women with increased risk of breast cancer. Of note is that this publication is a follow-on publication by the group that published the health related quality of life assessment for participants in the NSABP P1 trial (Day 1999). This publication has not been included in the dossier for reasons that are not apparent (**TGA Clinical Question Search Strategy and Results 3**). The abstract is included below.

Day 1999

This publication was not provided in the dossier. The evaluator was unable to obtain a copy of the publication but the abstract is publically available and included here.

This publication was not provided in the dossier. The evaluator was unable to obtain a copy of the publication but the abstract is publically available and included here.

Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999;17:2659–69.

Abstract

PURPOSE:

This is the initial report from the health-related quality of life (HRQL) component of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. This report provides an overview of HRQL findings, comparing tamoxifen and placebo groups, and advice to clinicians counseling women about the use of tamoxifen in a prevention setting.

PATIENTS AND METHODS:

This report covers the baseline and the first 36 months of follow-up data on 11,064 women recruited over the first 24 months of the study. Findings are presented from the Center for Epidemiological Studies-Depression Scale (CES-D), the Medical Outcomes Study 36-Item Short Form Health Status Survey (MOS SF-36) and sexual functioning scale, and a symptom checklist.

RESULTS:

No differences were found between placebo and tamoxifen groups for the proportion of participants scoring above a clinically significant level on the CES-D. No differences were found between groups for the MOS SF-36 summary physical and mental scores. The mean number of symptoms reported was consistently higher in the tamoxifen group and was associated with vasomotor and gynecologic symptoms. Significant increases were found in the proportion of women on tamoxifen reporting problems of sexual functioning at a definite or serious level, although overall rates of sexual activity remained similar.

CONCLUSION:

Women need to be informed of the increased frequency of vasomotor and gynecologic symptoms and problems of sexual functioning associated with tamoxifen use. Weight gain and depression, two clinical problems anecdotally associated with tamoxifen treatment, were not increased in frequency in this trial in healthy women, which is good news that also needs to be communicated

Cushman 2003

Publication identifier	**Cushman 2003, Safety, Secondary Supportive**
Citation	Cushman M, Costantino JP, Bovill EG, Wickerham DL, Buckley L, Roberts JD, et al. Effect of tamoxifen on venous thrombosis risk factors in women without cancer: the Breast Cancer Prevention Trial. Br J Haematol. 2003;120(1):109-16
Study description	Subset analysis of NSABP P1 participants (participants at a single site in the trial) to evaluate the effects of 6 months treatment with preventative tamoxifen on venous thrombosis risk in women without cancer
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *Funding source: US Public Health Service grant U10-CA-7377, and U10-CA-699974 from the National Cancer Institute, and HL03618 from the National Heart, Lung and Blood Institute (to M.C.).*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2003

Publication identifier	Cushman 2003, Safety, Secondary Supportive
Study Method	Peripheral blood was collected in trial participants at baseline and at 6 months. Activated protein C (APC) ratio and concentrations of antithrombin, protein C antigen, and total protein S were measured. Comparison was made between women randomised to receive tamoxifen and women randomised to receive placebo
Blinding	As above
Results	There were 111 women recruited to the trial at this site. Of these, there were 100 for whom appropriate blood specimens were available (54 women assigned to placebo and 46 assigned to tamoxifen). All 100 women completed 6 months of the trial and compliance with treatment was > 98% according to pill counts. Over 6 months of follow-up, the concentrations of the three anticoagulant proteins did not change substantially in the placebo group, while significant declines in antithrombin and protein S, but not protein C, were noted in the tamoxifen group
Conclusion	*"It is not known whether the observed effect size of tamoxifen on antithrombin or protein S would translate to a clinical effect"*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This retrospective sub-group analysis involving a small proportion of affected women (15%) provides a limited amount of information regarding laboratory changes that may be seen with tamoxifen. No clinical correlation of the findings of minor changes in levels of protein S and antithrombin with 6 months of tamoxifen treatment is made

Cushman 2001

Publication identifier	Cushman 2001, Safety, Secondary Supportive
Citation	Cushman M, Costantino JP, Tracy RP, Song K, Buckley L, Roberts JD, et al. Tamoxifen and cardiac risk factors in healthy women: Suggestion of an anti-inflammatory effect. Arterioscler Thromb Vasc Biol. 2001;21(2):255-61.
Study description	Subset analysis of NSABP P1 participants (participants at a single site in the trial) to evaluate the effects of 6 months treatment with preventative tamoxifen on factors related to inflammation, hemostasis and lipids in women without cancer
Funding source, Ethics approval, Conflicts of interest	The following statements are provided:
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2001
Study Method	Peripheral blood was collected in trial participants at baseline and at 6 months. After trial completion, specimens were assayed for total cholesterol, triglyceride levels, fibrinogen, factor VIIc, prothrombin fragments 1-2 and C-reactive protein. Comparison was made between women randomised to receive tamoxifen and women randomised to receive placebo.
Blinding	As above
Results	There were 111 women recruited to the trial at this site. Of these, there were 100 for whom appropriate blood specimens were available (54 women assigned to placebo and 46

Publication identifier	Cushman 2001, Safety, Secondary Supportive
	assigned to tamoxifen). All 100 women completed 6 months of the trial and compliance with treatment was > 98% according to pill counts. Over 6 months of follow-up, tamoxifen was associated with a significant decline in fibrinogen, C-reactive protein and cholesterol.
Conclusion	The publication did not establish if these changes were clinically meaningful.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This sub-group analysis provides a limited amount of information regarding laboratory changes that may be seen with tamoxifen. No clinical correlation of the findings of changes in levels of fibrinogen, C-reactive protein and cholesterol after 6 months of tamoxifen treatment is made

Abramson 2002

Publication identifier	Abramson 2002, Safety, Secondary Supportive
Citation	Abramson N, Aster RH. Retrospective assessment of hypercoagulability in breast cancer prevention trial. J Clin Oncol. 2002;20(19):4133-4 Comment: this was published as a "letter to the editor"
Study description	Retrospective cohort study of women who participated in the NSABP P1 trial and who developed phlebitis, PE or stroke, with assessment for the detection of hypercoagulability abnormalities performed retrospectively
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *AstraZeneca (Wilmington, DE) agreed to reimburse expenses for all blood testing and shipments*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2001
Study Method	The 155 individuals recorded in NSABP P1 trial who had developed phlebitis, pulmonary embolism, and strokes were contacted (via the principle investigator at the relevant sites) and invited to participate. Of these, 24 (15%) consented and had peripheral blood collected for hypercoagulability testing. Treatment groups were uncoded after testing was complete.
Blinding	As above
Results	Of the 24 subjects, 8 women were from the placebo arm and 16 from the tamoxifen arm. Twenty of the subjects (83%) had abnormalities of hypercoagulability.
Conclusion	*"there were no statistically significant findings to support a role of drug treatment in the outcome of vascular disease"* although "*the limited number of subjects studied represented too small a subset of the overall BCPT group, thereby limiting statistical analysis of an effect by tamoxifen"*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence III by the sponsor. This is appropriate. This retrospective sub-group analysis involving a small proportion of affected women (15%) provides a limited amount of information regarding laboratory changes that may be seen with tamoxifen.

Abramson 2006

Publication identifier	Abramson 2006, Safety, Secondary Supportive
Citation	Abramson N, Costantino JP, Garber JE, Berliner N, Wickerham DL, Wolmark N. Effect of Factor V Leiden and prothrombin G20210→A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. J Natl Cancer Inst. 2006;98(13):904-10
Study description	Nested, matched, case–control (1 : 4) retrospective design and compared women in the BCPT who had experienced venous thromboembolic events with women who did not according to Factor V Leiden and prothrombin G20210 →A(PT20210) mutations
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: *IRB approvals were provided by participating organisations* *Supported by Public Health Service grants U10-CA-37377, U10- CA-69974, U10CA-12027, and U10CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by AstraZeneca Pharmaceuticals, Wilmington, DE.* *The study sponsors had no role in any aspect of study design, data collection, analysis, and interpretation of data, or in the development of the manuscript.* *Per contractual arrangement, the manuscript was submitted to AstraZeneca before submission.* *Dr. Wickerham is on the AstraZeneca speaker's bureau*
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2006
Study Method	Case patients were defined as women who participated in the NSABP P1 trial and who had experienced a pulmonary embolism or a deep vein thrombosis. Controls were matched to these women by age at entry, (±5 years), race (white, African American, other), treatment (tamoxifen, placebo), smoking status at entry (current smoker, former smoker, never smoker), and duration of treatment (+ 3 months). Where possible, 4 control subjects were selected for every case patient. The final analysis was of 76 cases and 295 controls.
Blinding	As above
Results	DNA quantities sufficient for genotyping were extracted from the peripheral blood specimens of 76 of the 81 NSABP P1 participants who experienced thromboembolic events. There was no significant difference in baseline characteristics except for a higher mean BMI in the case patients (30.0 compared to 27.1). Nine of the 76 case patients and 20 of the 295 control subjects had FVL and/or PT20210 mutations
Conclusion	A significant relationship between the use of tamoxifen, the development of venous thromboembolic events, and the presence of FVL and PT20210 genetic abnormalities could not be demonstrated.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence III-2 by the sponsor. This retrospective sub-group analysis adds little information of relevance although it suggests that testing for these hypercoagulable mutations prior to commencement of preventative tamoxifen is unlikely to assist with risk stratification for development of VTE.

Chalas 2005

Publication identifier	Chalas 2005, Safety, Secondary Supportive

Publication identifier	Chalas 2005, Safety, Secondary Supportive
Citation	Chalas E, Costantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, et al. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. Am J Obstet Gynecol. 2005;192(4):1230-7.
Study description	Subgroup analysis of women participating in NSABP P1 with an intact uterus at enrolment to describe benign gynaecological conditions that occurred in these women
Funding source, Ethics approval, Conflicts of interest	The following statements are provided: Nil
Study Dates	Recruitment to NSABP P1 was between 1992 and 1997. This analysis was published in 2005
Study Method	Clinical sites participating in the BCPT were required to report the following gynaecologic conditions diagnosed during the study period: leiomyomas, polyps, endometritis.endometriosis, and ovarian cysts. Surgical interventions, such as curettage, hysteroscopy, laparoscopy, oophorectomy, and hysterectomy were also recorded. For this analysis, only those events occurring up to the time of unblinding were included. The incidence rates of several benign gynaecologic conditions were determined and risks were compared among women receiving tamoxifen and those receiving placebo based on risk ratios (RRs) with 95% CIs. Comparisons included stratification by menopausal status, body mass index. and history of oestrogen use
Blinding	As above
Results	Compared with women taking placebo, pre- and post-menopausal women taking tamoxifen had a significantly greater incidence of endometrial hyperplasia, endometrial polyps, leiomyomas, endometriosis and gynaecologic surgical procedures, including hysterectomy – see table below.
Conclusion	*Supports the oestrogen agonist role of tamoxifen as the causative factor for the increased risk of developing endometrial polyps, leiomyomas. endometriosis, and endometrial hyperplasia*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This retrospective sub-group analysis of prospectively collected data provides additional information regarding the possible effects of preventative tamoxifen therapy on the uterus.

Table IV Number and average annual rate per 1000 participants of gynecologic conditions and procedures, by menopausal status at entry

	Premenopausal			Postmenopausal			Total		
	Rate per 1000			Rate per 1000			Rate per 1000		
Condition or procedure	Placebo	Tamoxifen	RR (95% CI)	Placebo	Tamoxifen	RR (95% CI)	Placebo	Tamoxifen	RR (95% CI)
Conditions									
Leiomyomas	31.07	41.33	1.3 (1.14-1.55)	13.19	18.08	1.4 (1.04-1.80)	23.25	31.21	1.3 (1.17-1.54)
Ovarian cysts	17.77	25.95	1.5 (1.20-1.78)	4.96	5.96	1.2 (0.76-1.92)	12.21	17.27	1.4 (1.18-1.70)
Polyps	12.98	25.03	1.9 (1.55-2.41)	8.69	20.66	2.4 (1.76-3.24)	11.14	23.17	2.1 (1.74-2.45)
Endometriosis	5.30	10.07	1.9 (1.35-2.70)	1.60	4.15	2.6 (1.29-5.58)	3.71	7.55	2.0 (1.50-2.78)
Endometritis	2.09	1.72	0.8 (0.41-1.64)	0.27	0.27	1.0 (0.07-14.26)	1.31	1.11	0.8 (0.44-1.62)
Procedures									
Curettage	21.75	32.06	1.5 (1.23-1.77)	8.66	32.85	3.8 (2.86-5.09)	16.04	32.39	2.0 (1.74-2.35)
Hysterectomy	19.23	29.93	1.6 (1.29-1.88)	7.41	16.25	2.2 (1.60-3.13)	14.10	24.16	1.7 (1.46-2.02)
Bilateral oophorectomy	13.89	20.75	1.5 (1.19-1.87)	4.69	9.94	2.1 (1.39-3.27)	9.91	16.11	1.6 (1.34-1.98)
Laparoscopy	10.54	13.28	1.3 (0.96-1.65)	4.03	8.83	2.2 (1.40-3.51)	7.72	11.38	1.5 (1.17-1.85)
Hysteroscopy	4.30	5.90	1.4 (0.91-2.09)	1.73	5.98	3.5 (1.82-6.99)	3.20	5.93	1.9 (1.33-2.62)

STAR trial – description of individual publications

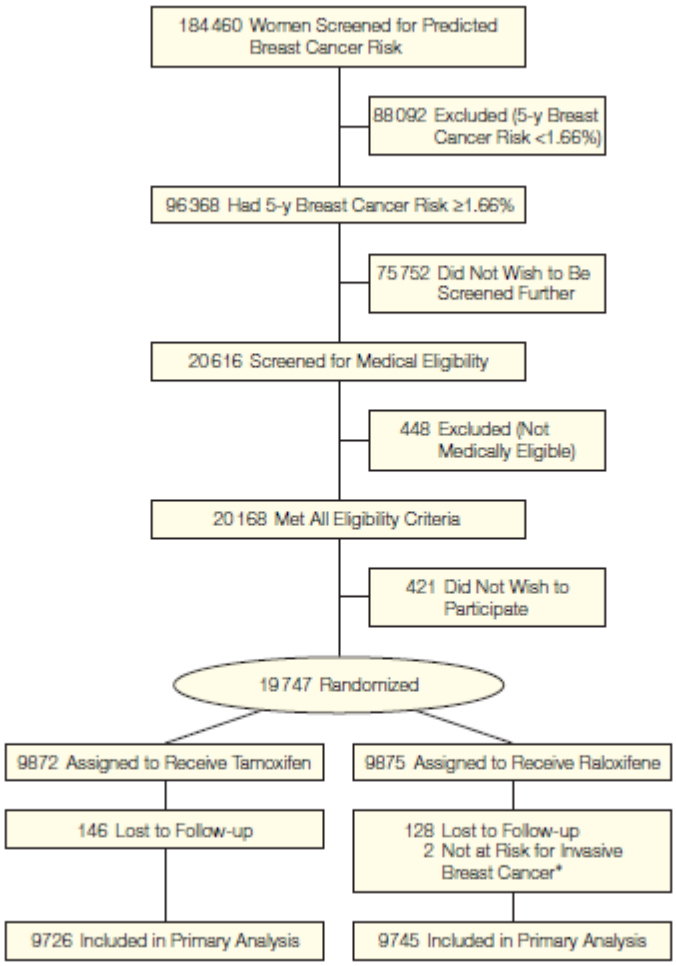
The NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial (clinicaltrials.gov identifier NCT01579734 and the European Institute of Oncology as IEO S51/200)		
Trial description	Randomised double-blind controlled trial in the USA and Canada comparing tamoxifen and raloxifene. The primary objective was to determine whether raloxifene is more or less effective than tamoxifen in significantly reducing the incidence rate of invasive breast cancer in postmenopausal women. To be eligible, women had to be ≥35 years of age and have a five-year predicted risk of breast cancer of at least 1.66% based on the Gail algorithm. All women had a mammogram within 180 days before randomisation to exclude pre-existing breast cancer. Recruitment of subjects was from 1999. After unblinding of the NSABP P1 trial in 1998, participants in the placebo group were given the opportunity either to receive a 5-year course of tamoxifen or to be randomized to the Study of Tamoxifen and Raloxifene (STAR) trial	
Related Publications		
Key Publication (s)	Relationship to Trial	Page
Vogel 2006	First publication of results (median follow-up 47 months after randomisation)	128
Vogel 2010	Long term results – 10 year follow up (median follow-up 81 months after randomisation)	134
Related Publications**		
Safety		
Land 2006	Comparison of patient-reported symptoms for the whole STAR cohort; quality of life assessments in a convenience sample of the cohort	138
Legault 2009	Ancillary study to compare the effects of tamoxifen and raloxifene specific cognitive function in a convenience sample of the cohort	141
Runowicz 2011	Comparison of the gynaecological conditions reported in post-menopausal women with intact uterus	143
*Trial acronyms refer to the trials described above ** A list of citations is provided in Section 19, starting on page68 of this report		
Comment: A detailed description of the trial method is provided in the description of the first publication. This is supplemented with information from subsequent publications where appropriate (and identified as such). The description of the trial method is not repeated for the subsequent publications. A brief description of each publication is provided with results described in appropriate details. All figures and Tables are copied from the relevant publication (with original captions) unless otherwise specified. Both safety and efficacy results are provided in the publication description		

STAR - Key Publications (Efficacy and Safety)

Vogel 2006

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive
Citation	Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727-41.
Relationship to trial	First report of results 1999-2005 with analysis triggered by occurrence of 327 cases of invasive breast cancer were diagnosed in the study cohort
Documented GCP or ethics approval	The following statements are provided: *The protocol and consent form were approved by the National Cancer Institute and the institutional review boards of all participating institutions.*
Conflict of Interest	The following statements are provided: *Dr Vogel reports having served on the speaker's bureau and as a consultant for, and having received honoraria from, Eli Lilly and Astra Zeneca. Dr Wickerham reports having served on the speaker's bureau for, and having received honoraria from, AstraZeneca. Dr Cronin reports having served on the Adherence Advisory Board for AstraZeneca. Dr Margolese reports having served on the speaker's bureau for AstraZeneca. Dr Wolmark reports having received honoraria from Eli Lilly. No other authors reported disclosures.*
Funding source(s)	The following statements are provided: *This study was supported by Public Health Service grants U10-CA-37377, U10-CA-69974, U10CA-12027, and U10CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by AstraZeneca Pharmaceuticals and Eli Lilly and Co.* ***Role of the Sponsor:*** *The study sponsors had no role in any aspect of study design; in the collection, analysis, and interpretation of data; or in the development of the manuscript. Per contractual arrangement, the manuscript was submitted to AstraZeneca and Eli Lilly before submission.*
Study design	Randomised double blind multicentre study to compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes in post-menopausal women.
Study Location	200 sites in USA and Canada
Study Dates	July 1, 1999 to data cutoff date December 31, 2005 for this analysis
Study treatment	Oral tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years Follow-up occurred every 6 months after treatment initiation for 5 years and then annually. Clinical breast examination was to be performed every 6 months, and bilateral mammograms were to be performed annually. Gynaecologic examinations, complete blood cell counts, and routine serum chemistry tests were to be obtained annually. Self-reported symptoms were collected at each contact, and in-depth quality-of-life assessments were performed at selected clinical centre s on a subset of 1983 participants
Study population	Healthy post-menopausal women
Key selection	Inclusion criteria: 5-year predicted breast cancer risk of at least 1.66% (Gail model) ; age ≥ 35 years of age and postmenopausal, with menopause defined as (1) a history of at least 12 months without

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive
criteria	spontaneous menstrual bleeding or (2) a documented hysterectomy and bilateral salpingo-oophorectomy or (3) age 55 years or older with a hysterectomy with or without oophorectomy;or (4) age younger than 55 years, either with a hysterectomy without oophorectomy or with unknown ovary status, and with a documented level of follicle-stimulating hormone confirming elevation in the postmenopausal range Exclusion criteria: use of tamoxifen, raloxifene, hormone therapy (HRT), oral contraceptives (OCP), or androgens in the previous 3 months; use of either warfarin or cholestyramine; history of stroke, pulmonary embolism, or deep vein thrombosis (DVT); history of any serious malignancy diagnosed less than 5 years before randomisation; uncontrolled atrial fibrillation, uncontrolled diabetes, or uncontrolled hypertension; any psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity
Concurrent medications	HRT not allowed
Outcome measure(s)	Primary end point was invasive breast cancer.
Safety measure(s)	Secondary end points included endometrial cancer, in situ breast cancer, cardiovascular disease, stroke, pulmonary embolism, DVT, transient ischemic attack, osteoporotic fracture, cataracts, death, and quality of life. Data on all other invasive cancers also were collected prospectively
Randomisation	*Randomisation was accomplished using a biased-coin minimization algorithm.*
Blinding	Participants and their clinicians were blinded to which of the 2 treatments the participant was receiving. Comment: Additional detail from Runowicz 2011, *Because the formulations of tamoxifen and raloxifene tablets were dissimilar, it was necessary to use placebo tablets to maintain the double blinding of treatment assignment.*
Statistical analysis	The women were stratified by age (35-49, 50-59, _60 years), race/ ethnicity (white, African American, Hispanic, other), history of LCIS (yes, no), and 5-year predicted risk of breast cancer (<2.5%, 2.5%-3.9%, and ≥4.0%). All analyses were according to intention to treat. Comparison between treatment groups of the study end points was based on the determination of rates per 1000 person-years, the risk ratio (RR) contrasting the rate in the raloxifene group to the rate in the tamoxifen group, and the 95% CIs for the RR.

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive
Participant Flow	**Figure 1.** Study Flow—NSABP STAR Trial  *Both had undergone bilateral mastectomy prior to randomization. NSABP STAR indicates National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene. Mean Follow-up and Compliance The mean time of follow-up was 3.9 (SD, 1.6) years (median 47 months). At the time of the cut-off for this analysis, the percentage of women persistent with the protocol regimen was 68.3% for those in the tamoxifen group and 71.5% for those in the raloxifene group. The mean duration of treatment was 3.1 (SD, 1.7) and 3.2 (SD, 1.6) years for the tamoxifen and raloxifene groups.

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive
Baseline Character-istics of Participants	**Table 1.** Participant Characteristics—NSABP STAR Trial Abbreviation: NSABP STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene. *Determined by the modified Gail model.[31]
Age Distribution	See table above
Distribution of Risk Factor(s) for the development of Breast Cancer	See table above
Efficacy Results	Invasive Breast Cancer There was no significant difference in the primary outcome variable of invasive breast cancer: there were 163 cases in the women assigned to tamoxifen and 168 cases in those assigned to raloxifene; the rate per 1000 was 4.30 in the tamoxifen group and 4.41 in the raloxifene group (RR, 1.02; 95% CI, 0.82-1.28); the *P* value testing the difference between treatment groups (including the stratification factors as covariates) was 0.96; the cumulative incidence through 72 months for the 2 treatment groups was 25.1 and 24.8 per 1000 for the tamoxifen and raloxifene groups, respectively (*P*=.83). Comparison by baseline categories and tumour characteristics revealed no significant differences between the treatment groups (see table below).

Characteristic	No. (%) Tamoxifen (n = 9726)	No. (%) Raloxifene (n = 9745)
Age, y		
≤49	884 (9.1)	877 (9.0)
50-59	4850 (49.9)	4848 (49.7)
60-69	3133 (32.2)	3173 (32.6)
≥70	859 (8.8)	847 (8.7)
Race/ethnicity		
White	9096 (93.5)	9108 (93.5)
African American	233 (2.4)	241 (2.5)
Hispanic	191 (2.0)	193 (2.0)
Other	206 (2.1)	203 (2.1)
First-degree relatives with breast cancer		
0	2835 (29.1)	2789 (28.6)
1	5041 (51.8)	5130 (52.6)
2	1532 (15.8)	1559 (16.0)
≥3	318 (3.3)	267 (2.7)
History of hysterectomy		
No	4732 (48.7)	4712 (48.4)
Yes	4994 (51.3)	5033 (51.6)
History of lobular carcinoma in situ		
No	8833 (90.8)	8849 (90.8)
Yes	893 (9.2)	896 (9.2)
History of breast atypical hyperplasia		
No	7540 (77.5)	7505 (77.0)
Yes	2186 (22.5)	2240 (23.0)
5-y predicted breast cancer risk*		
≤2.00	1055 (10.8)	1097 (11.3)
2.01-3.00	2988 (30.7)	2893 (29.7)
3.01-5.00	3039 (31.2)	3082 (31.6)
≥5.01	2644 (27.2)	2673 (27.4)

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive

Table 2. Rates of Invasive Breast Cancer by Patient and Tumor Characteristics—NSABP STAR Trial

Participant and Tumor Characteristic at Baseline	No. of Events		Rate per 1000			
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR (95% CI)†
By Participant Characteristics						
Age at entry, y						
≤49	7	8	2.07	2.39	−0.32	1.15 (0.37-3.74)
50-59	83	78	4.38	4.09	0.29	0.93 (0.68-1.29)
≥60	73	82	4.69	5.22	−0.53	1.11 (0.80-1.55)
History of LCIS						
No	130	135	3.76	3.89	−0.13	1.03 (0.81-1.33)
Yes	33	33	9.83	9.61	0.22	0.98 (0.58-1.63)
History of atypical hyperplasia						
No	122	121	4.06	4.03	0.03	0.99 (0.76-1.28)
Yes	41	47	5.21	5.81	−0.60	1.12 (0.72-1.74)
5-y predicted breast cancer risk						
≤3.00	32	44	2.03	2.83	−0.80	1.40 (0.87-2.28)
3.01-5.00	61	47	5.18	3.88	1.30	0.75 (0.50-1.11)
≥5.01	70	77	6.77	7.35	−0.58	1.09 (0.78-1.52)
No. of first-degree relatives with breast cancer						
0	52	53	4.99	5.18	−0.19	1.04 (0.69-1.55)
1	72	78	3.62	3.81	−0.19	1.05 (0.75-1.47)
≥2	39	37	5.16	5.00	0.16	0.97 (0.60-1.56)
By Tumor Characteristics‡						
Tumor size, cm						
≤1.0	47 (29.7)	62 (37.3)	1.24	1.63	−0.39	1.31 (0.88-1.96)
1.1-3.0	96 (60.8)	91 (54.8)	2.53	2.39	0.14	0.94 (0.70-1.27)
≥3.1	15 (9.5)	13 (7.8)	0.40	0.34	0.06	0.86 (0.38-1.94)
Unknown	5	2	0.13	0.05	0.08	0.40 (0.04-2.43)
Nodal status						
Negative	117 (75.5)	133 (80.6)	3.09	3.49	−0.40	1.13 (0.87-1.46)
Positive	38 (24.5)	32 (19.4)	1.00	0.84	0.16	0.84 (0.51-1.38)
Unknown	8	3	0.21	0.08	0.13	0.37 (0.06-1.55)
Estrogen receptor status						
Negative	44 (27.7)	51 (31.9)	1.16	1.34	−0.18	1.15 (0.75-1.77)
Positive	115 (72.3)	109 (68.1)	3.04	2.86	0.18	0.93 (0.72-1.24)
Unknown	4	8	0.11	0.21	−0.10	1.99 (0.53-9.02)
Total	163	168	4.30	4.41	−0.11	1.02 (0.82-1.28)

Abbreviations: CI, confidence interval; LCIS, lobular carcinoma in situ; NSABP STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene; RR, risk ratio.
*Rate in the tamoxifen group minus rate in the raloxifene group.
†RR for women in the raloxifene group compared with those in the tamoxifen group.
‡Values in parentheses in first 2 columns indicate percentage of women with known information.

Non-invasive breast cancer

There were fewer non-invasive breast cancers in the tamoxifen group than in the raloxifene group: 57 compared to 80 with a rate of 1.51 per 1000 women assigned to tamoxifen and 2.11 per 1000 women assigned to raloxifene [RR, 1.40; 95% CI, 0.98-2.00].), although this difference did not reach statistical significance (see also table below)

Safety Results

Discontinuations

Not described

Women's self-reported symptoms

Comment: Not described in this publication. Reported separately in Land 2006

Uterine Conditions

There was a trend toward a decreased incidence of uterine cancer in the raloxifene group but the difference was not statistically significant—36 cases (tamoxifen) vs 23 (raloxifene). There was however a lower incidence of endometrial hyperplasia and hysterectomy in the raloxifene group.

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive

Table 3. Rates of Noninvasive Breast Cancer and Uterine Disease/Hysterectomy—NSABP STAR Trial

Disease/Uterine Event Type	No. of Events		Rate per 1000			
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR (95% CI)†
Noninvasive Breast Cancer						
DCIS	30	44	0.79	1.16	−0.37	1.46 (0.90-2.41)
LCIS	21	29	0.56	0.76	−0.20	1.37 (0.76-2.54)
Mixed	6	7	0.16	0.18	−0.02	1.16 (0.33-4.18)
Total	57	80	1.51	2.11	−0.60	1.40 (0.98-2.00)
Uterine Disease and Hysterectomy‡						
Invasive cancer	36	23	2.00	1.25	0.75	0.62 (0.35-1.08)
Hyperplasia§	84	14	4.69	0.76	3.93	0.16 (0.09-0.29)
Without atypia§	72	13	4.02	0.71	3.31	0.18 (0.09-0.32)
With atypia§	12	1	0.67	0.05	0.62	0.08 (0-0.55)
Hysterectomy during follow-up§	244	111	13.57	6.04	7.53	0.44 (0.35-0.56)

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; NSABP STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene; RR, risk ratio.
*Rate in the tamoxifen group minus rate in the raloxifene group.
†RR for women in the raloxifene group compared with those in the tamoxifen group.
‡Women at risk were those with an intact uterus at entry.
§Among women not diagnosed with uterine cancer.

Comment: from the subsequently published erratum included at the end of the Land 2006 publication, I*n the "invasive cancer" row of Table 3, the rate per 1000 for tamoxifen should have been reported as 1.99, the difference in rate per 1000 as 0.74, and the RR as 0.63. Also in Table 3, in the "hysterectomy during follow-up" row, the number of events for tamoxifen should have been reported as 221 and for raloxifene as 87, the rate per 1000 for tamoxifen as 12.24 and for raloxifene as 4.72, the difference per 1000 as 7.52, and the RR (95% confidence interval [CI]) as 0.39 [0.30-0.50]).*

Ischaemic cardiac disease

There were 114 events in those assigned to tamoxifen and 126 in those assigned to raloxifene. This difference was not statistically significant (RR, 1.10; 95% CI, 0.85-1.43). Analysis according to types of events also found no significant differences between the treatment groups.

Stroke, transient ischemic attack, pulmonary embolism, DVT

There was no statistically significant difference between tamoxifen and raloxifene in the number of strokes of transient ischemic attacks that occurred.

There was a statistically significant increase in the incidence of thromboembolic events in the tamoxifen group. Overall, there were 141 events with tamoxifen and 100 with raloxifene, (RR, 0.70; 95% CI, 0.54-0.91) – see excerpt of Table 5 below.

Table 5. Annual Rates of Ischemic Heart Disease and Vascular-Related Events, Osteoporotic Fractures, and Cataracts—NSABP STAR Trial

Type of Event	No. of Events		Rate per 1000			
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR (95% CI)†
Thromboembolic events	141	100	3.71	2.61	1.10	0.70 (0.54-0.91)
Pulmonary embolism	54	35	1.41	0.91	0.50	0.64 (0.41-1.00)
Deep vein thrombosis	87	65	2.29	1.69	0.60	0.74 (0.53-1.03)

Osteoporotic fracture

There was no difference between treatment groups in the total number of hip, spine or Colle's fractures or in the number for any of the specific types of fracture

Cataracts

Among those who were cataract-free at baseline, 707 developed cataracts during the course of follow-up with the incidence significantly higher in the tamoxifen group: 394 reports in the tamoxifen group and 313 in the raloxifene group (RR 0.79, 95% CI, 0.68-0.92).

Other invasive malignancies

There were no statistically significant differences between the treatment groups in regard to the number of women who developed any other cancer, in total or by specific site of diagnosis.

Publication Identifier	Vogel 2006, Efficacy and Safety, Primary Supportive
	Deaths There were 101 deaths in those assigned to tamoxifen and 96 in those assigned to raloxifene, resulting in a rate per 1000 of 2.64 and 2.49, respectively (RR, 0.94; 95% CI, 0.71-1.26). Distribution by cause of death did not differ by treatment group. Quality of life Comment: Not described in this publication. Reported separately in Land 2006
Missing data	No data was provided regarding premature discontinuation of treatment or women's self-reported symptoms or the quality of life measures
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level II by the sponsor. This is reasonable, although it describes only a subset of the women at risk (post-menopausal women) and has an active comparator. The study appears to have been well run with minimisation of potential bias. There is a potential for influence by the sponsor given that "*Per contractual arrangement, the manuscript was submitted to AstraZeneca and Eli Lilly before submission".* The publication found that, in post-menopausal women, tamoxifen and raloxifene had equivalent effects in reducing risk of invasive breast cancer in all examined subgroups and that there was a trend to lower risk of non-invasive breast cancer with tamoxifen. The use of tamoxifen was associated with a greater risk of thromboembolic disease and a trend to higher risk of uterine cancer..

Vogel 2010

Publication Identifier	Vogel 2010, Efficacy and Safety, Primary Supportive
Citation	Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res. 2010;3(6):696-706
Relationship to trial	Follow-up report of results after median follow-up of 81 months
Documented GCP or ethics approval	The following statements are provided: *reviewed and approved by the National Cancer Institute and the institutional review boards of all participating institutions*
Conflict of Interest	The following statements are provided:
Funding source(s)	The following statements are provided: *Funding from Public Health Service grantsU10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974 from the National Cancer Institute, Department of Health and Human Services.*
Study design	Randomised multicentre two arm study with open follow up from 2006
Study Location	As above, Vogel 2006
Study Dates	July 1, 1999 to cut-off date of March 31, 2009

Study treatment	As above, Vogel 2006
Study population	As above, Vogel 2006
Key selection criteria	As above, Vogel 2006: women who were postmenopausal, at least 35 years of age, and who had a 5-year predicted breast cancer risk of at least 1.66%
Concurrent medications	As above, Vogel 2006
Outcome measure(s)	As above, Vogel 2006
Safety measure(s)	As above, Vogel 2006
Randomisation	As above, Vogel 2006
Blinding	The trial was unblinded in April 2006 after the original report (Vogel 2005)
Statistical analysis	As above, Vogel 2006
Participant Flow	Of the originally randomized 19,747 women, 19,490 (9,736 in the tamoxifen group and 9,754 in the raloxifene group) are included in this publication: • 274 women were not included due to lack of follow-up information (146 tamoxifen; 128 raloxifene). Since the time of the initial report, follow-up information was collected on 20 of the women (10 tamoxifen; 10 raloxifene) who lacked follow-up information at the time of the original report. • 2 women (in the raloxifene group) were excluded because they had received a prophylactic • bilateral mastectomy before randomisation and were not at risk for the development of invasive breast cancer. • One woman (in the raloxifene group) in the original report has been excluded from the follow-up analyses because she was discovered to have been diagnosed with invasive breast cancer before randomization. <u>Duration of treatment and Crossover</u> The mean duration of adherence to treatment was 43.5 months (SD, 20.7) for the tamoxifen group and 46.8 months (SD, 20.0) for the raloxifene group. Protocol medication drop-off rates were 38.9% in the tamoxifen group and 27.4%in the raloxifene group. After unblinding of treatment assignment in 2006, 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 - 879 women chose this option
Baseline Character-istics of Participants	As above, Vogel 2006
Age Distribution	As above, Vogel 2006
Distribution of Risk Factor(s)	As above, Vogel 2006

for the development of Breast Cancer	
Efficacy Results	Invasive breast cancer There were 310 cases of invasive breast cancer in the raloxifene group and 247 in the tamoxifen group. The invasive breast cancer RR (raloxifene:tamoxifen) is 1.24 (95% CI, 1.05–1.47), indicating that the rate in the raloxifene group is about 24% higher than the rate in the tamoxifen group. The number of events and the point estimates of the rate are higher in the raloxifene arm than in the tamoxifen arm for all categories of participant characteristics – see table below

Table 2

Annual rates of invasive breast cancer—NSABP STAR Trial (P-2)

Participant characteristic at baseline	Number of events		Rate per 1000				
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR†	RR (95%CI)
Age at entry (years)							
≤ 49	10	15	1.84	2.80	−0.96	1.53	0.64–3.80
50–59	125	155	4.09	5.03	−0.94	1.23	0.97–1.57
≥ 60	112	140	4.47	5.48	−1.01	1.22	0.95–1.58
History of lobular carcinoma *in situ*							
No	197	253	3.54	4.50	−0.96	1.27	1.05–1.54
Yes	50	57	9.14	10.34	−1.20	1.13	0.76–1.69
History of atypical hyperplasia							
No	187	218	3.90	4.52	−0.62	1.16	0.95–1.42
Yes	60	92	4.58	6.79	−2.21	1.48	1.06–2.09
5-year predicted breast cancer risk (%)							
≤ 3.00	61	81	2.39	3.21	−0.82	1.34	0.95–1.90
3.01–5.00	84	91	4.43	4.63	−0.20	1.05	0.77–1.42
≥ 5.01	102	138	6.13	8.17	−2.04	1.33	1.02–1.74
No. 1[0] relatives with breast cancer							
0	82	105	4.77	6.17	−1.40	1.29	0.96–1.75
1	112	135	3.51	4.10	−0.59	1.17	0.90–1.51
≥ 2	53	70	4.44	5.96	−1.52	1.34	0.93–1.96
Total	247	310	4.04	5.02	−0.98	1.24	1.05–1.47

Abbreviations: CI, confidence interval; NSABP STAR, National Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene; RR, risk ratio.

*Rate in the tamoxifen group minus rate in the raloxifene group.

†Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.

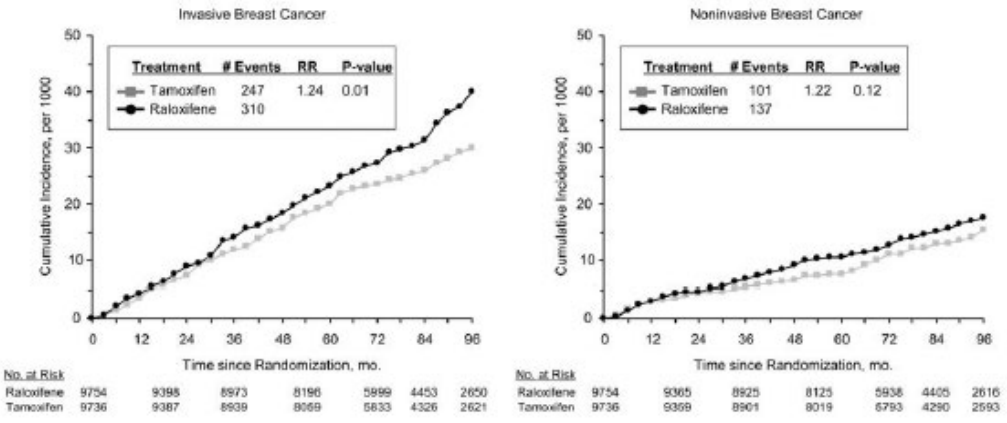


Fig. 1.
Cumulative incidence of invasive and noninvasive breast cancer.

Non-invasive breast cancer

	There are 137 cases in the raloxifene group compared with 111 in the tamoxifen group, for an RR of 1.22 (95% CI, 0.95–1.59).
Safety Results	Uterine Disease The incidence of invasive uterine cancer was significantly lower in the raloxifene group (P = 0.003). The annual average rate per 1,000 was 2.25 in the tamoxifen group compared with 1.23 in the raloxifene group (RR = 0.55; 95% CI, 0.36–0.83). The average annual incidence rate of uterine hyperplasia, the majority of which was hyperplasia without atypia, was 5 times higher in the tamoxifen group (4.40 per 1,000) than in the raloxifene group (0.84 per 1,000; RR = 0.19; 95% CI, 0.12–0.29). The number of hysterectomies performed in the tamoxifen group (349), including those done for benign disease, was more than double that performed in the raloxifene group (162; RR = 0.45; 95% CI, 0.37–0.54).

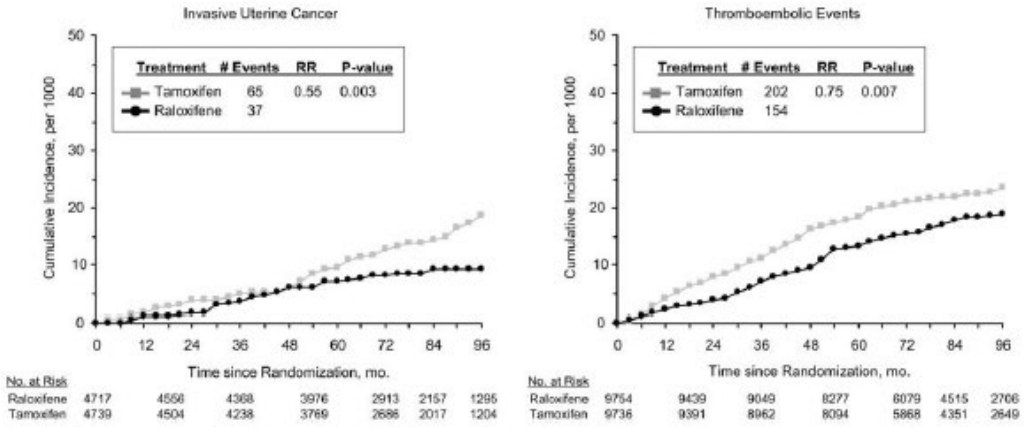


Fig. 2.
Cumulative incidence of invasive uterine cancer and thromboembolic events.

Pulmonary embolism, deep-vein thrombosis (DVT)

The incidence of pulmonary embolism and DVT events was significantly elevated in the tamoxifen group compared with the raloxifene group (P = 0.007). The average annual rates of thromboembolic events were 3.30 per 1,000 (tamoxifen) and 2.47 per 1,000 (raloxifene; RR = 0.75; 95% CI, 0.60–0.93).

Table 5

Rates of thromboembolic events, cataracts and cataracts surgery—NSABP STAR Trial (P-2)

Type of Event	Events, *n*		Rate per 1,000				
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR†	RR (95% CI)
Thromboembolic events							
Thromboembolic events	202	154	3.30	2.47	0.83	0.75	0.60-0.93
Pulmonary embolism	84	68	1.36	1.09	0.27	0.80	0.57-1.11
Deep-vein thrombosis	118	86	1.93	1.38	0.55	0.72	0.54-0.95
Cataracts and Cataract Surgery							
Developed cataracts during follow-up‡	739	603	14.58	11.69	2.89	0.80	0.72-0.89
Developed cataracts and had cataract surgery‡	575	462	11.18	8.85	2.33	0.79	0.70-0.90

Abbreviations: CI, confidence interval; NSABP STAR, National Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene; RR, risk ratio.

*Rate in the tamoxifen group minus rate in the raloxifene group.

†Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.

‡Women at risk were those with no prior history of cataracts at entry (8,341 and 8,336 tamoxifen and raloxifene participants, respectively).

Cataracts

The rate of cataract development (RR = 0.80; 95% CI, 0.72–0.89) and the rate of cataract surgery (RR

	= 0.79; 95% CI, 0.70–0.90) was significantly less in the raloxifene group than in the tamoxifen group. Other invasive malignancies Comparisons between treatment groups of the average annual rates of invasive cancer of sites other than the breast or uterus showed no significant differences. Deaths Overall, 236 deaths occurred in the tamoxifen group and 202 deaths in the raloxifene group, RR of 0.84, (95% CI, 0.70–1.02). When the differences between treatment groups are compared by specific causes of death, no significant differences were identified.
Missing data	A number of end-points described in the original trial description (Vogel 2006) were not described. These include: ischaemic heart disease, stroke & TIAs, osteoporotic fractures and quality of life. Apart from the measures of mean duration of adherence to treatment and "protocol medication drop-off rates", no data regarding early discontinuations from treatment are provided.
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. It is important to note that this trial used an active comparator arm, only included post-menopausal women and had open follow-up from 2006. Given this it may be more appropriate to consider it as a primary supportive publication. Unlike the original report (Vogel 2005), this analysis found that tamoxifen was associated with a significantly lower incidence of invasive breast cancer and higher incidence of uterine cancer. The findings of significantly higher incidence of VTE, hysterectomies for benign disease and cataracts with tamoxifen therapy were confirmed.

STAR - Related Publications (Safety)

Land 2006

Publication identifier	**Land 2006, Safety, Pivotal**
Citation	Land SR, Wickerham DL, Costantino JP, Ritter MW, Vogel VG, Lee M, et al. Patient reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.[Erratum appears in JAMA. 2007 Sep 5;298(9):973]. JAMA. 2006;295(23):2742-51.
Study description	To compare the differences in patient-reported symptoms for the whole STAR cohort and quality of life assessments in a sub-group of the cohort.
Ethics approval or GCP	The following statements are provided: *The protocol and consent form were approved by the National Cancer Institute and the institutional review boards of all participating institutions* *Eligible CCOP institutions elected to participate in the QOL substudy and indicated the completion of their institutional review board approval by submitting a substudy initiation form to the NSABP.*
Conflicts of interest	The following statements are provided: *Dr Wickerham has reported serving as a consultant for and on the speaker's bureau of AstraZeneca Pharmaceuticals; Dr Vogel has reported serving on the speaker's bureau of AstraZeneca Pharmaceuticals and Eli Lilly; and Dr Wolmark has reported receiving honorarium from Eli Lilly.*
Funding source	The following statements are provided: *This study was supported by Public Health Service grants U10-CA-37377, U10-CA-69974, U10CA-12027, and U10CA-69651 from the National Cancer Institute, National Institutes of Health, Department of*

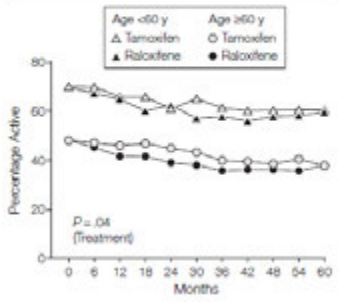
	Health and Human Services, and AstraZeneca Pharmaceuticals and Eli Lilly and Company *The study sponsors had no role in any aspect of study design, data collection, analysis and interpretation of data, or in the development of the manuscript. Per contractual arrangement, the manuscript was submitted to AstraZeneca and Eli Lilly before submission*.
Study Dates	Recruitment occurred between July 1, 1999, and November 4, 2004. Data cutoff for this analysis was December 31, 2005 Comment: data cutoff for this analysis is before treatments were unblinded in April 2006
Study Method	Patient reported symptoms and an assessment of quality of life was an outcome measure for the main trial (see Vogel 2006). Follow-up occurred every 6 months after treatment initiation for 5 years and then annually. Patient-reported symptoms were collected from all participants using a 36-item symptom checklist. In-depth quality-of-life assessments were self-completed by a subset of 1983 women using the Medical Outcomes Study Short-Form Health Survey (SF-36), the Center for Epidemiologic Studies-Depression (CES-D), and the Medical Outcomes Study Sexual Activity Questionnaire. , Questionnaires were administered before treatment, every 6 months for 60 months and at 72 months. However, this analysis is restricted to assessments performed through to 60 months on study due to the small number of study participants who had reached the 72-month assessment at the data cutoff date. The subset of women in whom in-depth assessments of quality of life were performed was a convenience sample selected according to ability to speak English and attendance at selected clinical centres for follow-up (institutions in the Community Clinical Oncology Program who elected to participate in the sub-study)
Blinding	As above – Vogel 2006
Results	Patient characteristics are shown below: **Table 1.** Patient Characteristics No. (%)* QOL Study Participants Variables / Full Cohort (N = 19512)† / Tamoxifen (n = 973) / Raloxifene (n = 1010) / *P* Value / All (n = 1983) / QOL Study Nonparticipants (Concurrently Accrued) (n = 5450) / *P* Value (Participants vs Nonparticipants) Age, y 35-44 — 277 (1) / 7 (1) / 16 (2) / .22 / 23 (1) / 80 (1) / .65 45-49 — 1517 (8) / 80 (8) / 99 (10) / / 179 (9) / 433 (8) / 50-54 — 4514 (23) / 250 (26) / 234 (23) / / 484 (24) / 1307 (24) / 55-59 — 5180 (27) / 236 (24) / 258 (26) / / 494 (25) / 1437 (26) / 60-64 — 3805 (20) / 191 (20) / 178 (18) / / 369 (19) / 1010 (19) / 65-69 — 2503 (13) / 115 (12) / 123 (12) / / 238 (12) / 675 (12) / 70-74 — 1232 (6) / 73 (8) / 70 (7) / / 143 (7) / 365 (7) / ≥75 — 484 (2) / 21 (2) / 32 (3) / / 53 (3) / 143 (3) / Race‡ White — 18 245 (94) / 902 (93) / 946 (94) / .40 / 1848 (93) / 5131 (94) / .13 Nonwhite — 1267 (6) / 71 (7) / 64 (6) / / 135 (7) / 319 (6) / Hysterectomy — 10010 (51) / 518 (53) / 551 (55) / .56 / 1069 (54) / 2785 (51) / .03 History of LCIS — 1729 (9) / 77 (8) / 68 (7) / .31 / 145 (7) / 461 (8) / .11 Atypical hyperplasia — 4407 (23) / 166 (17) / 170 (17) / .89 / 336 (17) / 1095 (20) / .002 5-Year breast cancer risk, %§ ≤2.00 — 2173 (11) / 101 (10) / 130 (13) / .37 / 231 (12) / 598 (11) / .71 2.01-3.00 — 5908 (30) / 306 (31) / 311 (31) / / 617 (31) / 1669 (31) / 3.01-5.00 — 6131 (31) / 296 (30) / 304 (30) / / 600 (30) / 1715 (31) / ≥5.01 — 5300 (27) / 270 (28) / 265 (26) / / 535 (27) / 1468 (27) / Abbreviations: LCIS, lobular cancer in situ; QOL, quality of life. *Percentages may not sum to 100 due to rounding. †Includes all participants who provided a baseline symptom assessment. ‡Includes black, Hispanic, and other. §Computed according to the Gail model.[14] As of December 31, 2005, the median potential follow-up time was 4.6 years in the full cohort and 5.4 years among the QOL participants. The mean duration of treatment was3.03 years (range, 0-5 years) and 3.14 years (range 0-5 years) for the tamoxifen and raloxifene groups. Of participants in the tamoxifen group, 6576 (67.49%) vs 6910 (70.73%) in the raloxifene group continued their protocol-assigned therapy up to the time of analysis. Quality-of-life forms completion ranged from 76% to 95% at all of the time points from 0 to 60

months. Symptom checklist form completion ranged from 83% to 99%. There was no significant difference in completion rates between the treatment arms.

QOL assessments

In the substudy of 1983 women, there were no significant differences between tamoxifen and raloxifene in the quality of life assessment and scores on all of these measures were within the normal ranges for healthy women of this age. There were, however, significant differences in sexual function, with a slightly greater greater percentage of the tamoxifen group sexually active at nearly every assessment time point.

Figure 2. Sexual Activity (Percentage Active) Over Time by Age and Treatment Group



The *P* value is based on repeated measures analysis.

Symptom Checklists

The following groupings were used for the analysis:

- Musculoskeletal problems -joint pain, muscle stiffness, general aches and pains
- Vasomotor: night sweats, hot flashes, and cold sweats;
- Gastrointestinal: vomiting, nausea;
- Dyspareunia: vaginal dryness, pain with intercourse
- Bladder: difficulty with bladder control (when laughing or crying) and difficulty with bladder control (at other times)
- Gynaecological: vaginal discharge, genital itching or irritation, and vaginal bleeding or spotting.

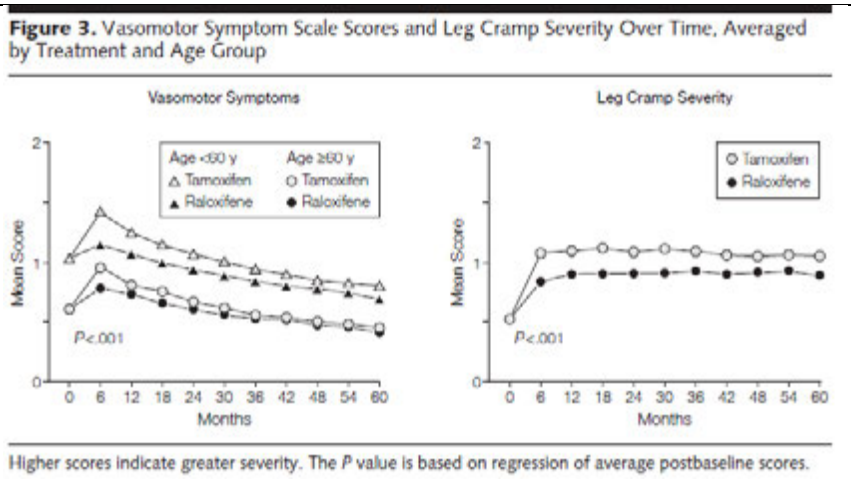
Statistically significant differences were noted between the tamoxifen and raloxifene groups for average severity of symptoms after baseline. Tamoxifen participants experienced significantly greater vasomotor symptoms, bladder problems, gynaecological problems and leg cramps. The raloxifene group experienced significantly greater musculoskeletal problems, dyspareunia, and weight gain.

Table 2. Treatment Differences in Symptom Scales*

	Raw Mean Severity†				
Symptom Scale	Tamoxifen	Raloxifene	Treatment Effect‡	*P* Value	Effect Size§
Forgetfulness	0.99	0.98	NA	.85	NA
Gastrointestinal	0.11	0.11	NA	.86	NA
Musculoskeletal	1.10	1.15	0.04	.002	<0.1
Dyspareunia	0.68	0.78	0.11	<.001	0.1
Weight gain	0.76	0.82	0.06	<.001	0.1
Vasomotor	0.96	0.85	–0.14	<.001	0.2
Bladder	0.88	0.73	–0.16	<.001	0.2
Leg cramps	1.10	0.91	–0.2	<.001	0.2
Gynecological	0.29	0.19	–0.1	<.001	0.3

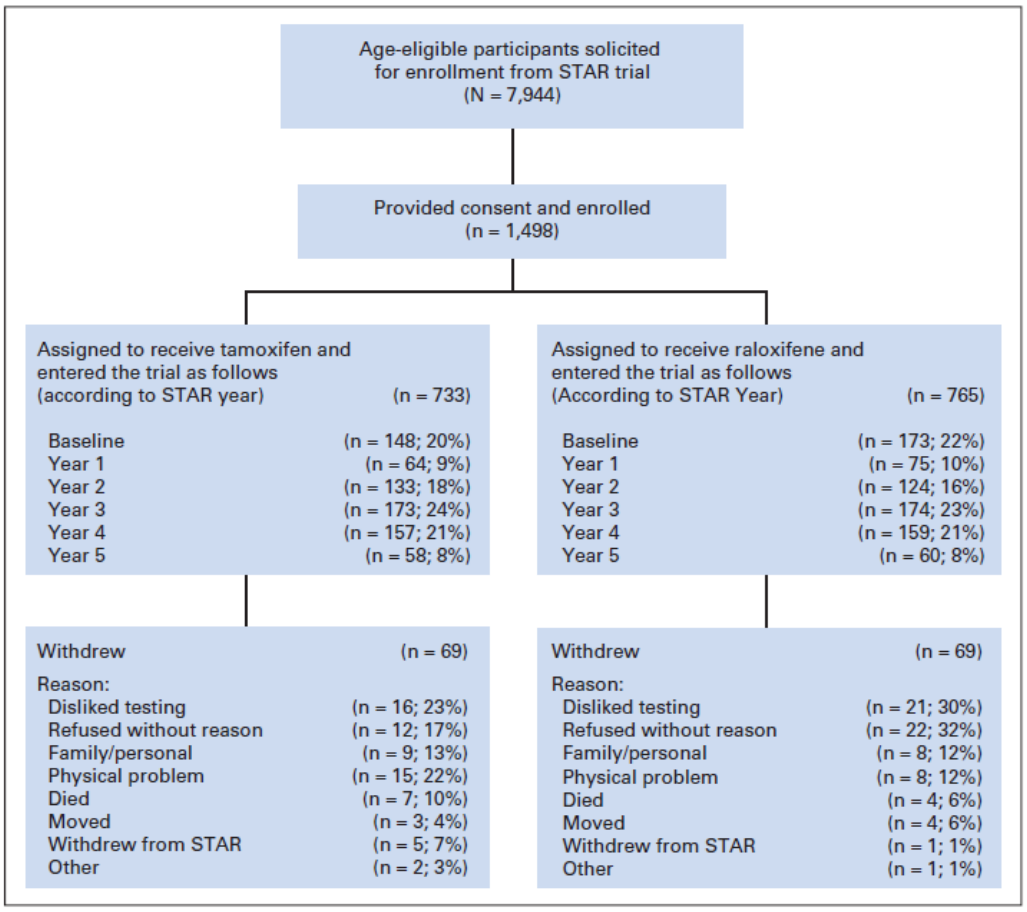
Abbreviation: NA, not applicable.
*Scores represent symptom severity on a scale of 0 to 4, with higher scores indicating greater severity.
†Average severity of assessments after baseline through 60 months.
‡Main effect of treatment from regression model. This is an estimate of the increase in average severity with raloxifene relative to tamoxifen, adjusted for baseline severity and, in the case of vasomotor symptoms, also adjusted for age. A positive treatment effect favors tamoxifen and a negative value favors raloxifene.
§Mean difference/SD.

Vasomotor symptoms were less severe in women aged 60 years or more.

	 **Figure 3.** Vasomotor Symptom Scale Scores and Leg Cramp Severity Over Time, Averaged by Treatment and Age Group Higher scores indicate greater severity. The *P* value is based on regression of average postbaseline scores.
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" with NHMRC level of evidence II by the sponsor. This is reasonable although it is important to note that this trial used an active comparator arm, only included post-menopausal women and that the quality of life assessment was performed on a small sub-group. With regards the latter, follow-up analysis was for 60 months instead of the planned 72 months. The publication found that in the quality of life assessment, there was no difference between tamoxifen and raloxifene in the sub-group, except for sexual activity, with women in the tamoxifen arm more likely to report having been sexually active. With regard to patient-reported symptoms, vasomotor symptoms, bladder problems, and leg cramps were more common in women in the tamoxifen arm.

Legault 2009

Publication identifier	**Legault 2009, Safety, Secondary Supportive**
Citation	Legault C, Maki PM, Resnick SM, Coker L, Hogan P, Bevers TB, et al. Effects of tamoxifen and raloxifene on memory and other cognitive abilities: cognition in the study of tamoxifen and raloxifene. J Clin Oncol. 2009;27(31):5144-52
Study description	Cognition in the Studyof Tamoxifen and Raloxifene (Co-STAR), a STAR ancillary study to compare the effects of tamoxifen and raloxifene on global and domain-specific cognitive function
Funding source, Conflicts of interest	The following statements are provided: *Co-STAR was coordinated by the Wake Forest University School of Medicine, approved by its institutional review board, and sponsored by the National Institute on Aging* Regarding disclosures of potential conflicts of interest**:** ***Employment or Leadership Position:*** *None* ***Consultant or Advisory Role:*** *Therese B. Bevers, Eli Lilly (C)* ***Stock Ownership:*** *None* ***Honoraria:*** *Susan M. Resnick, Eli Lilly, AstraZeneca* ***Research Funding:*** *Pauline M. Maki, Wyeth Pharmaceuticals; Therese B. Bevers, Eli Lilly, National Cancer Institute* ***Expert Testimony:*** *None* ***Other Remuneration:*** *None*
Study Dates	CoSTAR enrolment began in October 2001 (18 months after STAR enrolment started) and continued until the unblinding of STAR in June 2006
Study Method	Women who were randomised in STAR at selected sites and who were age 65 years and older, and were not diagnosed with dementia could be enrolled in the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) trial at any time during their first 4 years of follow-up. Women were assessed on enrolment in Co-STAR, and then annually for a maximum of 3 assessments.

	Each assessment was comprised of a cognitive test battery modeled after the cognitive battery used in the Women's Health Initiative Study of Cognitive Aging and designed to include measures that have been shown to be sensitive to subtle cognitive changes associated with aging and hormone therapy. The test battery additionally included the Modified Mini Mental State Examination (3MS) to assess global cognitive function and the Positive and Negative Affect Schedule (PANAS) and Geriatric Depression Scale to measure changes in positive affect and negative affect and depression
Blinding	As for STAR (Vogel 2006)
Results	Participant flow:  **Fig 1.** Cognition in the Study of Tamoxifen and Raloxifene (STAR) study flow. Baseline characteristics The average age (standard deviation) of the cohort at the time of Co-STAR enrollment was 69.9 (4.2) years ranging from 65 to 83 years, and 60% of women had had their last menstrual period more than 20 years ago. The baseline characteristics of the two arms were similar with respect to age; duration of follow-up; ethnicity; education levels reached; history of smoking, depression, psychiatric problems, diabetes; prior use of HRT. Timing of assessment: Women were enrolled into Co-STAR after a mean of 2.3 years of participation in STAR – for most women, a baseline cognitive assessment prior to treatment with raloxifene or tamoxifen was not performed. A separate analysis of the 237/1498 women who were assessed prior to treatment was performed. Separate analyses were also performed according to the number of completed assessments. Cognitive assessment results:

	There were no significant differences in adjusted mean cognitive scores, or on global or domain-specific cognitive function between the two treatment groups across visits. The lack of a robust difference between the two treatments was evident in all 1,498 enrolled women and in an analysis restricted to 273 women with pretreatment baseline data.
Conclusion	*tamoxifen and raloxifene are associated with similar patterns of cognitive function in healthy postmenopausal women at increased risk of breast cancer*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This substudy of a convenience sample of women aged 65 years or more, treated with tamoxifen or raloxifene, showed no significant difference in cognitive function according to the testing performed. Interpretation of the results is limited by the small number of women in whom a pre-treatment baseline assessment was performed.

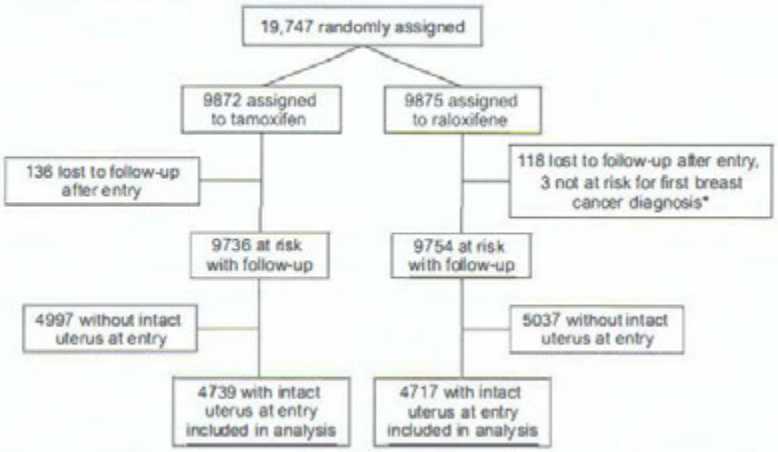
Runowicz 2011

Publication identifier	**Runowicz 2011, Safety, Secondary Supportive**
Citation	Runowicz CD, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Ford LG, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). Am J Obstet Gynecol. 2011;205(6):535.e1-5.
Study description	Comparison of the gynaecological conditions reported in post-menopausal women with intact uterus who were randomised to tamoxifen or raloxifene.
Funding source, Conflicts of interest	The following statements are provided: *approved by local human investigations committees or institutional review boards* *Supported by Public Health Service Grant nos. U10-CA-37377. U 10 -CA-69974, U1 O·CA-12027 , and U1 O-CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by AstraZeneca Pharmaceuticals and Eli Lilly and Company.* *D.L. W. declares a consultancy with Eli Lilly and an honoria from AstraZeneca. None of the other authors report a conflict of interest*
Study Dates	The enrolment period began on June 1, 1999, and ended on November 4, 2004. This report is based on a cutoff date of March 31, 2009. Comment: The trial was unblinded in April 2006 after the original report (Vogel 2005)
Study Method	The following information is provided: *women were monitored for symptoms of hot flashes, vaginal discharge, vaginal dryness, and abnormal vaginal bleeding; the occurrence of numerous gynecologic conditions that were diagnosed during the study period were reported and included endometrial adenocarcinomas, endometrial hyperplasia, leiomyomas, polyps, endometritis, endometriosis, and ovarian cysts. Surgical interventions (such as dilation and curettage, hysteroscopy, laparoscopy, oophorectomy, and hysterectomy) similarly were recorded* *in the study database*
Blinding	Comment: The trial was unblinded in April 2006, prior to the data cutoff point for this analysis. This is not discussed in the publication.
Results	Participant flow:

Publication identifier	Runowicz 2011, Safety, Secondary Supportive

FIGURE

CONSORT diagram: National Surgical Adjuvant Breast and Bowel Project P-2



The *asterisk* indicates that 2 women with bilateral mastectomy before entry and 1 woman with a diagnosis of breast cancer before entry were discovered after random assignment.

Runowicz. Gynecologic conditions in STAR/P-2 trial participants. Am J Obstet Gynecol 2011.

4739 women who received tamoxifen and 4717 women who received raloxifene had an intact uterus on trial entry. The groups were similar in baseline characteristics including

age, parity, body mass index, history of oral contraceptive or estrogen use, family history of breast cancer, diabetes mellitus, hypertension, and smoking status.

Median follow-up in this analysis was 81 months. Significant differences were found in self-reported bothersome hot flashes vaginal discharge, and vaginal bleeding in patients who received tamoxifen, compared with raloxifene *(P* < .0001 for each variable). Vaginal dryness was more common in patients who received raloxifene *(P* < .0001).

The incidence of invasive cancer; the incidence of endometrial hyperplasia and other gynaecological conditions, the rate of hysterectomy and other surgical procedures were significantly lower in the raloxifene group compared with the tamoxifen group (see tables below).

TABLE 3

Average annual rates of uterine disease

	Events, n		Rate per 1000 women				
Type of uterine disease	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference[a]	Risk ratio[b]	95% CI
Invasive cancer	65	37	2.25	1.23	1.02	0.55	0.36–0.83
Hyperplasia	126	25	4.40	0.84	3.56	0.19	0.12–0.29
Without atypia	104	21	3.63	0.70	2.93	0.19	0.11–0.31
With atypia	22	4	0.77	0.13	0.64	0.17	0.04–0.51
Hysterectomy during follow-up period[c]	349	162	12.08	5.41	6.67	0.45	0.37–0.54

CI, confidence interval.

[a] Rate in the tamoxifen group minus rate in the raloxifene group. [b] Risk ratio for women in the raloxifene group compared with women in the tamoxifen group. [c] For conditions other than invasive cancer.

Runowicz. Gynecologic conditions in STAR/P-2 trial participants. Am J Obstet Gynecol 2011.

Publication identifier	Runowicz 2011, Safety, Secondary Supportive
	TABLE 4 **Average annual rates of gynecological conditions and procedures by treatment group** Events, n / Rate per 1000 women Variable | Tamoxifen | Raloxifene | Tamoxifen | Raloxifene | Difference[a] | Risk ratio[b] | 95% CI Condition Leiomyomas | 757 | 443 | 28.40 | 15.56 | 12.84 | 0.55 | 0.49–0.62 Ovarian cysts | 236 | 147 | 8.32 | 5.01 | 3.31 | 0.60 | 0.49–0.74 Polyps | 575 | 185 | 21.06 | 6.28 | 14.78 | 0.30 | 0.25–0.35 Endometriosis | 190 | 64 | 6.60 | 2.14 | 4.46 | 0.32 | 0.24–0.43 Procedure Dilation and curettage | 673 | 218 | 24.30 | 7.32 | 16.98 | 0.30 | 0.26–0.35 Bilateral oophorectomy | 371 | 192 | 12.80 | 6.46 | 6.34 | 0.50 | 0.42–0.60 Laparoscopy | 14 | 4 | 0.46 | 0.13 | 0.33 | 0.28 | 0.07–0.90 Hysteroscopy | 493 | 151 | 17.32 | 5.03 | 12.29 | 0.29 | 0.24–0.35 CI, confidence interval. [a] Rate in the tamoxifen group minus rate in the raloxifene group. [b] Risk ratio for women in the raloxifene group compared with women in the tamoxifen group. *Runowicz. Gynecologic conditions in STAR/P-2 trial participants. Am J Obstet Gynecol 2011.*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This sub-group analysis of women with an intact uterus provides more detail regarding gynaecological conditions than that provided in the main publications for the STAR trial. The publication found a significant increase in both gynaecological conditions and gynaecological procedures in women from the tamoxifen group compared to the raloxifene group.

Publications with results from NSABP P1 and STAR

There were three publications that used results from both the NSABP P1 trial and the STAR trial

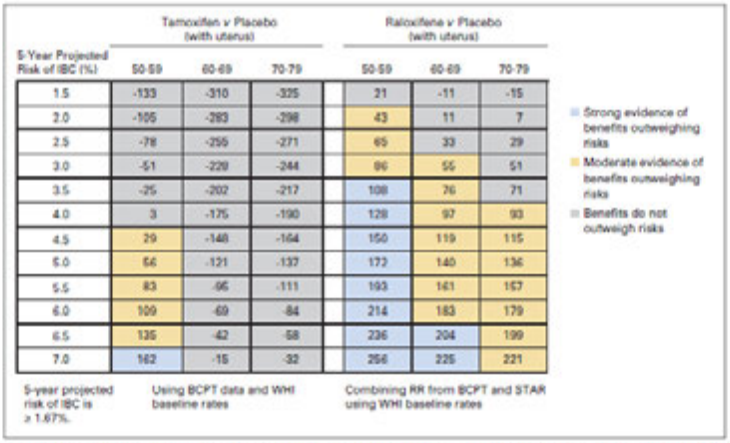
Publications with results from NSABP P1 and STAR	
Publication Identifier	**Publication objective (results of NSABP P1 and STAR used)**
Freedman 2011,	Development of a risk/benefit model
Cecchini 2012	Retrospective analysis of the relationship between BMI and invasive breast cancer in the NASBP P1 and STAR cohorts
Goetz 2011	Retrospective sub-group (age > 50years) analysis of the effect of CYP2D6 genotypes and inhibitors

Freedman 2011

Publication identifier	Freedman 2011, Secondary supportive, efficacy and safety
Citation	Freedman AN, Yu B, Gail MH, Costantino JP, Graubard BI, Vogel VG, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older.[Erratum appears in J Clin Oncol. 2013 Nov 10;31(32):4167]. J Clin Oncol. 2011;29(17):2327-33.
Included trials	NSABP-P1, STAR
Study description	Development of benefit/risk indices to compare raloxifene or tamoxifen treatment to no treatment using data from the NSABP P1 and STAR trials and from the Surveillance, Epidemiology and End

Publication identifier	Freedman 2011, Secondary supportive, efficacy and safety
	Results Program; and the Women's Health Initiative
Funding source, Conflicts of interest	The following statements are provided: *all authors completed the disclosure declaration:* ***Employment or Leadership Position**: None **Consultant or Advisory Role**: Victor G. Vogel, Eli Lilly (C) **Stock Ownership**: None **Honoraria**: None **Research Funding**: None **Expert Testimony**: None **Other Remuneration**: None*
Study Dates	Not applicable
Study Method	Weights were assigned to various health outcomes. Background incidence rates for relevant health outcomes in the absence of raloxifene and tamoxifen, relative risk (RR) estimates of the effects of raloxifene and tamoxifen on these incidence rates from BCPT and STAR and projected 5-year risks of invasive breast cancer (as determined using the Gail model) were used to calculate net benefit/risk indices for tamoxifen and raloxifene.. These were displayed in a risk matrix.
Blinding	As for NSABP P1 and STAR trials. It is not clear from the publication if data from the unblinded follow-up period of each trial is used
Results	Baseline incidence rates of major risks in the absence of tamoxifen or raloxifene: **Table 1.** Incidence Rates per 1,000 Woman-Years by Race Incidence Rates for Women (by age groups, in years) White / Black / Hispanic Type of Event: 50-59, 60-69, 70-79 (White); 50-59, 60-69, 70-79 (Black); 50-59, 60-69, 70-79 (Hispanic) Hip fracture*: 0.43, 1.41, 4.84, 0.22, 0.3, 1.9, 0.25, 0.61, 1.32 Endometrial cancer†: 0.92, 1.80, 1.70, 0.53, 1.48, 1.11, 0.5, 0.71, 0.86 Stroke*: 0.93, 2.22, 5.49, 2.03, 3.69, 6.19, 0.75, 2.56, 5.14 Pulmonary embolism*: 0.56, 0.86, 1.09, 0.82, 0.9, 1.43, 0.0, 0.1, 0.95 Deep vein thrombosis*: 0.66, 1.28, 2.04, 0.99, 1.47, 2.28, 0.25, 0.89, 0.96 Colles fracture*: 0.97, 1.34, 1.64, 0.32, 0.35, 0.49, 0.64, 1.13, 2.0 Spine fracture*: 0.98, 2.13, 4.40, 0.26, 0.3, 0.83, 0.59, 1.01, 1.62 Cataracts‡: 15.91, 52.18, 98.49, 15.91, 52.18, 98.49, 15.91, 52.18, 98.49 *Age-specific incidence rates for stroke, pulmonary embolism, deep vein thrombosis, and fractures of the proximal femur (hip), vertebra (spine), and distal forearm (Colles fractures) were obtained from the placebo arm of the Women's Health Initiative.[15] †We based estimates of endometrial cancer incidence rates on age- and race-specific incidence rates from the Surveillance, Epidemiology and End Results (SEER) Program for 1998 through 2002. To predict risk for women with a uterus, SEER rates were divided by the estimated age-specific prevalence of having a uterus by using data from the 2000 National Health Interview Survey.[16] ‡Baseline estimates of cataract incidence were calculated from data in the placebo arm of the Breast Cancer Prevention Trial because this cohort reflects current ophthalmologic practice and is the largest cohort with reports on cataracts in women.[1] A benefit/risk matrix for tamoxifen and raloxifene according to the projected risk of invasive breast cancer and the presence or absence of the uterus was developed:

Publication identifier	Freedman 2011, Secondary supportive, efficacy and safety

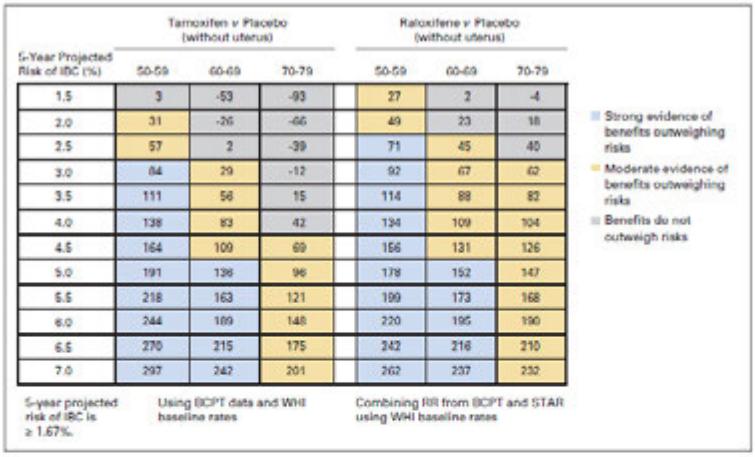


5-Year Projected Risk of IBC (%)	Tamoxifen v Placebo (with uterus) 50-59	60-69	70-79	Raloxifene v Placebo (with uterus) 50-59	60-69	70-79
1.5	-133	-310	-335	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-229	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	136
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

Strong evidence of benefits outweighing risks
Moderate evidence of benefits outweighing risks
Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.
Using BCPT data and WHI baseline rates
Combining RR from BCPT and STAR using WHI baseline rates

Fig 1. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic women with a uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > .9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events ($P < .6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.



5-Year Projected Risk of IBC (%)	Tamoxifen v Placebo (without uterus) 50-59	60-69	70-79	Raloxifene v Placebo (without uterus) 50-59	60-69	70-79
1.5	3	-53	-93	27	2	-4
2.0	31	-26	-66	49	23	18
2.5	57	2	-39	71	45	40
3.0	84	29	-12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	262	237	232

Strong evidence of benefits outweighing risks
Moderate evidence of benefits outweighing risks
Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.
Using BCPT data and WHI baseline rates
Combining RR from BCPT and STAR using WHI baseline rates

Fig 2. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk of invasive breast cancer (IBC) for white non-Hispanic women without uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 114 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > 0.9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would also result in the prevention of 111 life-threatening events ($P < 0.9$; blue). Among 10,000 non-Hispanic white women without a uterus, age 70 to 79 years, and with a 5-year IBC risk of 3.0%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P \geq 0.6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 12 excess life-threatening events ($P < 0.6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

Conclusion	The benefit/risk indices in this article indicate that raloxifene may is better than tamoxifen for women age 50 years or older with a uterus. For women without a uterus, the benefit/risk profile for raloxifene is similar to that for tamoxifen
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence III-2 by the sponsor. This is appropriate. The risk/benefit model developed from this retrospective analysis of the results of the NSABP P1 and STAR publications looks only at women aged 50 years or more. It may provide some additional assistance in determining the risk/benefit ratio for individual women.

Cecchini 2012

Publication identifier	Cecchini 2012, Secondary supportive, efficacy
Citation	Cecchini RS, Costantino JP, Cauley JA, Cronin WM, Wickerham DL, Land SR, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res. 2012;5(4):583-92.
Included trials	NSABP P1, STAR
Study description	Analysis of the women enrolled in the NSABP P1 and STAR trials for whom BMI data were available to explore the relationship between BMI and invasive breast cancer
Funding source, Conflicts of interest	The following statement is provided: *This work was supported by: 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 and by AstraZeneca Pharmaceuticals LP and Eli Lilly and Company*
Study Dates	As for NSABP-P1 and STAR
Study Method	The study included all participants of P-1 and STAR with follow-up information and known menopausal status and BMI at entry. In both P-1 and STAR, each participant's height and weight were measured and recorded by clinical staff members at each participating site. These measurements were used to calculate individual BMIs. For this analysis, the participants BMI were categorised into three groups: normal (18.5 – 24.9), overweight (25.0 – 29.9), and obese (≥ 30.0) - the "Normal" category also included the small number of underweight women (BMI <18.5) in this population. The Cox proportional hazards regression was used to calculate unadjusted and adjusted hazard ratios of developing invasive breast cancer for each of these categories in post-menopausal and premenopausal women. Univariate and multivariate analyses were performed.
Blinding	As for NSABP-P1 and STAR. It is not clear from the publication if data from the unblinded follow-up period of each trial is used.
Results	The analyses included 12,243 participants with 253 invasive breast cancer events from the NSABP P1 trial and 19,488 participants with 557 events from the STAR trial. In postmenopausal women, there was no statistically significant trend of breast cancer risk across BMI categories. Adjustment for possible explanatory variables had little effect on the point estimates of the hazard ratios or the tests of trend.

Publication identifier	Cecchini 2012, Secondary supportive, efficacy
	Table 2 Body mass index and incidence of invasive breast cancer among postmenopausal women

		STAR Postmenopausal				P-1 Postmenopausal				STAR/P-1 Postmenopausal [a]			
Form of Cox Regression Model	Body mass index	N	No. of Events	HR	95% CI	N	No. of Events	HR	95% CI	N	No. of Events	HR	95% CI
Univariable assessment	< 25.0	5870	159	1.00		2204	42	1.00		7883	194	1.00	
	25.0–29.9	6703	191	1.06	0.86 – 1.30	2188	48	1.21	0.80 – 1.84	8641	228	1.08	0.89 – 1.30
	≥ 30.0	6915	207	1.14	0.93 – 1.40	1987	37	1.07	0.69 – 1.66	8633	231	1.11	0.92 – 1.34
	p-value (trend)			*0.22*				*0.74*				*0.29*	
Full multivariable assessment [b]	< 25.0	5829	159	1.00		2194	42	1.00		7833	194	1.00	
	25.0–29.9	6658	190	1.03	0.83 – 1.27	2182	48	1.23	0.81 – 1.86	8591	227	1.06	0.87 – 1.28
	≥ 30.0	6870	206	1.13	0.92 – 1.40	1978	36	1.07	0.68 – 1.67	8581	229	1.12	0.92 – 1.36
	p-value (trend)			*0.24*				*0.73*				*0.25*	
Final multivariable assessment [c]	< 25.0	5870	159	1.00		2204	42	1.00		7883	194	1.00	
	25.0–29.9	6703	191	1.04	0.85 – 1.29	2188	48	1.22	0.81 – 1.85	8641	228	1.07	0.88 – 1.30
	≥ 30.0	6915	207	1.16	0.94 – 1.42	1987	37	1.09	0.70 – 1.69	8633	231	1.14	0.94 – 1.38
	p-value (trend)			*0.16*				*0.68*				*0.17*	

In premenopausal women, all assessments indicated a statistically significant trend of increasing breast cancer risk with increasing categories of BMI. Adjustment for explanatory variables had very little effect on the hazard ratio estimates or the conclusions regarding the tests of trend. In the final multivariable model, the hazard ratios for the upper BMI categories were 1.59 and 1.70, and the test of trend was statistically significant (p=0.01).

Table 3

Body mass index and incidence of invasive breast cancer among premenopausal women

		P-1 Premenopausal			
Form of Cox Regression Model	Body mass index	N	No. of Events	HR	95% CI
Univariable assessment	< 25.0	2596	43	1.00	
	25.0-29.9	1785	45	1.57	1.04 – 2.39
	≥ 30.0	1483	38	1.63	1.06 – 2.53
	p-value (trend)			0.02	
Full multivariable assessment [a]	< 25.0	2590	43	1.00	
	25.0-29.9	1780	45	1.55	1.02 – 2.36
	≥ 30.0	1480	38	1.66	1.06 – 2.58
	p-value (trend)			0.02	
Final multivariable assessment [b]	< 25.0	2596	43	1.00	
	25.0-29.9	1785	45	1.59	1.05 – 2.42
	≥ 30.0	1483	38	1.70	1.10 – 2.63
	p-value (trend)			0.01	

There was no evidence of a significant interaction between BMI and treatment with SERMs (tamoxifen or raloxifene).

There was no evidence of a significant interaction between BMI and history of oestrogen use among STAR/ NSABP P1 postmenopausal women (p=0.93), or between BMI and history of oral contraceptive use among premenopausal women (p=0.66).

Conclusion	There was a statistically significant positive association between the risk of invasive breast cancer and BMI among premenopausal women older than 35 years that were already at high risk for developing breast cancer but not for post-menopausal women. The authors note that *According to existing literature, high BMI has been associated with a significantly increased breast cancer risk in postmenopausal women and is believed to be protective in premenopausal women*.
Allocation by	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the

Publication identifier	Cecchini 2012, Secondary supportive, efficacy
sponsor and Evaluator assessment	sponsor. This is reasonable given the two studies on which the analysis is based were both DB RCTs. This retrospective analysis provides some information regarding a possible relationship between high BMI and risk of invasive breast cancer in pre-menopausal women although the authors express concern that this finding is not consistent with other publications.

Goetz 2011

Publication identifier	Goetz 2011, secondary supportive, efficacy
Citation	Goetz MP, Schaid DJ, Wickerham DL, Safgren S, Mushiroda T, Kubo M, et al. Evaluation of CYP2D6 and efficacy of tamoxifen and raloxifene in women treated for breast cancer chemoprevention: results from the NSABP P1 and P2 clinical trials.[Erratum appears in Clin Cancer Res. 2012 Jun 15;18(12):3491]. Clin Cancer Res. 2011;17(21):6944-51.
Included trials	NSABP P1 and STAR
Study description	Case control, nested, retrospective study to determine the impact of CYP2D6 genotype, CYP2D6 inhibitor use, as well as metaboliser status (CYP2D6 genotype combined with CYP2D6 inhibitor use) on breast cancer events. Background: Tamoxifen is a weak anti-oestrogen but is extensively metabolised to the potent anti-oestrogen, 4-hydroxy N-desmethyl tamoxifen (endoxifen). The rate-limiting step for this is the CYP2D6-mediated. Common genetic variations in CYP2D6 and/or drug-induced inhibition of CYP2D6 enzyme activity are associated with significant reductions in endoxifen concentrations in tamoxifen treated humans
Funding source, Conflicts of interest	The following statements are provided: • *approval by local Institutional Review Boards in accordance with assurances filed with and approved by the Department of Health and Human Services (NCT00967239)* • *Supported in part by NIH grants U01GM61388, U01GM63173, P50CA116201, U10CA77202, U10CA37377, U10CA69974, U24CA114732, and the Biobank Japan Project funded by the Ministry of Education, Culture, Sports, Science and Technology, Japan*
Study Dates	As for NSABP P1 and STAR (P2) trials
Study Method	Women who were ≥ 50 years old and who developed breast cancer (both non-invasive and invasive) while on five years of tamoxifen or raloxifene therapy (cases) were matched to controls free of breast cancer. 93% of women enrolled in the NSABP P1 and STAR clinical trials provided a blood sample for the pharmacogenetic study including 89 percent of the cases and 95 percent of the controls. *CYP2D6* genotyping was performed for alleles associated with absent, reduced, and increased enzyme activity. Information regarding the use of CYP2D6 inhibitors was recorded.
Blinding	As for NASBP P1 and STAR. It is not clear from the publication if data from the unblinded follow-up period of each trial is used
Results	591 cases were matched 1:2 to 1126 controls. Of the cases, 318 were from the tamoxifen arms of the trials. DNA was genotyped in >97% of cases and controls In patients treated with tamoxifen, there was no association of CYP2D6 genotype [OR(extensive/poor metaboliser): 0.90; 95% CI 0.46-1.74, p=0.74), use of a potent CYP2D6 inhibitor (OR 0.92 95% CI 0.575-1.486), or CYP2D6 metaboliser status (OR 1.03; 95% CI 0.669-1.607) with breast cancer occurrence.
Conclusion	These data strongly suggest that variations in the active metabolites of tamoxifen are not related to

Publication identifier	Goetz 2011, secondary supportive, efficacy
	the efficacy of tamoxifen in the prevention setting.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence III-2 by the sponsor. This is appropriate. This retrospective sub-group analysis is limited to women over 50 years (to enable use of like populations from the NASBP P1 and STAR trials), includes as cases women who developed invasive or non-invasive breast cancer and women who were on tamoxifen or raloxifene. It suggests that the effect of tamoxifen on reducing the risk of invasive and non-invasive breast cancer is not affected by CYP2D6 genotype and CYP2D6 inhibitors.

The Royal Marsden Hospital (Royal Marsden) trial

The Royal Marsden Hospital (Royal Marsden) trial (controlled-trials.com as ISRCTN07027313)	
Trial description	Double-blind placebo controlled randomised trial in the UK of women aged 30 to 70 years with an increased risk of breast due to family history. To be eligible, women had to have at least 1 of the following: (1) ≥1 first-degree relative who was younger than 50 years when diagnosed with breast cancer; (2) a first-degree relative with bilateral breast cancer; (3) a first-degree relative with breast cancer who was diagnosed at any age plus ≥ 1 other affected first- or second-degree relative with breast cancer; (4) a history of benign breast biopsy and a first-degree relative with breast cancer (N=2450). Healthy volunteers were identified in screening and symptomatic breast clinics, with recruitment from 1986 to 1996
Related Publications	
Key Publication (s)	**Relationship to Trial**
Powles 1998a	First publication of results (median follow-up 70 months after randomisation)
Powles 2007	Long term results – 20 year follow up (median follow-up 13 years after randomisation)
Related Publications**	
Efficacy	
Kote-Jarai 2007	Proportion of BRAC1/2 mutations in the 70 women who developed breast cancer at the time of the interim analysis (1998)
Safety	
Jones 1992	Sub group analysis (approximately 200) of the effects of tamoxifen on the levels of fibrinogen, anti-thrombin III, Protein C, Protein S and cross linked fibrin degradation products (XL-FDP).
Kedar 1994	Cohort study of 111 women from the pilot study to assess the effect of preventative tamoxifen on the uterus and ovaries (ultrasound, endometrial biopsies)
Powles 1994	Description of pilot study (1986 to 1993) with results for 2012 women; median duration of follow-up not described
Powles 1996	Sub-group analysis of convenience sample of 179 women to assess the effect of preventative tamoxifen on bone mineral density

The Royal Marsden Hospital (Royal Marsden) trial (controlled-trials.com as ISRCTN07027313)	
Chang 1996	Sub-group analysis of the interaction between HRT and tamoxifen on serum cholesterol, fibrinogen, antithrombin III (AT III) and bone mineral density (BMD) in postmenopausal healthy women
Chang 1998	Sub-group analysis of women who became amenorrhoeic during treatment with tamoxifen or placebo to assess the effect pf preventative tamoxifen on endometrial thickness
Powles 1998b	Sub-group analysis of post-menopausal healthy women to identify the incidence of endometrial thickening, polyps and cysts by transvaginal ultrasound screening and to evaluate the possible benefit from the use of intermittent norethisterone (NE) in women with persistent changes
Fallowfield 2001	Ancillary study of the psychosocial implications of tamoxifen in a convenience sample of participants in the Royal Marsden and IBIS-1 trials

*Trial acronyms refer to the trials described above

** A list of citations is provided in Section 19, starting on page68 of this report

Comments:

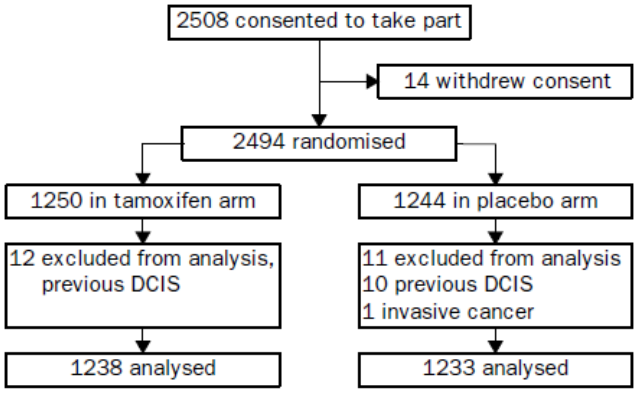
- A detailed description of the trial method is provided in the description of the first publication. This is supplemented with information from subsequent publications where appropriate (and identified as such). The description of the trial method is not repeated for the subsequent publications. A brief description of each publication is provided with results described in appropriate details.
- All figures and Tables are copied from the relevant publication (with original captions) unless otherwise specified.
- Both safety and efficacy results are provided in the publication description
- The evaluator's opinion of the publication results is provided following the publication description. It can be identified by Calibri font and shading

Royal Marsden - Key Publications – safety and efficacy

Powles 1998a

Publication Identifier	**Powles 1998a, Efficacy and Safety, Pivotal**
Citation	Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet. 1998;352(9122):98-101..
Relationship to trial	Interim analysis after median follow-up 70 months after randomisation)
Documented GCP or ethics approval	The following statements are provided: *The trial was approved by the Royal Marsden Hospital ethics committee*
Conflict of Interest	The following statements are provided: Nil
Funding source(s)	The following statements are provided: *This trial is supported by the Cancer Research Campaign*

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
Study design	Randomised, double blinded placebo controlled. This trial was commenced as a pilot study in 1986. Recruitment was continued until 2500 women were recruited in 1996. Ongoing follow-up was planned after completion of 8 years of treatment.
Study Location	UK (single centre)
Study Dates	Recruitment occurred between October 1986 and April 1996. Follow-up data to 1998 was analysed
Study treatment	Women were recruited from the Royal Marsden screening and symptomatic breast clinics. After assessment of eligibility (see key selection criteria below) and informed consent, women were randomised to receive placebo or tamoxifen 20mg daily for up to 8 years. Menopausal status at randomisation was defined as premenopausal if the woman had had a normal period within the previous 6 months, perimenopausal if the last period was 6 months to a year previously, and postmenopausal if longer than 12 months. Participants who had had a hysterectomy were considered postmenopausal if aged 50 or more Follow-up every 6 months included clinical examination and assessment of acute toxicity with an oral checklist. Other diseases and medical problems including gynaecological evaluation, and any changes in the family history of breast cancer, were recorded at each visit. Mammography was repeated annually. Compliance was assessed by direct questioning and checked against random blood testing of participants for tamoxifen.7 Serum cholesterol was measured before treatment and then every 6 months. From 1992, blood samples were collected to enable future screening for breast-cancer genes. Comment: additional information is available in the publication describing the pilot study (Powles 1994): *Safety monitoring involved assessment of coagulation factors, lipids, bone mineral density, ovarian cysts, and uterine thickness. Antithrombin 3 (AT III), fibrinogen, total cholesterol were measured before treatment, at 6 months, and then annually. Radial bone mineral density was measured before treatment and every 6 months*.
Study population	Healthy women aged between 30 and 70 years with increased risk of breast cancer due to family history
Key selection criteria	Inclusion criteria: • age between 30 and 70 years • no clinical or screening evidence of breast cancer • family history of breast cancer - at least one first-degree relative aged under 50 with breast cancer, or one first-degree relative bilateral breast cancer, or one affected first-degree relative of any age plus another affected first-degree or second-degree relative Exclusion criteria: • history of any cancer or of deep-vein thrombosis or pulmonary embolism • premenopausal women who were considering further pregnancies or who were taking oral contraception • Initial entry criteria allowed patients who had had ductal carcinoma-in-situ to be included. This disorder was later made an exclusion criterion and 22 such patients have been excluded from analysis.
Concurrent medications	Postmenopausal women taking hormone-replacement therapy were eligible without having to stop such therapy. Women in the trial were allowed to start hormone-replacement therapy if indicated.
Outcome	The primary endpoint was the occurrence of invasive breast cancer. Compliance and changes in

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
measure(s)	cholesterol level was also measured
Safety measure(s)	Discontinuations, clinically significant adverse events
Randomisation	randomised by the hospital pharmacy to receive tamoxifen 20 mg per day by mouth for up to 8 years or identical placebo (Orion Pharma).
Blinding	Treatment allocation was concealed from all participants, clinicians, and data staff
Statistical analysis	Based on the accrual rate in 1993 and the relative risk of breast cancer in the study population, it was estimated that it a 75% effect of tamoxifen should be able to be detected in 1996 and a 50% effect in 1998 (two-sided α=5%, power=90%). Interim analyses were planned for these times. The results of the 1998 interim analysis are reported here. Baseline characteristics were compared by χ2 and *U* tests. Breast cancer-free survival was analysed with Kaplan-Meier and log rank techniques. Adjustments for possible confounding variables (age, menopausal status, family history of breast and ovarian cancer, use of hormone-replacement therapy) were made with Cox's proportional hazards model. Compliance was analysed by a survival (time to stopping treatment) analysis. The numbers of participants who stopped treatment prematurely were compared by the χ2 test. To analyse the effectiveness of treatment, women were deemed compliant if they had taken at least 6 months' treatment. Percentage changes from pretreatment values for cholesterol were calculated and analysed by *t* test
Participant Flow	2471 women were included in the analysis (see figure below). The median follow-up was 70 months in both groups and 1033 (42%) participants are no longer taking the tablets. 156/2471 (6.3%) have completed 8 years of treatment and 877/2471 (35.5%) have discontinued prematurely.  Figure 1: **Trial profile** DCIS=ductal carcinoma-in-situ. Exceptions to intention-to-treat analysis: • Initial entry criteria allowed patients who had had ductal carcinoma-in-situ to be included. This disorder was later made an exclusion criterion and 22 such patients were excluded from analysis. • One placebo participant was found to have pre-existing invasive cancer • Administrative errors led to 11 participants being re-randomised by the pharmacy. The data for these women have been censored at the time of their second randomisation. Premature discontinuations and loss to follow-up: • 877 prematurely discontinued treatment, either for nontoxic reasons or because of side-

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
	effects (tamoxifen 320, placebo 176, p<0·0005). • 280 (11%) of the women in the trial have been lost to follow-up for over 18 months
Baseline Character-istics of Participants	The following information was provided regarding baseline characteristics:

	Tamoxifen (n=1250)	Placebo (n=1244)
Age		
Median (range)	47 (31–70)	47 (30–70)
<50	774	749
Menopausal status		
Pre/peri	822	812
Post	416	421
Family history		
First-degree relative <50	698	668
2 or more, any age	225	205
Previous benign lump excised	280	263
On HRT at start	187	202

HRT=hormone-replacement therapy.

Table 1: **Clinical characteristics**

Comment: more detail regarding baseline characteristics is available from the Powles 2007 publication as shown in the table below

Table 1. Possible prognostic factors*

Factor	Tamoxifen arm	Placebo arm	P	Test
No. of patients	1238	1233		
Age, No.				
<50 y	774	749	.5	MW
50–59 y	367	374		
≥60 y	974	110		
Median age, y (range)	7 (31–70)	47 (30–70)		
Menopausal status, No.				
Premenopausal	801	798	.9	χ^2
Perimenopausal	49	43		
Postmenopausal	388	392		
No. of first-degree relatives with breast cancer				
0/nk	43	58	.1	χ^2_{trend}
1	959	959		
2	210	201		
≥3	26	15		
No. of first-degree relatives aged <50 y				
0	531	555	.2	χ^2_{trend}
1	631	612		
≥2	76	66		
No. of first-degree relatives with bilateral breast cancer				
0	1161	1156	1.0	χ^2_{trend}
1	75	73		
≥2	2	4		
No. of first- or second-degree relatives with breast cancer				
0/nk	8	10	.6	χ^2_{trend}
1	373	372		
2	476	496		
3	257	228		
4	81	82		
≥5	43	45		
Previous benign lump, No.	280	267	.6	Fisher
Previous breast surgery, No.	336	323	.6	Fisher
Benign breast disease, No.	96	93	.9	Fisher
Previous atypical hyperplasia/LCIS, No.	4	5	.8	Fisher
Nulliparous, No.	159	172	.4	Fisher
On HRT at randomization, No.				
Estrogen alone	87	102	.5	χ^2
Combined	102	103		
Menopausal status at last follow-up†, No. (%)	1009 (81.5)	1000 (81.1)	.8	Fisher
HRT on treatment, No.				
Estrogen alone	195	192	.7	χ^2
Combined	255	272		
HRT after treatment, No.				
Estrogen alone	218	180	.1	χ^2
Combined	245	245		

* MW = Mann–Whitney *U* test; nk = not known; LCIS = lobular carcinoma in situ; HRT = hormone replacement therapy.

† Postmenopausal (or age >50 years if no data on status at last follow-up).

HRT

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
	During the trial 523 women on tamoxifen took HRT (187 at start and a further 336 during treatment) and 507women on placebo (202 at start and a further 305 during treatment).
Age Distribution	Comment: Only provided as number with age < 50years in initial report. More detail provided in the subsequent report – see table above
Distribution of Risk Factor(s) for the development of Breast Cancer	Comment: Not provided in 1998 publication. Some details provided in Powles 2007 – see table above
Efficacy Results	**Occurrence of breast cancer:** 70 cases of breast cancer were reported, including 8 non-invasive ductal carcinomas-in-situ (4 in each treatment arm). There was no difference in frequency of breast cancer for women on tamoxifen or placebo (tamoxifen 34, placebo 36; relative risk=1·06 [95% CI 0·7-1·7], An analysis of prognostic factors was performed (see table below).

Variable	Relative risk of breast cancer	95% CI	p
Age-group			
<50	1·0		
⩾50	1·1	0·7–1·8	0·6
Menopausal status			
Pre	1·0		
Peri	1·1	0·3–3·5	0·9
Post	1·0	0·6–1·6	
Number of first-degree relatives with breast cancer			
1	1·0		
2	1·2	0·8–1·8	0·3
3	1·5	0·7–3·3	
Relatives aged <50 with breast cancer			
None	1·0		
1	1·1	0·7–1·5	0·7
2	1·2	0·6–2·3	
Relatives with bilateral breast cancer			
No	1·0		
Yes	1·2	0·5–3·0	0·7
Previous benign lump			
No	1.0		
Yes	0·8	0·1–6·9	0·8
Nulliparous			
No	1·0		
Yes	2·0	1·1–3·4	0·02
On HRT at randomisation			
No	1·0		
Yes	1·9	1·1–3·3	0·04
Started HRT during trial			
No	1·0		
Yes	0·4	0·2–0·7	0·01
Randomised treatment			
Tamoxifen	1·0		
Placebo	1·06	0·7–1·7	0·8

Table 4: **Univariate analysis of prognostic factors for breast-cancer-free survival in all 2494 participants**

After adjustment for confounding variables, the randomised treatment of tamoxifen or placebo was not predictive of breast cancer. There appeared to be no interaction between the use of hormone-

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
	replacement therapy and any effect of tamoxifen on breast-cancer occurrence: 12 breast cancers were reported cancers in the 523 women who received hormone replacement therapy on tamoxifen compared with 13 of 507 women on placebo (p=0·6). **Compliance:** Compliance was assessed by direct questioning at each visit. An assessment of the accuracy of volunteered history of compliance was by measurement of serum levels of tamoxifen and its metabolites in the 55 patients who developed breast cancer: • Neither tamoxifen nor its metabolites were detected in 29 placebo patients and in ten tamoxifen patients who said they were not compliant at the time of blood testing. • Tamoxifen and its metabolites were detected in 15 of 16 tamoxifen patients who claimed to be compliant at the time of blood sampling. This was said to demonstrate 96% accuracy for volunteered history of compliance in relation to blood testing. Comment: actual compliance results were was not described in the publication nor was the survival time analysis of compliance described in the statistical plan presented. From the 2007 publication - *Participant compliance, as assessed by self-reporting, was approximately 8% less in the tamoxifen arm than in the placebo arm (P = .002). This difference was evident at 1 year after the start of treatment and remained constant over the treatment period*. **Cholesterol levels:** Cholesterol levels were measured in a random subset of 793 women who self-described as compliant and who did not develop breast cancer. The subset included 390 women from the tamoxifen arm and 403 from the placebo arm. In the women from the placebo arm, mean post-treatment cholesterol was 98·2% (95% CI 97·0–99·4) of the pre-treatment level. In the women from the tamoxifen arm, the corresponding figures were 90·4% (88·8–91·9), indicating around a 10% fall. Cholesterol levels were also measured in a random subset of women who developed breast cancer and for whom blood samples were available. Of the 34 women in this subset, mean post-treatment level in 18 placebo patients was 100·7% (93·6–107·9) of the pretreatment level; for the 16 breast-cancer participants on tamoxifen the figures were 94·8% (86·1–103·5). For the 12/16 women on tamoxifen who also self-described as compliant, the figures were 89·2% (80·8–97·6). Comment: the process of selection of these "random subsets" was not described nor were the time intervals at which cholesterol levels were performed.
Safety Results	**Discontinuations:** 877 have discontinued treatment prematurely (tamoxifen 320, placebo 176, p<0·0005). The most frequent side-effects leading to discontinuation of tamoxifen were hot flushes and other vasomotor symptoms, gynaecological problems including period irregularities, vaginal discharge, and benign abnormalities found on transvaginal ultrasonography

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal

	Tamoxifen	Placebo	p
Median follow-up (months)	70	70	>0·9
Stopped medication	576	457	<0·0005
Completed 8 years	79	77	0·5
Premature stop	497	380	<0·0005
Non-toxic	177	204	0·2
Toxic	320	176	<0·0005
Nausea	12	6	0·2
Headaches	13	14	0·8
Hot flushes	51	13	<0·0005
Weight gain	6	12	0·2
Period abnormality	18	6	0·01
Gyneacological problems	69	18	<0·0005
Mood change	8	1	0·02
Other or not known	143	106	0·01
HRT during trial	336	305	0·2
Lost to follow-up >18 months	141	139	0·9

Table 2: **Follow-up and compliance**

Adverse events:

The occurrence of clinically significant adverse events, including other cancers, thromboembolisms, and nonbreast-cancer deaths, was described as low (see table below). It was stated that there was no significant difference between tamoxifen and placebo, although there are four cases of endometrial cancer in the tamoxifen group compared with one in the placebo group.

Comment: the data with regard to statistical significance was not provided although this is available in the 2007 publication by Powles – see below.

	Tamoxifen	Placebo
Other cancers	19	24
Endometrium	4	1
Ovarian	2	5
Gastrointestinal	3	3
Other	10	15
Deep-vein thrombosis	4	2
Pulmonary embolism	3	2
Death		
Cancer of breast	4	1
Other causes	5	5

Table 3: **Other cancers and events**

Missing data	Limited data regarding adverse events was provided although a more comprehensive table of adverse effects is provided in the 2007 publication – see below
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. This is a relatively small study. Of note is that the interim results of the trial as shown in this publication did not show a reduction in breast cancer incidence with tamoxifen treatment. This analysis was published shortly after the initial results of the NASBP P1 trial, which showed a considerable reduction in invasive breast cancer frequency in women at increased risk of breast cancer treated with tamoxifen 20 mg daily for 5 years. The Discussion section of this publication proposes that a difference in study populations may account for the differing results, with the Royal Marsden trial only including women with a family history whereas risk in the NASBP P1 trial was determined using the Gail model which incorporates other risk factors such as age, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. The difference in duration of follow-up was also described as a possible factor with

Publication Identifier	Powles 1998a, Efficacy and Safety, Pivotal
	median follow-up of 54.6 months for NSABP-P1 compared to 70 months. Measurement of cholesterol levels in a number of participants suggests that the use of tamoxifen may be associated with a reduction in cholesterol level. Limited information is provided in this brief publication regarding conduct of the trial.

Powles 2007

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal
Citation	Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 2007;99(4):283-90.
Relationship to trial	20-year follow-up (median follow-up = 13 years)
Documented GCP or ethics approval	The following statements are provided: *The trial was approved by the Royal Marsden Hospital ethics committee*
Conflict of Interest	The following statements are provided: Nil
Funding source(s)	The following statements are provided: *Funding for this trial was principally by the National Health Service for the clinical resources at the Royal Marsden Hospital required for this trial and the Cancer Research Campaign (now Cancer Research UK) for research grants to support data management. The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript forpublication, and the writing of the manuscript.*
Study design	As above
Study Location	UK (single centre)
Study Dates	Recruitment occurred between October 1986 and April 1996. Data cut-off date for this analysis was September 1 2006. This analysis was initiated after the occurrence of 200 breast cancer events
Study follow-up	Follow-up visits occurred every 6 months and included a clinical breast examination and assessment of acute toxicity. Other diseases and medical problems, including gynaecologic problems, and any changes in the family history of breast cancer were recorded at each visit. Data forms were completed at each visit and continuously updated on the computer database at the Royal Marsden. A mammographic examination occurred annually
Study population	As above
Key selection criteria	As above
Concurrent	As above

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal
medications	
Outcome measure(s)	The primary endpoint was the occurrence of invasive breast cancer Other measures included compliance
Safety measure(s)	
Randomisation	
Blinding	Participants, clinicians, and data-processing staff have remained blinded to the treatment options throughout follow-up.
Statistical analysis	Breast cancer – free survival was analysed by Cox proportional hazards model in both univariate and multivariable analyses. Variables investigated in the analysis included age, menopausal status, parity, family history of breast cancer, previous benign breast disease and use of hormone replacement therapy (HRT). These variables were determined while the data were still blinded. A secondary planned analysis of ER-positive invasive breast cancer was also done. Survival was analysed by the Kaplan – Meier method. Six cancers were not clearly defi ned as invasive or noninvasive and six cancers were of unknown ER status - robustness test showed that inclusion or non-inclusion of these cancers made no difference to the results.
Participant Flow	
Baseline Character-istics of Participants	See above – Powles 1998 including table from Powles 2007
Efficacy Results	**Occurrence of Invasive Breast Cancer** (see also table below): After a median follow-up of 13 years and 2 months (maximum = 19 years and 10 months), 209 women had developed breast cancer (96 on tamoxifen and 113 on placebo; HR = 0.84, 95% CI = 0.64 to 1.10; *P* = .2). There was a trend for fewer invasive breast cancers to be diagnosed in women in the tamoxifen arm, but this also did not reach significance (82 in the tamoxifen arm versus 104 in the placebo arm, HR = 0.78, 95% CI = 0.58 to 1.04; P = .1). After multivariable adjustment for prognostic factors at the time of entry, the result was still similar (HR = 0.77, 95% CI = 0.57 to 1.02; P = .07).

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal

Table 2. Breast cancer events and deaths*

	Tamoxifen arm		Placebo arm				
Event	No.	Rate†	No.	Rate†	HR (95% CI)	P‡	$P_{interaction}$§
Breast cancer–related event							
Any breast cancer	96	5.6	113	6.6	0.84 (0.64 to 1.10)	.2	
DCIS	14	0.8	9	0.5			
Invasive cancer‖	82	4.8	104	6.1	0.78 (0.58 to 1.04)	.1	
During treatment	44	4.5	49	5.0	0.91 (0.61 to 1.37)	.7	
Posttreatment	38	5.1	56	7.6	0.67 (0.44 to 1.01)	.05	
ER-negative	24	1.4	17	1.0	1.4 (0.7 to 2.6)	.3	
ER-positive¶	53	3.1	86	5.1	0.61 (0.43 to 0.86)	.005	
Treatment	30	3.1	39	4.0	0.77 (0.48 to 1.23)	.3	
Posttreatment	23	3.1	47	6.4	0.48 (0.29 to 0.79)	.004	
Menopausal status#							
Premenopausal	14	2.8	28	5.6	0.50 (0.26 to 0.95)	.03	.004
Postmenopausal	9	3.7	19	8.1	0.46 (0.21 to 1.02)	.06	
HRT use during treatment#							
Yes	12	3.6	25	7.9	0.46 (0.23 to 0.91)	.03	.004
No	11	2.7	22	5.3	0.51 (0.25 to 1.05)	.07	
Family history#							
0–2	14	2.7	28	5.3	0.51 (0.27 to 0.96)	.04	.004
≥3	9	3.9	19	9.1	0.43 (0.19 to 0.95)	.04	
Deaths							
Total	54		54		0.99 (0.68 to 1.44)	.95	
Breast cancer	12		9				
Other cancer	30		24				
Stroke	1		2				
Heart condition	6		2				
Other causes or nk	5		17				

* HR = hazard ratio; CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HRT = hormone replacement therapy; nk = not known.

† Rate = number of events per 1000 woman-years.

‡ Statistical significance of the difference between the tamoxifen arm and the placebo arm was determined with a two-sided likelihood ratio test.

§ *P* for interaction is the statistical significance of the interaction between tamoxifen and placebo, after adjusting for menopausal status at randomization, HRT use during treatment, and the number of relatives with breast cancer. Statistical significance was assessed by use of the likelihood ratio test.

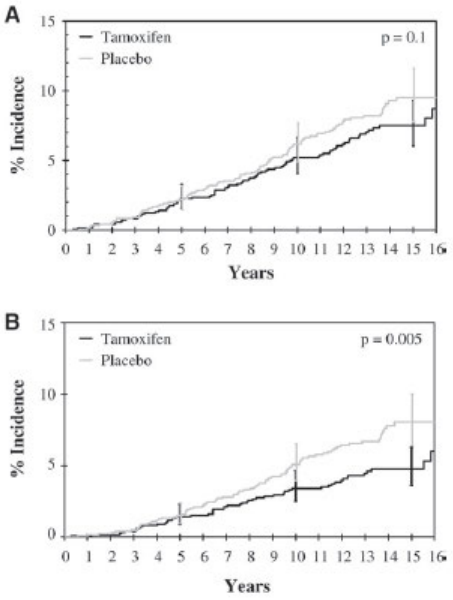
‖ Six cancers are of unknown invasive status and are assumed to be invasive in the above analysis.

¶ Six invasive cancers of unknown ER status were excluded.

Analysis was restricted to patients with ER-positive tumors diagnosed after treatment. Menopausal status at randomization is presented. Family history refers to the number of first- or second-degree relatives with breast cancer.

Analysis according to ER status

Information on the ER status was available for 180 (97%) of the 186 invasive cancers. Of the 180 cancers, 139 were ER positive — 53 (69%) of the 77 cancers in the tamoxifen arm and 86 (83%) of the 103 cancers in the placebo arm The incidence of ER-positive invasive breast cancers in the tamoxifen arm was 39% less (HR = 0.61, 95% CI = 0.43 to 0.86; P = .005) - see also table above and figure below.

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal
	 **Fig. 2.** Kaplan–Meier analysis for breast cancer incidence. **A**) Incidence of all invasive breast cancers. **B**) Incidence of estrogen receptor–positive breast cancer. At 5, 10, and 15 years, 95% confidence intervals for the percentage incidence have been inserted. At 5, 10, and 15 years, the numbers of participants at risk in the tamoxifen arm were 1144, 1013, and 243, respectively, and in the placebo arm were 1151, 993, and 241, respectively. **Compliance:** Participant compliance, as assessed by self-reporting, was approximately 8% less in the tamoxifen arm than in the placebo arm (P = .002). Comment: actual compliance rates for each arm were not provided.
Safety Results	**Discontinuations:** Not provided **Deaths:** The same number of deaths occurred in each arm (54). There were 12 deaths due to breast cancer in the tamoxifen arm compared to 9 in the placebo arm. **Adverse events**: The serious adverse events of venous thromboembolic events, endometrial cancer and other major gynaecological conditions (as indicated by hysterectomy) occurred more commonly in the tamoxifen arm. Of these, only the difference in the number of hysterectomies reached significance. Other potential tamoxifen effects of hot flushes, vaginal discharge and menstrual abnormalities were significantly more common in the tamoxifen arm, with this persisting throughout follow-up.

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal

Table 3. Adverse events in the two treatment groups during and after treatment*

Adverse event	No. on treatment or for whole follow-up†			No. after treatment		
	Tamoxifen arm	Placebo arm	P	Tamoxifen arm	Placebo arm	P
Nausea	131	147	.3	8	4	.3
Vomiting	17	26	.2	2	2	1.0
Headaches	227	244	.4	18	14	.5
Hot flushes	598	394	<.001	73	47	.001
Weight gain	275	319	.03	26	12	.02
Period abnormality	496	439	.02	119	87	.008
Breast symptoms	65	60	.7	10	14	.5
Mood change	112	119	.6	13	14	1.0
Vaginal discharge	321	167	<.001	41	17	.001
Eye problems	94	86	.6	10	2	.02
Fluid retention	60	68	.5	2	0	.3
Hair or nail problems	92	79	.3	3	0	.1
Skin rash	103	107	.8	8	3	.1
Sleep disturbance	41	40	.7	5	1	.1
Indigestion	13	16	.6	3	1	.4
Other abdominal problems	70	55	.2	8	3	.1
Aches in joints	67	57	.4	4	4	1.0
Dizzy	54	57	.8	4	3	.7
Bowel, constipation, or diarrhea	42	45	.7	2	2	1.0
Bladder symptoms	27	25	.9	3	1	.4
Vasomotor symptoms	162	96	<.001	19	10	.1
Weight loss or appetite change	23	28	.5	3	7	.3
Lethargy	77	79	.9	7	7	1.0
Hypertension	26	30	.6	3	0	.1
Vaginal symptoms	37	17	.008	1	0	.5
Muscular cramps	32	19	.09	2	1	.5
General malaise	34	25	.3	0	3	.3
Loss of libido	23	26	.7	1	2	1.0
Voice change	12	19	.2	0	0	–
Gynecologic problems	37	13	.001	1	1	1.0
Cardiovascular problems	10	12	.7	11	14	.7
Venous thromboembolic events	8	3	.2	5	6	1.0
Stroke	7	9	.6	3	7	.3
Cataracts	9	1	.02	3	2	1.0
Fractures	19	22	.6	9	11	.8
Hysterectomy†	177	96	<.001			
Endometrial cancer†	13	5	.06			
Cancers other than endometrial or breast cancer†	64	70	.8			

* Events were reported from at least 3 months after treatment was stopped until the end of follow-up. Data were available for 1079 participants in the tamoxifen arm and 1034 participants in the placebo arm. Statistical significance between tamoxifen and placebo was assessed by Fisher's exact test. All statistical tests were two-sided.

† These events are reported for the entire follow-up period; other events are reported during treatment only.

Comparison across time periods of follow-up

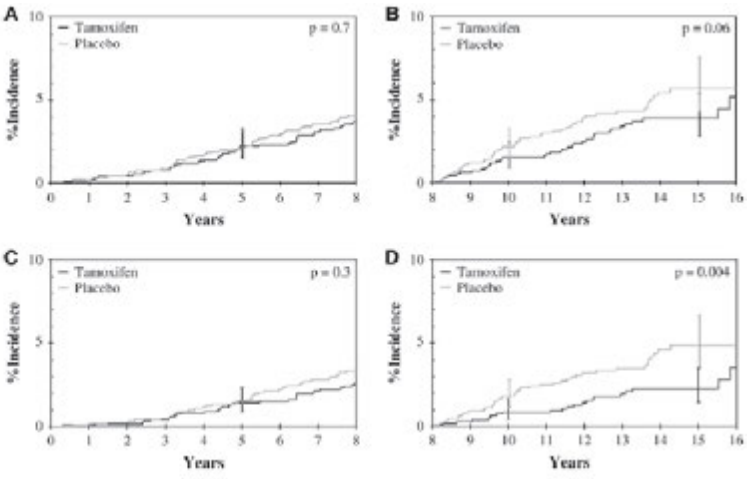


Fig. 3. Kaplan–Meier analysis for breast cancer incidence. A) Incidence of all invasive breast cancer during the 8-year treatment period. B) Incidence of all invasive breast cancer during the posttreatment period. C) Incidence of estrogen receptor (ER)–positive invasive breast cancer during the 8-year treatment period. D) Incidence of ER-positive invasive breast cancer during the posttreatment period. At 5, 10, and 15 years, 95% confidence intervals for the percentage incidence have been inserted. At 5, 10, and 15 years, the numbers of participants at risk were 1144, 1013, and 243, respectively, in the tamoxifen arm and 1151, 993, and 241, respectively, in the placebo arm.

Missing data

No description of the numbers remaining in follow-up against years of follow-up was provided (except for the median follow-up duration of 13 years). Of note is that the Kaplan Meier curve above shows that there were only 484/2471 (19.5%) of women still at risk at 15 years of follow-up

Publication Identifier	Powles 2007, Efficacy and Safety, Pivotal
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" and NHMRC level 2 by the sponsor. This is appropriate. This is a relatively small, single institution study. As with the earlier report from this trial, the results do not show a reduction in the occurrence of invasive breast cancer with tamoxifen treatment. However, a significant reduction in the occurrence of ER+ breast cancer was shown in the tamoxifen arm with most of the reduction occurring during the post-treatment phase..

Royal Marsden Related Publications (Efficacy and Safety)

Kote-Jarai 2007

Publication identifier	Kote-Jarai 2007, Efficacy and Safety, Secondary Supportive
Citation	Kote-Jarai Z, Powles TJ, Mitchell G, Tidy A, Ashley S, Easton D, et al. BRCA1/BRCA2 mutation status and analysis of cancer family history in participants of the Royal Marsden Hospital tamoxifen chemoprevention trial. Cancer Lett. 2007;247(2):259-65.
Study description	Compared calculated breast cancer heterozygote risk to BRAC1/2 mutations in the 70 women who had had breast cancer diagnosed at the time of the 1998 analysis
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: *The trial and associated studies were approved by the Royal Marsden Hospital Research Ethics Committee* *This work was supported by a donation from Tony Maxse and Hugh Knowles in memory of the late Georgina Knowles and by Cancer Research UK, the legacy of the late Marion Silcock, The Royal Marsden Hospital NHS Foundation Trust and the Institute of Cancer Research*
Study Dates	Recruitment occurred between 1986 and 1996. This analysis included women who developed breast cancer at the time of the interim analysis in 1998.
Study Method	Family history of first-degree members, plus any other family members with cancer, was collected with details including current age or age at death, cancer diagnosis and age at cancer diagnosis of these relatives. This information was used to compute a breast cancer heterozygote risk measure for the 70 women who had had breast cancer diagnosed. The women were divided into two groups (the higher risk group who had a higher/equal risk than the mean and a lower risk group with a calculated risk lower than the mean. Breast cancer specimens were examined for the presence of markers and oestrogen and progesterone receptors were semi-quantitatively measured. DNA sequencing was performed for each of the 70 women to determine if BRAC1 or BRAC2 mutations were present.
Blinding	As above. An additional statement is provided that pathologists reviewing the cancer specimens were blinded to the treatment arm.
Results	70 women had developed breast cancer (34 on tamoxifen. 36 on placebo) at data cutoff. Pedigree information for estimating risk was available from all 70 participants, blood DNA samples were available from 62 patients and tumour samples for analysis of phenotypic molecular markers were available from 67 patients. Analysis of the number of breast cancers according to the genetic risk found a non-significant reduction in the incidence of breast cancers in women from the low risk group who were in the tamoxifen arm. Women with a higher calculated genetic risk who were treated with tamoxifen had no such benefit. Of the 62 patients who had DNA samples available for testing, only 4 (6%) were found to have protein truncating mutations (1 in *BRCA I,* 3 in *BRCA2).* Of these, 3 had a calculated genetic risk of >80% and

Publication identifier	Kote-Jarai 2007, Efficacy and Safety, Secondary Supportive
	one had a genetic risk of 10%. Histochemical analysis according to treatment allocation of the 67 available cancers showed a significantly lower frequency of ER positive cancers (50% versus 74%, $p = 0.04$) and a lower median ER ($p = 0.03$) in the cancers developing in tamoxifen-treated patients
Conclusion	*many women who have inherited an increased risk of breast cancer, may develop cancers which are tamoxifen resistant or even promoted by tamoxifen*
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This sub-group analysis of patients who developed breast cancer found that there was a low incidence of BRAC1/2 mutations. This publication adds little to establishing efficacy of preventative tamoxifen.

Royal Marsden Related Publications (Safety)

Jones 1992

Publication identifier	Jones 1992, Safety, Secondary Supportive
Citation	Jones AL, Powles TJ, Treleaven JG, Burman JF, Nicolson MC, Chung HI, et al. Haemostatic changes and thromboembolic risk during tamoxifen therapy in normal women. Br J Cancer. 1992;66(4):744-7.
Study description	Evaluation of the effects of preventative tamoxifen in healthy women on the levels of fibrinogen, anti-thrombin III, Protein C, Protein S and cross linked fibrin degradation products (XL-FDP).
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: nil
Study Dates	Recruitment occurred between 1986 and 1996. This analysis was published in 1992
Study Method	515 patients had pre-treatment blood samples taken for fibrinogen and antithrombin III assays and samples were repeated on treatment at 6 monthly intervals. A subset of 39 consecutive patients had pre-treatment and on-treatment samples at 6 months for Protein C, Protein S and XL-FDP. Levels were analysed according to treatment arm and menopausal state.
Blinding	Not described
Results	Results are provided for approximately 200 women with around 100 from each treatment arm, with slightly different numbers included for each laboratory variable. Comment: no explanation of the relationship between these approximately 200 patients in the analysis and the 515 patients who had blood specimens collected was given. Nor was it explained why the analysis population varied with laboratory variables. Fibrinogen levels were significantly reduced in both pre- and post-menopausal women in the first 12 months. There was a reduction in antithrombin 3 for postmenopausal women but no reduction in premenopausal women. For premenopausal women there was no change in Protein S or Protein C on treatment. For postmenopausal women there was an overall marginal reduction in Protein S antigen to 90% of pretreatment levels at 6 months ($P = 0.05$) but no change in Protein C levels. There were no significant changes in crosslinked FDP's

Publication identifier	Jones 1992, Safety, Secondary Supportive
	for either pre or postmenopausal women on treatment. No thromboembolic events had been recorded in either arm.
Conclusion	Changes in fibrinogen, ATIII, & Protein S antigen may be seen with tamoxifen treatment.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This was a retrospective sub-group analysis from early in the Royal Marsden trial. No description of how the sub-group was selected was provided, Interpretation of the results of this analysis is also limited by the small number of women who had measurements performed after the first 6 months (initial numbers of around 100 had halved by 12 months and fallen to fewer than 20 by 24 months). No clinical correlation was made with the minor changes in levels observed.

Kedar 1994

Publication identifier	Kedar 1994, Safety, Secondary Supportive
Citation	Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet. 1994;343(8909):1318-21.
Study description	Cohort study of the effect of preventative tamoxifen on the uterus and ovaries
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: *RPK was supported by a grant from ZenecaPharmaceuticals, Macclesfield, Cheshire*
Study Dates	Not described
Study Method	The cohort consisted of 111 consecutive post menopausal women from a follow-up clinic for the Pilot Breast Cancer Prevention Trial at the Royal Marsden Hospital. At some time after commencing treatment, transvaginal ultrasonography with colour doppler imaging and microscopic examination of endometrial biopsies removed at the time of the scan n ultrasound scan was performed. The concentrations of FSH, LH and sex-hormone binding globulin (SHBG) together with oestradiol and progesterone were measured at the time of the scan. Tamoxifen and its metabolite, desmethyl tamoxifen, were also measured as part of a compliance measure for the main trial.
Blinding	Not described
Results	Of the 111 women, 50 were from the tamoxifen arm and 61 from the placebo arm. Ultrasound scans were performed a median of 22 months (range 3-75) and 24 months (range 0-74)after commencing treatment for the tamoxifen and placebo arms respectively. Tamoxifen and desmethyl tamoxifen levels were consistent with the treatment arm the woman was randomised to, except for 6 women in the tamoxifen arm who had unrecordable levels, suggesting non-compliance. Significantly more women in the tamoxifen group had a thick cystic endometrium and increased uterine arterial and subendometrial blood velocity. 39% of women in the tamoxifen group had histological evidence of an abnormal endometrium compared with 10% in the control group, and 16% of women taking tamoxifen had evidence of atypical hyperplasia compared with none taking the placebo. The values for FSH and LH were significantly ($p < 0\text{-}001$) lower in the tamoxifen group. Mean SHBG (nmol/L) was higher in the tamoxifen group but the difference was not significant.

Publication identifier	Kedar 1994, Safety, Secondary Supportive
	Concentrations of oestradiol and progesterone in both groups were below detection limits. 8 in the placebo group and 8 in the tamoxifen group were taking hormone replacement therapy (HRT) at the time of investigations. 1 taking tamoxifen and HRT had atypical endometrial hyperplasia; 3 taking placebo and HRT had a proliferative endometrium, mitotic cells, or a polyp.
Conclusion	Both ultrasonographic and histological results suggest that tamoxifen has a stimulatory effect on the uterine body and endometrium.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This sub-group analysis provides some information regarding the effect of tamoxifen treatment on the endometrium.

Powles 1994

Publication identifier	Powles 1994, Safety, Secondary Supportive
Citation	Powles TJ, Jones AL, Ashley SE, O'Brien ME, Tidy VA, Treleavan J, et al. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. Breast Cancer Res Treat. 1994;31(1):73-82.
Study description	Report of the initial pilot study - randomised double blind placebo controlled trial of preventative tamoxifen for 8 years in women at increased risk of breast cancer on the basis of family history.
Funding source, Conflicts of interest	The following statements are provided: *The trial had ethical approval by the Hospital Ethics Committee* *We thank the Cancer Research Campaign for support for data management for this trial, Farmos, Finland for supply at cost of tamoxifen and placebo,*
Study Dates	October 1986 until June 1993
Study Method	Eligible women were randomised to tamoxifen or placebo. During follow-up, clinical examination and assessment of toxicity (by an oral check list) were performed every 6 months and mammography repeated annually. Compliance was assessed by direct questioning together with requested return of unused tablets. Safety monitoring involved assessment of coagulation factors, lipids, bone mineral density, ovarian cysts, and uterine thickness. Antithrombin III (AT III), fibrinogen, total cholesterol were measured before treatment, at 6 months, and then annually. Radial bone mineral density was measured before treatment and every 6 months. Ovarian ultrasound was performed – baseline scans were not available. Scans were performed at different times during the follow-up period.
Blinding	Participants and investigators were blinded to treatment allocation
Results	2012 women were randomised. Of these most were followed-up

Table 7. Follow-up.

Not seen for > 12 months	122
Not seen for > 18 months	59
Deaths (non-malignant)	2
Breast carcinomas	11
Other carcinomas	
Endometrial	2
Sarcoma	1
Pregnancy	1

205 women discontinued from the tamoxifen group and 150 from the placebo group.

Baseline characteristics are shown below:

Table 1. Clinical characteristics of participants

Tamoxifen	Placebo	
Numbers	1005	1007
Assessable (> 3 months)	920	926
Median age (range)	48 (31–70)	48 (30–70)
Age by Decade		
30–40 yrs	82	61
40–50 yrs	507	531
50–60 yrs	321	313
60–70 yrs	94	100
> 70 yrs	1	2
Menopausal Status		
Pre	609	632
Peri	36	31
Post	360	344
Previous benign breast biopsy	238	222
Family History		
1st degree relative + 1 other	397	416
1st degree relative + 2 others	144	132
1st degree relative + > 2 others	58	55
1st degree relative aged < 45 yrs	167	142
1st degree bilateral	5	10
Other family history	85	100
No family history	22	25

ATIII, fibrinogen and cholesterol levels were reduced in the tamoxifen group. There was no significant difference in measured bone density between women on tamoxifen or placebo

Adverse Effects:

"Acute toxicity" effects are shown below:

Table 2. Acute toxicity

	Tamoxifen	Placebo	Significance
Total number	920	926	
Hormone replacement therapy			
Before randomisation	131	134	NS
On Tamolac	126	119	NS
Total	257	253	NS
Never on HRT	663	673	
Nausea	41 (6%)	65 (10%)	p < 0.025
Vomiting	3 (< 1%)	9 (1%)	NS
Headache	82 (12%)	96 (14%)	NS
Hot flushes			
Premenopausal	151 (36%)	75 (17%)	p < 0.005
Postmenopausal	66 (29%)	54 (25%)	NS
Total	225 (34%)	134 (20%)	p < 0.005
Weight gain	44 (7%)	71 (11%)	p < 0.025
Menstrual irregularities	93 (14%)	57 (9%)	p < 0.005
Mood change	15 (3%)	13 (3%)	NS
Vaginal discharge			
Premenopausal	53 (13%)	12 (3%)	p < 0.005
Postmenopausal	53 (24%)	17 (8%)	p < 0.005
Total	108 (16%)	30 (4%)	p < 0.005

There was a significant increase in hot flushes (34 % versus 20%) mostly in premenopausal women ($p < 0.005$), vaginal discharge (16% versus 4%, $p < 0.005$), and menstrual irregularities (14% versus 9%, $p < 0.005$). The requirements for hormone replacement therapy for women on tamoxifen or placebo were the same.

Ovarian screening demonstrated a significantly increased risk ($p < 0.005$) of detecting benign ovarian cysts in pre-menopausal women who had received tamoxifen for more than 3 months compared to those on placebo – see table below

Table 4. Incidence of non-malignant ovarian cysts detected by transvaginal ovarian ultrasound examinations undertaken at various intervals after commencement of tamoxifen or placebo.

	Premenopausal		Postmenopausal	
Months	Tamoxifen	Placebo	Tamoxifen	Placebo
0–2	78/236 (33%)	66/231 (28%)	11/112 (10%)	11/96 (11%)
3–11	61/156 (39%)*	44/170 (26%)	7/75 (9%)	7/93 (10%)
12–23	58/151 (38%)**	31/143 (22%)	7/93 (8%)	4/65 (4%)
24+	44/118 (37%)***	40/174 (23%)	13/113 (12%)	4/103 (4%)

* $p < 0.025$; ** $p < 0.005$; *** $p < 0.01$

There was an increased likelihood of detecting fibroids in pre- and postmenopausal on tamoxifen ($p < 0.01$) compared to placebo. There was no significant increase in the requirement of dilation and curettage, ovarian surgery, laparotomy, or laparoscopy for women on tamoxifen compared to placebo but there was an increased requirement for hysterectomy for patients on tamoxifen compared to placebo (29 vs 16, $p < 0.05$).– see table below.

	Table 6. Incidence of gynaecological surgery undertaken on women receiving tamoxifen or placebo. | | Tamoxifen | Placebo | Significance | |---|---|---|---| | Dilatation and curettage | 25 | 19 | NS | | Hysterectomy | 29 | 16 | NS ($p < 0.05$) | | Ovarian surgery | 14 | 15 | NS | | Laparotomy/-oscopy | 4 | 5 | NS | | Any surgery | 69 | 47 | NS ($p < 0.05$) | There were no episodes of thromboembolism requiring anticoagulation, or coronary heart disease. Discontinuations: Of the 205 women (22%) who discontinued tamoxifen, 97 (11 %) gave toxicity as the reason, compared with 60 (6%) of the 150 patients who discontinued placebo ($p < 0.005$). imilarly, among the women who did not attribute toxicity as the cause for non compliance, there was a higher incidence of recorded side effects (42 women, 5%) in the tamoxifen arm compared with placebo (20 women; 2%). The main difference in symptomatic toxicity causing cessation of therapy was hot flushes (tamoxifen 43; placebo 8; $p < 0.001$) and problems with menstruation (tamoxifen 14; placebo 4; $p < 0.025$).
Conclusion	using tamoxifen in a chemoprevention trial is safe and feasible
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. Given that the participants of this pilot study have been included in the 1998 and 2007 reports of the Royal Marsden trial, this publication adds little information.

Powles 1996

Publication identifier	**Powles 1996, Safety, Secondary Supportive**
Citation	Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol. 1996;14(1):78-84.
Study description	Sub-group analysis of bone mineral density in women participating in the Royal Marsden trial who attended the Sutton site for follow-up where DEXA scans were available from 1990.
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: nil
Study Dates	1990 to ?
Study Method	Women recruited to the trial underwent a pre-treatment scan and subsequent scans were repeated annually. Women who were on hormone replacement therapy (HRT) at the time of randomization were not included in this study and if a participant started HRT during the study, any subsequent BMD measurements were excluded from analysis. Changes in BMD after 1, 2, and 3 years of treatment were calculated as percentages of each subject's pretreatment value. For each time point, a significant change from the pretreatment value was tested using a two-sided paired t test, and the differences in mean BMD for the two treatment groups were

Publication identifier	Powles 1996, Safety, Secondary Supportive
	tested using a two-sided unpaired t test
Blinding	
Results	**Table 2. Subject Characteristics** Postmenopausal: Tamoxifen (n = 30); Placebo (n = 24) Premenopausal: Tamoxifen (n = 62); Placebo (n = 63) Age, years: 56.5 ± 5.6; 59.0 ± 4.7; 43.7 ± 4.7; 43.7 ± 3.9 Years since menopause: 10.2 ± 6.6; 9.9 ± 6.8 Weight (kg): 67.8 ± 10.9; 70.21 ± 12.5; 64.5 ± 11.4; 64.5 ± 11.9 Body mass index (kg/m²): 25.2 ± 4.5; 26.7 ± 4.7; 24.4 ± 4.2; 24.2 ± 4.5 Lumbar BMD: .97 ± .13; .91 ± .13; 1.05 ± .14; 1.07 ± .14 Hip BMD (g/cm²): .88 ± .11; .89 ± .11; .94 ± .13; .97 ± .12 NOTE. There were no significant differences. In premenopausal women, the mean spinal and hip BMD for women on tamoxifen were significantly less than for women on placebo. In postmenopausal women, there was a significant increase in BMD at both the lumbar spine and the hip in the tamoxifen group and a small but not significant decrease in BMD at the lumbar spine and hip, so that there was a significant increase in BMD in the tamoxifen group compared to the placebo group.
Conclusion	Tamoxifen may have contrasting effects on bone density according to the prevailing oestrogen levels
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This sub-group analysis of a convenience sample provides some information regarding the effect of tamoxifen on bone density. No clinical correlation with respect to fractures or fracture risk is made.

Chang 1996

Publication identifier	Chang 1996, Safety, Secondary Supportive
Citation	Chang J, Powles TJ, Ashley SE, Gregory RK, Tidy VA, Treleaven JG, et al. The effect of tamoxifen and hormone replacement therapy on serum cholesterol, bone mineral density and coagulation factors in healthy postmenopausal women participating in a randomised, controlled tamoxifen prevention study. Ann Oncol. 1996;7(7):671-5..
Study description	Sub-group analysis of the interaction between HRT and tamoxifen on serum cholesterol, fibrinogen, antithrombin III (AT III) and bone mineral density (BMD) in postmenopausal healthy women
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: *This trial has ethical approval by the Hospital Ethical Committee*
Study Dates	1986 to ?. This analysis was published in 1996
Study	Follow-up and investigations as described for the pilot study (Powles 1994). There were 6

Publication identifier	Chang 1996, Safety, Secondary Supportive
Method	categories of participants in this analysis: women who were treated with tamoxifen (group A) or placebo (group B); women in whom HRT was subsequently added to tamoxifen (group C) or placebo (group D); women who were on HRT before randomisation to tamoxifen (group E) or placebo (group F).
Blinding	
Results	2405 women had been recruited to the main study. The median time of follow-up of this analysis was 4 years. *Table 1.* Effect of tamoxifen and HRT on serum cholesterol, fibrinogen, AT III, BMD. Group A: −13% (153) P<0.001; −14% (90) P<0.001; −8% (93) P<0.001; +1% (38) P<0.1; +2% (38) P<0.01 Group B: −2% (149) P<0.05; +2% (90) P=NS; +1% (91) P=NS; −0.5% (26) P=NS; 0% (26) P=NS Group C: 0% (20) P=NS; −4% (15) P=NS; 0% (19) P=NS; +1% (10) P=NS; +2% (10) P<0.05 Group D: −5% (14) P=0.1; −4% (11) P=NS; −8% (13) P=NS; +1.5% (7) P=NS; 0% (7) P=NS Group E: −7% (44) P<0.02; +1% (28) P=NS; −6% (28) P=NS; 0% (5) P=NS; +3% (5) P=NS Group F: 1% (41) P=NS; +7% (24) P=NS; 0% (24) P=NS; 0% (13) P=NS; 0% (13) P=NS Group A: Women on tamoxifen; Group B: Women on placebo; Group C: Women who were on tamoxifen before the addition of HRT; Group D: Women who were on placebo before the addition of HRT; Group E: Women who were on HRT before the addition of tamoxifen; Group F. Women who were on HRT before the addition of placebo. Comment: No overview table indicating the total number of women included and the number of women in each of the 6 categories is provided.
Conclusion	In healthy postmenopausal women, tamoxifen lowered serum cholesterol to a greater degree than oestrogen replacement, tamoxifen lowered fibrinogen and ATIII levels in the absence of HRT and tamoxifen increased bone mineral density with this additive if HRT was also administered.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence II by the sponsor. This is appropriate. This sub-group analysis of post-menopausal women adds some information regarding possible effects of tamoxifen in the absence or presence of HRT.

Chang 1998

Publication identifier	Chang 1998, Safety, Secondary Supportive
Citation	Chang J, Powles TJ, Ashley SE, Iveson T, Gregory RK, Dowsett M. Variation in endometrial thickening in women with amenorrhea on tamoxifen. Breast Cancer Res Treat. 1998;48(1):81-5
Study description	Sub-group analysis of women who became amenorrhoeic during treatment with tamoxifen or placebo. An analysis of the 5 women who developed endometrial cancer in the trial to that date was also presented

Publication identifier	Chang 1998, Safety, Secondary Supportive
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: Nil
Study Dates	1986-?
Study Method	Menstrual histories were documented at each 6 monthly visit and venous blood collected for storage. These samples were analysed for follicular stimulating hormone (FSH) and plasma estradiol (E2). Women who developed amenorrhea with intact uterii and not on hormone replacement therapy were offered regular transvaginal ultrasound surveillance with assessment for endometrial thickening
Blinding	As above
Results	2274 women had been recruited to the main trial at the time of this analysis. Of these, 1154 women categorised as premenopausal at trial entry subsequently became amenorrhoeic. This was seen disproportionately in the tamoxifen group – see table below. *Table 1.* Patient characteristics Placebo / Tamoxifen Total no. of women in prevention study: 1135 / 1139 No. of women with hysterectomy: 288 / 277 No. of postmenopausal women at start of prevention study (i.e. amenorrhea > 6 months): 216 / 239 ET measured: 180 (83%) / 194 (81%) No. premenopausal at start of prevention study (i.e. regular periods): 631 / 623 subsequent amenorrhea (> 6 mths): 74 (12%) / 150 (24%) p < 0.0005 ET and E2 measured: 16 (22%) / 31 (21%) In both postmenopausal women and recently amenorrhoeic women with low plasma estradiol, tamoxifen significantly increased endometrial thickening ($p < 0.0001$ and $p < 0.005$ respectively). However, in women who developed amenorrhoea with maintained ovarian function (E2 >450 pmol/L), tamoxifen did not cause endometrial thickening. There were 5 women (tamoxifen, 4; placebo, 1) who developed endometrial cancer ,all of whom were premenopausal at entry. Three of the women presented with vaginal bleeding, two of them before transvaginal screening was commenced in 1990. Transvaginal ultrasound screening detected 2 further women with endometrial cancer who developed amenorrhea and were found to have low E2 (32 and 51 pmol/L) and increased endometrial thickness (17 and 17 mm respectively)
Conclusion	Premenopausal women who became amenorrhoeic on tamoxifen may be at special risk of endometrial cancer
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with NHMRC level of evidence by the sponsor. This is appropriate. This sub-group analysis adds some information regarding a sub-group that may be at greater risk of developing endometrial cancer during preventative treatment with tamoxifen

Powles 1998b

Publication identifier	Powles 1998b, Safety, Secondary Supportive
Citation	Powles TJ, Bourne T, Athanasiou S, Chang J, Grubock K, Ashley S, et al. The effects of norethisterone on endometrial abnormalities identified by transvaginal ultrasound screening of healthy post-menopausal women on tamoxifen or placebo. Br J Cancer. 1998;78(2):272-5
Study description	Sub-group analysis of post-menopausal healthy women to identify the incidence of endometrial thickening, polyps and cysts by transvaginal ultrasound screening and to evaluate the possible benefit from the use of intermittent norethisterone (NE) in women with persistent changes.
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: Nil
Study Dates	1990-?
Study Method	Postmenopausal women in the trial who had an intact uterus and who were not on HRT underwent regular transvaginal ultrasound screening. Oral norethisterone 2.5 mg was prescribed daily for 21 days out of 28 days for three consecutive cycles to women confirmed with an endometrial thickness (ET) > 8 mm. Endometrial biopsies were taken at the start of the study on an outpatient basis. Hysteroscopy, with resection biopsies and/or dilatation and curettage, was performed if there was persistent endometrial abnormality on ultrasound scan after 3 months of intermittent norethisterone.
Blinding	All ultrasound examinations and subsequent analyses were undertaken without breaking the code for tamoxifen or placebo,
Results	There were 463 post-menopausal women with intact uteri who were enrolled in the trial. A persistent ET > 8 mm was identified in 56 (24%) of the 235 women on tamoxifen compared with 5 (2%) of the 228 women on placebo (P < 0.0005). Using hydrosonography, it was possible to identify in these women with endometrial thickening, cysts in 7%, polyps in 3% and both cysts and polyps in 8%. There were 51 women who were eligible for, and consented to, the norethisterone trial (47 in the tamoxifen group and 4 in the placebo group). After 3 months of cyclical norethisterone, 39 of the 47 women on tamoxifen and 3 of the 4 women on placebo had persistent abnormalities. All 42 of these women underwent hysteroscopy with the findings as shown below:

Publication identifier	Powles 1998b, Safety, Secondary Supportive
	Table 4 Histological findings in 42 women having persistent TVUS abnormalities after 3 months of norethisterone Tamoxifen / Placebo Hysteroscopy 39 / 3 Endometrial biopsy 28 / 2 Inadequate sample/atrophic 19 / 2 Proliferative 5 / 0 Hyperplastic with atypia 4 / 0 Polypectomy Simple polyp 12 / 0 Hyperplastic 3 / 0
Conclusion	Endometrial thickening >8mm is significantly increased in patients taking tamoxifen. This may predispose to endometrial cancer.
Allocation by sponsor and Evaluator assessment	This was described as a "secondary supportive publication" with no NHMRC level of evidence by the sponsor. This is appropriate. This sub-group analysis found that endometrial thickening is significantly increased in patients taking tamoxifen. A relationship between this and the development of endometrial cancer is not made

Fallowfield 2001

Publication identifier	Fallowfield 2001, primary supportive, safety
Citation	Fallowfield L, Fleissig A, Edwards R, West A, Powles TJ, Howell A, et al. Tamoxifen for the prevention of breast cancer: psychosocial impact on women participating in two randomized controlled trials. J Clin Oncol. 2001;19(7):1885-92.
Included trials	IBIS-1, Royal Marsden
Study description	To evaluate the psychosocial implications of tamoxifen versus placebo in women who are at increased risk of breast cancer
Ethics approval, Funding source, Conflicts of interest	The following statements are provided: *Separate ethical approval for the psychosocial study was obtained and the women who participated provided written informed consent*
Study Dates	1992 to 1999
Study Method	Consecutive women who were considering entry into the main trials (IBIS-I or Royal Marsden) were invited to join the psychological study. Those who agreed to participate were sent a baseline questionnaire followed by postal questionnaires every 6 months for 5 years. In the baseline questionnaire, women provided sociodemographic and medical history details and information about their attitudes toward and knowledge of breast cancer. The following questionnaires were also completed at baseline: the Multidimensional Health Locus of Control,

Publication identifier	Fallowfield 2001, primary supportive, safety
	which determines where an individual believes that responsibility for her healthlies primarily; the Spielberger State/Trait Anxiety Inventory (STAI) to evaluate anxiety proneness; and the General Health Questionnaire 30 (GHQ-30), a screening tool to determine general psychiatric morbidity or emotional distress in clinical settings or community studies; a sexual activity questionnaire (SAQ) that was developed for this study. Subsequently, the STAI, the GHQ-30, and the SAQ were administered at 6-month intervals for 5 years. Participants were also asked about tablet adherence, periods, and use of hormone replacement therapy (HRT) and to comment on changes in well-being. A 42-item symptom checklist was also included with the 48-month questionnaires. Respondents who scored above the recommended GHQ-30 threshold of 4 were identified as probable "cases" of psychological morbidity.
Blinding	Randomisation and blinding was as for the IBIS-1 and Royal Marsden trials. As treatment allocation was concealed from all participants and staff, the unblinding of data for the psychosocial study was conducted by an independent statistician. An intention-to-treat analysis was used and nonparametric statistical tests were applied as the data were not distributed normally. Formal adjustments for multiple comparisons were not made.
Results	Of the 550 women invited,488 sent back baseline questionnaires: 416 women from Royal Marsden (217 randomised to tamoxifen, 199 to placebo) and 72 from the Manchester site for IBIS (37 randomised to tamoxifen and 35 to placebo). Almost three quarters (71.1% [347 of 488]) of participants returned at least 8 of 10 of their follow-up questionnaires, 46.9% (229 of 488) returned all. Twenty-six women did not return any questionnaires after baseline, but this includes 11 women who had withdrawn from the main trials. Baseline characteristics: The women in the tamoxifen and placebo groups were well matched on age, risk-related family history, menopausal status, and use of HRT. Two thirds (67.4%) were younger than 50 years, 26.4% were between 50 and 59 years, and 6.1% were 60 years or older. The psychosocial and sexual activity characteristics of the tamoxifen and placebo groups were also similar at trial entry. GHQ threshold: The proportion of respondents who scored above the GHQ-30 threshold of 4 varied between 22% and 30% during the trial. After adjustment for time on study and baseline GHQ score, there was a marginally significant effect favouring the tamoxifen-treated group (OR, 0.72; 95% CI, 0.53 to 1.00). Anxiety level: Differences in anxiety level compared with baseline were estimated using a random effects linear model. The coefficient for the effect of treatment was not significant (*P* 5 .09). Sexual activity: Throughout the trial, approximately three quarters of the women who completed the SAQ were sexually active and there was no treatment effect (OR adjusting for baseline sexual activity status and time on study, 1.63; 95% CI, 0.86 to 3.08). Symptom checklist: From the symptom checklist completed 48 months after joining the trial completed , most women (90% [314 of 347, data missing for 19]) reported at least one symptom that had caused a considerable problem (somewhat/quite a bit/very much). The number of problems reported was

Publication identifier	Fallowfield 2001, primary supportive, safety
	associated with anxiety; women whose trait anxiety score was under 40 reported a median of six symptoms compared with nine among those with a trait anxiety score of 40 or more (Mann-Whitney *U* test, *P* , .001). The number of symptoms reported was not associated with age or treatment group. Women in the tamoxifen group were more likely to report vasomotor symptoms (night sweats, hot flushes, and cold sweats) and vaginal discharge, whereas members of the placebo group were more likely to report low energy, breast sensitivity or tenderness, and blurring of vision – see also table below
Conclusion	*Changes in psychosocial well-being measured during a 5-year period were not associated with tamoxifen. Although women in the tamoxifen group were more likely to report vasomotor symptoms and vaginal discharge, these problems did not seem to have a major impact on either their measured psychological or their sexual well-being.*
Allocation by sponsor and Evaluator assessment	This was described as a "primary supportive publication" with NHMRC level of evidence I by the sponsor. This is appropriate. This is an ancillary study of a convenience d sample of women enrolled in the Royals Marsden and IBIS-1 trials. A surprisingly high return rate was achieved, given the number of questionnaires to be completed at each time point. This study suggests that the use of preventative tamoxifen in women at increased risk of breast cancer is not associated with changes in psychological well-being.

Table 2. Symptoms Reported at 48 Months as Having Been Somewhat/Quite a Bit/Very Much of a Problem Since Taking Part in the Trial

Symptom	No. of Patients*	Tamoxifen (%)	Placebo (%)	Tamoxifen/Placebo Odds Ratio	Tamoxifen/Placebo 95% CI	χ^2 (*P*)
Weight gain	358	40.76	47.13	0.77	0.51-1.17	.225
Joint pains	356	36.26	43.1	0.75	0.49-1.15	.187
Feeling bloated	358	34.24	39.08	0.81	0.53-1.25	.342
Night sweats	355	43.09	28.74	1.88	1.21-2.92	.005
Hot flashes	359	41.6	28.74	1.77	1.14-2.74	.011
Low energy	358	27.72	40.8	0.56	0.36-0.87	.009
Muscle stiffness	353	29.83	32.56	0.88	0.56-1.38	.581
Leg/hand pains	356	29.67	29.89	0.99	0.63-1.56	.965
Forgetfulness	357	30.6	28.74	1.09	0.69-1.72	.700
Breast sensitivity/tenderness	355	22.95	36.63	0.52	0.32-0.82	.005
Difficulty with bladder control (when laughing or coughing)	355	26.92	27.75	0.96	0.60-1.53	.862
Brittle nails	356	31.69	22.54	1.59	0.99-2.56	.053
Headaches	361	24.32	29.55	0.77	0.48-1.22	.263
Vaginal dryness	359	21.74	29.14	0.68	0.42-1.09	.107
Mood swings	358	22.4	26.29	0.81	0.50-1.31	.392
Anxiety	355	22.53	24.86	0.88	0.54-1.44	.606
Increase in appetite	357	19.23	25.14	0.71	0.43-1.17	.179
Irritability	355	18.13	24.28	0.69	0.41-1.15	.156
Light headedness	356	16.85	23.26	0.67	0.40-1.13	.131
Swelling of hands or feet	356	17.58	21.84	0.76	0.45-1.29	.312
Depression	357	16.85	21.39	0.75	0.44-1.27	.275
Irregular periods	322	21.56	16.13	1.43	0.81-2.51	.214
Difficulty concentrating	356	16.94	19.65	0.83	0.49-1.43	.508
Shortness of breath	357	16.48	18.29	0.88	0.51-1.53	.653
Blurring of vision	354	10.56	22.41	0.41	0.23-0.74	.003
Heavier periods	321	13.77	16.88	0.79	0.43-1.45	.439
Constipation	357	12.71	17.05	0.71	0.39-1.28	.249
Vaginal discharge	356	17.68	10.29	1.87	1.01-3.48	.045
Difficulty with bladder control, not only when laughing or coughing	355	14.75	11.63	1.32	0.71-2.45	.385
Vaginal itching/irritation	358	16.39	9.71	1.82	0.97-3.44	.061
Abdominal cramps	346	12.36	13.69	0.89	0.48-1.66	.713
Pain/discomfort with intercourse	339	12.5	11.67	1.08	0.56-2.08	.812
Diarrhea	355	7.78	8.57	0.90	0.42-1.92	.785
Skin rashes	356	8.24	7.47	1.11	0.51-2.41	.787
Thinning of hair	354	7.78	7.47	1.04	0.48-2.29	.914
Nausea	356	5.46	7.51	0.71	0.30-1.67	.432
Vaginal bleeding or spotting	357	5	8	0.60	0.25-1.42	.240
Cold sweats	347	9.71	2.91	3.59	1.30-9.97	.009
Change in voice	356	3.87	2.86	1.37	0.43-4.39	.597
Weight loss	349	1.69	4.09	0.40	0.10-1.58	.178
Decrease in appetite	348	1.13	1.75	0.64	0.11-3.88	.625
Vomiting	355	1.09	1.74	0.62	0.10-3.77	.603

*Some women missed occasional items on the 42-item list, either in error or if they did not believe that the symptoms were applicable to them, eg, items relating to periods if they were postmenopausal or relating to sexual intercourse if they were not sexually active.

Other studies – HOT, The Italian Study, Imperato

Other studies – HOT, The Italian Study, Imperato	
Publication Identifier	**Publication description**
HOT	Randomised DB placebo controlled study of the effect of tamoxifen 5mg on occurrence of breast cancer in healthy post-menopausal women on HRT
Italian	Randomised DB placebo controlled study of the effect of tamoxifen 20mg on occurrence of breast cancer in healthy women who have had a hysterectomy
Imperato	Cohort study of the effect of tamoxifen (±HRT) on lipid profile in women with an increased risk of breast cancer who had previously had hysterectomy and oophorectomy

HOT, DeCensi 2013

Registered with clinicaltrials.gov as NCT01579734 and the European Institute of Oncology as IEO S51/200

Publication Identifier	HOT, DeCensi 2013, Efficacy and Safety, Secondary Supportive
Citation	DeCensi A, Bonanni B, Maisonneuve P, Serrano D, Omodei U, Varricchio C, et al. A phase-III prevention trial of low-dose tamoxifen in postmenopausal hormone replacement therapy users: the HOT study. Ann Oncol. 2013;24(11):2753-60.
Documented GCP or ethics approval, Conflict of Interest, Funding source(s)	The following statements are provided: • *The study was supported by the Italian Foundation for Cancer Research, Avon Italia, Legaltaliana per la Lottacontro i Tumori (LILT project number 51/2005), American Italian Cancer Foundation, ASL ptta di Milano, RegionePiemonte* • *Tarnoxifen and placebo were gifted by FIDIA FarmaceuticiS.p.a, AbanoTerme, Italy* • *The authors have declared no conflicts of interest*
Study design	Randomised, double-blind, placebo-controlled trial in healthy postmenopausal women undergoing hormone replacement therapy (HRT) to assess if low dose tamoxifen reduces the incidence of breast cancer.
Study Location	Italy
Study Dates	Recruitment occurred between I February 2002 to 31 July 2007. Data cutoff date for this analysis was 30 November 2011
Study Method	Eligible women were randomly allocated to either placebo or tamoxifen 5 mg/day for 5 years. Clinical examinations were repeated every 6 months and mammography was repeated annually. Transvaginal ultrasounds were carried out at baseline and repeated in case of atypical bleeding, followed by hysteroscopy on clinical judgment. At completion of the 5-year intervention clinical visit and mammography were repeated annually up to 10 years. Breast cancer risk was calculated using the Gail method and participants were divided into three categories according to 5 year risk (<1, 1-1.49, ≥1.5 %)
Key	Post-menopausal women with current HRT use or de novo HRT use for symptom relief and

Publication Identifier	HOT, DeCensi 2013, Efficacy and Safety, Secondary Supportive
selection criteria	negative mammography within 6 months
Outcome measure(s)	Primary end point was the incidence of breast cancer. Secondary measures were endometrial cancer, coronary heart syndrome, cerebrovascular events, venous thromboembolic events (VTEs). bone fractures, all cancers
Statistical analysis	Recruitment of 8500 women was initially planned. Recruitment was stopped early (with recruitment of 1884 women due to low recruitment following negative publicity regarding HRT. The main analysis was carried out on an intention-to-treat (ITI) basis. The two treatment groups were compared by the log-rank test. HRs and 95% Cls were obtained using a Cox proportional regression model after adjustment for age (in 5-year groups) and centre. P-values were at <0.05 level for the main end points and at <0.01 level for secondary end points and subgroup analyses to account for multiple comparisons..
Results	1884 women were randomised to either placebo (n = 946) or tamoxifen (n = 938). Compliance with tamoxifen/placebo treatment at the end of 5 years was 55.6% on placebo and 52.6% on tamoxifen (P = 0.19). The main subject characteristics were evenly distributed by allocated arm.. The mean ± SD age was 53.1 ± 5.1 on placebo and 53.5 ± 5.0 on tamoxifen. 519/1884 women had an estimated 5 year risk of breast cancer ≥1.5%. After a mean± SD follow-up of 6.2 ± 1.9 years, there were 24 breast cancers on placebo (annual rate 4.1/1000) and 19 on tamoxifen (annual rate 3.3/1000), with rate ratio (RR)= 0.80 (95% CI 0.44-1.46) Adverse events such as hot flashes were more common with even this low dose of tamoxifen and in the presence of HRT – see table below **Table 3.** Numbers and rates of selected adverse events by the allocated arm See table below Comment: Increased risk of breast cancer was not an inclusion criteria for the trial with grouping according to risk of breast cancer occurring after enrolment. Note that the NSABP P1 trial which also used the Gail model for breast cancer risk assessment required a risk ≥1.66% for inclusion in the trial
Allocation	This was described as a "secondary supportive publication" and NHMRC level II by the sponsor. It is

	No. of events		Rate per 1000 women			RR (95% CI)[b]
	Placebo	Tamoxifen	Placebo	Tamoxifen	Difference[a]	
Symptom/Event						
Hot flashes[c]	245	305	178.18	317.38	−139.20	1.78 (1.48–2.15)
(moderate or severe)	147	200	63.61	96.76	−33.15	1.52 (1.22–1.90)
Night sweats[c]	223	269	141.68	229.91	−88.24	1.62 (1.34–1.97)
(moderate or severe)	113	181	46.60	83.56	−36.97	1.79 (1.41–2.28)
Vaginal discharge[c]	134	241	52.30	111.42	−59.12	2.13 (1.71–2.65)
(moderate or severe)	23	58	7.43	20.49	−13.06	2.76 (1.70–4.48)
Vaginal bleeding[c]	108	129	37.50	47.58	−10.08	1.27 (0.98–1.65)
(moderate or severe)	24	28	7.73	9.53	−1.80	1.23 (0.71–2.13)
Vaginal dryness, pruritus[c]	286	356	153.52	228.06	−74.54	1.49 (1.25–1.76)
(moderate or severe)	71	93	24.64	35.20	−10.56	1.43 (1.04–1.95)
Dyspareunia[c]	89	105	36.90	46.44	−9.54	1.26 (0.94–1.68)
(moderate or severe)	35	48	12.18	17.72	−5.54	1.45 (0.94–2.26)
Endometrial polyps	6	27	1.89	8.98	−7.09	4.74 (1.96–11.5)
Serious adverse events						
Coronary heart syndrome[d]	6	4	1.89	1.33	0.56	0.70 (0.20–2.50)
Cerebrovascular events[e]	2	4	0.63	1.33	−0.70	2.11 (0.39–11.5)
VTEs	2	5	0.63	1.67	−1.03	2.64 (0.51–13.6)
Hysterectomy for benign disorders	7	18	0.63	3.33	−2.70	5.27 (1.15–24.1)
Endometrial cancers[f]	3	1	0.51	0.17	0.34	0.34 (0.04–3.25)

[a]Rate in the placebo group minus rate in the tamoxifen group.
[b]Risk ratio (RR) for women in the tamoxifen group relative to women in the placebo group. CI = confidence interval.
[c]Among women who were free of symptoms at baseline.
[d]Coronary heart syndrome includes: myocardial infarction (1P/3T), coronary stenting (1P/0T), cardiac arrhythmia (0P/1T), coronary ischemia (4P/0T).
[e]Cerebrovascular events includes four TIA on tamoxifen.
[f]Two endometrial cancers (2P/0T) were diagnosed during treatment, and two (1P/1T) were diagnosed after treatment.

Publication Identifier	HOT, DeCensi 2013, Efficacy and Safety, Secondary Supportive
by sponsor and Evaluator assessment	not clear why this study was included given that it was performed on a subset of the proposed population (post-menopausal women on HRT), many of the women enrolled had low risk of breast cancer and the dose of tamoxifen used is considerably lower than the proposed dose (5mg daily compared to 20mg). This was also an underpowered study resulting from the difficulty with recruitment .

The Italian study

Publication Identifier	The Italian Study
Citation	Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Rotmensz N *et al.* Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998;352:93-7.
Study description	Double-blind placebo-controlled, randomised trial of tamoxifen in women between the ages of 35 and 70, who had had a total hysterectomy and who did not have breast cancer. Women did not need to have increased risk of breast cancer to be eligible. The primary endpoints were occurrence of, and death from, invasive breast cancer. Use of estrogen replacement therapy was allowed at random assignment and/or during the trial. In June, 1997, the investigators and the data-monitoring committee decided to end recruitment due to the number of women dropping out of the study
Funding source, Conflicts of interest	The following statements are provided: • *the trial received authorization number 800.C.35/75.354 from the Italian National Ministry of Health*.
Study Location	Italy
Study Dates	Recruitment occurred between October 1992 and December 1997.
Study Method	Women were randomised to receive tamoxifen 20 mg per day or placebo, both orally for 5 years with follow-up to continue for a subsequent 5 years. During the treatment period (first 5 years), women had a physical examination every 6 months and blood testing (including white blood cell and platelet counts and measures of high-density lipoproteins, low-density lipoproteins, and total cholesterol and of alanine and aspartate aminotransferase) and mammography every 12 months. After completion of treatment, or in case of dropout, women were followed on an annual basis.
Blinding & randomisation	Participants and investigators were blinded to treatment allocation. Treatment allocation used a randomized permuted block design, with stratification by institution
Results	At median follow-up of 46 months: 5408 women were randomised – 2708 to placebo and 2700 to tamoxifen. Of these, 2119 (39.2%) interrupted treatment before completion (1407 voluntarily) and 3289 (60.8%) completed the 5-year treatment period. HRT was used in 14% of participants. Withdrawal rate (mainly due to menopausal ymptoms) differed according to HRT use, with compliance being 75% at 5 years for women who never took HRT, compared to 88% at five years for women who took HRT during

Publication Identifier	The Italian Study
	the trial. No significant difference was found between the placebo and tamoxifen arms for the occurrence of invasive breast cancer or deaths from breast cancer: there were 22 breast cancers in women on placebo and 19 in women on tamoxifen, and no deaths. In a sub-group of analysis of women who also used hormone-replacement therapy, there was a statistically significant reduction of breast cancer among during the trial: among the 390 women allocated to placebo, there were eight cases of breast cancer compared with one case among 362 women allocated to tamoxifen (RR = 0.13, 95% CI = 0.02-1.02).. Compared with the placebo group, there was a significantly increased risk of vascular events (38 women on tamoxifen vs. 18 women on placebo, P = 0.0053), mainly consisting of superficial phlebitis and hypertriglyceridaemia among women on tamoxifen. See also the follow-up study described below.
Allocation by sponsor and Evaluator assessment	This trial and related publications was not included in the dossier as women did not need to have an increased risk of breast cancer to enter the study. This was a relatively small study that ceased recruitment early due to a high drop-out rate. The small numbers of participants along with the low level of risk in this otherwise healthy group precluded an adequate assessment of the effect of tamoxifen in reducing the incidence of breast cancer
Citation	Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Oliviero P, Lovison F, Gucciardo G, Rosselli del Turco M, Muraca M, Pizzichetta MA, Conforti S, Decensi A For the Italian Tamoxifen Study GroupTamoxifen for the Prevention of Breast Cancer: Late Results of the Italian Randomized Tamoxifen Prevention Trial Among Women With Hysterectomy JNCI J Natl Cancer Inst 2007; 99:727-37
Study Dates	Recruitment occurred between October 1992 and December 1997. Cut-off date for this publication was December 31, 2005
Publication description	This second publication provides the results after 11 years of follow-up and includes an exploratory analysis by stratifying women according to their risk of developing invasive breast cancer
Study Method	Risk of hormone receptor – positive (HR+) breast cancer was determined by baseline characteristics at study entry including height, presence of at least one ovary, age of menarche, age of full-term pregnancy.
Blinding	As above
Efficacy Results	5408 women were randomly assigned to placebo (n = 2708) or to tamoxifen (n = 2700). On average, women underwent treatment for 4.0 years and were followed for 9.1 years. An average of 11.2 years elapsed from random assignment to data cutoff.

Publication Identifier	The Italian Study

Table 1. Women included in the analyses of the Italian Randomized Tamoxifen Prevention Trial and number followed

Accrual and follow-up status	Placebo	Tamoxifen	Total
Accrual, n			
Women randomly assigned	2708	2700	5408
Early withdrawals	1034	1085	2119
Ineligible	19	37	56
For major changes in protocol	50	49	99
For major adverse events	188	206	394
Voluntary withdrawals	686	721	1407
Lost to follow-up	86	68	154
Died	5	4	9
Completed 5 years of treatment	1674	1615	3289
Average duration of treatment, mo*	48.9	47.4	48.2
Average follow-up time until last contact, mo†	109.4	109.8	109.6
Average follow-up time until December 31, 2005, mo‡	134.3	134.7	134.5
Total person-years of follow-up			
Accumulated during treatment*	11046	10668	21714
Accumulated until last follow-up†	24681	24696	49376
Accumulated until the end of the study‡	30310	30303	60613

* Used for the evaluation of the rates of intercurrent events.

† Used for the evaluation of the rate of cancers other than of the breast.

‡ Used for the evaluation of the rate of breast cancer.

There was no significant difference in baseline characteristics between the placebo and tamoxifen groups.

The high risk group comprised 702 women (350 in the placebo arm and 352 in the tamoxifen arm who were taller than 160 cm (the median height of the group), had at least one intact ovary, were younger than age 14 years at menarche (the upper age tertile of the group), and had no full-term pregnancy before age 24 years (the median age at first pregnancy of the group). The remaining 1830 (34%) women with at least one intact ovary were classified as the low-risk group. The 2876 (53%) women who had had a bilateral oophorectomy were analysed separately. There was a significant reduction in the occurrence of ER + invasive breast cancer in the high risk group. There was no reduction in occurrence of breast cancer in women who had had bilateral oophorectomy.

Publication Identifier	The Italian Study

Table 3. Numbers and rates of breast cancer in the placebo and tamoxifen groups by selected participant characteristics

	No. of events		Rate per 1000 women-years			
Participant characteristic	Placebo	Tamoxifen	Placebo	Tamoxifen	Difference*	RR (95% CI)†
All women	74	62	2.48	2.07	0.41	0.84 (0.60 to 1.17)
Age at study entry, y						
≤49	22	22	1.98	1.87	0.11	0.95 (0.52 to 1.71)
50–54	27	19	2.98	2.06	0.92	0.69 (0.38 to 1.24)
55–59	16	13	2.52	2.41	0.11	0.96 (0.46 to 1.99)
≥60	9	8	2.71	2.25	0.45	0.83 (0.32 to 2.16)
Type of hysterectomy						
Hysterectomy alone	25	25	3.00	2.94	0.06	0.98 (0.56 to 1.71)
Hysterectomy + unilateral oophorectomy	20	13	3.66	2.18	1.48	0.60 (0.30 to 1.20)
Hysterectomy + bilateral oophorectomy	29	21	1.99	1.48	0.50	0.75 (0.43 to 1.31)
Hysterectomy + oophorectomy (NOS)‡	0	3	0	2.28	−2.28	NE
Age at hysterectomy, y						
≤39	11	11	1.80	1.80	0.00	1.00 (0.43 to 2.31)
40–44	20	16	2.30	1.76	0.54	0.77 (0.40 to 1.48)
45–49	30	22	3.13	2.31	0.82	0.74 (0.43 to 1.28)
≥50	13	13	2.41	2.51	−0.10	1.04 (0.48 to 2.24)
No. of first-degree relatives with breast cancer						
0	64	46	2.41	1.75	0.66	0.73 (0.50 to 1.06)
≥1	10	16	3.00	4.29	−1.29	1.43 (0.65 to 3.15)
Hormonal replacement therapy						
Never	47	47	2.21	2.22	−0.01	1.00 (0.67 to 1.50)
At baseline	21	9	3.97	1.72	2.25	0.43 (0.20 to 0.95)
During intervention only	6	6	1.82	1.71	0.11	0.94 (0.30 to 2.92)
Class of risk§						
Without ovaries	29	24	1.81	1.55	0.26	0.86 (0.50 to 1.47)
Low risk	21	32	2.09	3.05	−0.95	1.46 (0.84 to 2.53)
High risk	24	6	6.26	1.50	4.76	0.24 (0.10 to 0.59)

* Rate in the placebo group minus rate in the tamoxifen group.

† Risk ratio (RR) for women in the tamoxifen group relative to women in the placebo group. CI = confidence interval.

‡ NOS = not otherwise specified; NE = not able to estimate.

§ The high-risk group includes women taller than 160 cm, with at least one intact ovary, who had menarche at younger than age 14 years, and who had no full-term pregnancy before age 24 years; the low-risk group includes the remaining women, with at least one intact ovary.

Safety Results

Analysis of adverse events was limited to those occurring during the treatment period.

Table 4. Numbers and incidence rates of selected adverse events in the placebo and tamoxifen groups during treatment

	No. of events (%)		Rate per 1000 women-years			
Events	Placebo	Tamoxifen	Placebo	Tamoxifen	Difference*	RR (95% CI)†
Hot flashes‡	446	635	67.20	119.29	−52.1	1.78 (1.57 to 2.00)
Vaginal dryness‡	269	295	29.93	34.09	−4.16	1.14 (0.97 to 1.34)
Vaginal discharges‡	173	505	17.59	60.60	−43.0	3.44 (2.90 to 4.09)
Urinary disturbances	140	202	14.39	21.94	−7.55	1.52 (1.23 to 1.89)
Headache	95	63	9.26	6.31	2.94	0.68 (0.50 to 0.94)
Cardiac arrhythmias/atrial fibrillation	21	35	2.01	3.48	−1.47	1.73 (1.01 to 2.98)
Cerebrovascular events	7	12	0.67	1.19	−0.52	1.78 (0.70 to 4.52)
Thromboembolic events	28	44	2.72	4.45	−1.72	1.63 (1.02 to 2.62)

* Rate in the placebo group minus rate in the tamoxifen group.

† Risk ratio (RR) for women in the tamoxifen group relative to women in the placebo group. CI = confidence interval.

‡ Among women who were free of symptoms at baseline.

Of the total of 72 women who developed thromboembolic events (51 superfi cial phlebitis, 17 deep venous thrombosis, 2 pulmonaryembolism, including one who also had superfi cial phlebitis, one visceral venous thrombosis, and two retinal venous thrombosis) during the 5-year intervention period, 28 were on placebo and 44 on tamoxifen (RR = 1.63, 95% CI = 1.02 to 2.62; *P* = .04). Superficial phlebitis of the legs accounted for all of the excess in the tamoxifen group

A total of 91 cancers other than breast cancer developed among women who received placebo and 106 developed among those who received tamoxifen. No statistically significant differences by site were observed.

A total of 74 women (placebo, 38; tamoxifen, 36) died after theinitiation of the trial. Rates of death from all causes (RR = 0.95, 95% CI = 0.60 to 1.49) or from any specific cause were similar in the two groups

Evaluator assessment

Given the enrolment of women who were predominately at no, or low, increased risk of breast cancer, it is appropriate that this study was not included in the dossier. The exploratory analysis of women categorised at “high risk” is limited by the small numbers and idiosyncratic definition

Publication Identifier	The Italian Study
	of high risk.

Imperato 2003

Publication Identifier	Imperato 2003, secondary supportive, safety
Citation	Imperato F, Marziani R, Perniola G, Ebano V, Fruscella M, Mossa B. Effects of tamoxifen and estrogen replacement therapy on lipid metabolism and some other cardiovascular risk factors. A prospective study in hysterectomised women. Minerva Ginecologica. 2003;55(1):87-93.
Trial description	Non-randomised trial in women with an increased risk of breast cancer who had previously had hysterectomy and oophorectomy for a benign pathology to evaluate the relationship of tamoxifen and the risk factors of cardiovascular disease.
Funding source, Conflicts of interest	The following statements are provided: Nil
Study Location	Italy
Study Dates	between 1992 and 1998
Study Method	Women who had undergone hysterectomy with bilateral oophorectomy for a benign pathology and who had increased risk of breast cancer on the basis of family history and who were to receive tamoxifen 20mg for 5 years to reduce the risk of breast cancer were enrolled. Women with post-menopausal symptoms were also treated with HRT. Laboratory investigations including total cholesterol (T-C), high-density lipoproteincholesterol (HDL-C), low-density lipoproteincholesterol (LDL-C), triglycerides (TRG), fibrinogen (FBR), platelets (PLT) and anti-thrombin III (AT III).were performed before treatment was begun and after 12 and 24 months of therapeutic administration. For analysis, participants were divided into 4 groups according to presence of menopausal symptoms and use of oral (group A) or transdermal HRT (Group B) and absence of menopausal symptoms (Group C). A group of 21 women who did not receive tamoxifen and who did not have menopausal symptoms was used as a control group (Group D).
Blinding	Not applicable
Results	Comment: The copy of this publication as provided in the dossier was difficult to read due to poor quality reproduction of the figures. The number of sub-groups also made interpretation difficult. Among patients who received tamoxifen with or without oestrogen replacement therapy, decreased T-C, LDL-C and FBR ($p<0.01$) were observed after 24 months; serum concentration of HDL-C did not vary significantly as compared to the control group (p=NS); only the 26 patients of group A showed an increase of HDL-C ($p<0.02$). A significant decrease of TRG ($p<0.01$) was reached with the administration of tamoxifen and transdermal HRT. However, patients in groups A and C presented an increase of TRG ($p<0.05$). No significant difference was observed in the platelet count (p=NS)
Allocation by sponsor and	This was described as a "secondary supportive publication" and NHMRC level III-2 by the sponsor. This is appropriate. This prospective cohort study of a sub-group of the population at increased risk of breast cancer describes some of the changes seen in the lipid profile of a small number of women

Publication Identifier	Imperato 2003, secondary supportive, safety
Evaluator assessment	who were treated with preventative tamoxifen. No clinical correlation is established.

Meta-analyses

	Publication Identifier	Publication objective
Meta-analyses		
Efficacy/safety (IBIS-I, NSABP P1, Royal Marsden, Italian, STAR)	Cuzick 2013	Meta-analysis to assess the effectiveness of selective oestrogen receptor modulators (SERMs) on breast cancer incidence.
	Nelson 2013	Systematic review to update evidence about the effectiveness and adverse effects of medications to reduce breast cancer risk, patient use of such medications, and methods for identifying women at increased risk for breast cancer for the U.S. Preventive Services Task Force (USPSTF).
Safety		
IBIS-I, NSABP P1, Royal Marsden	Iqbal 2012	Systematic review to determine the risk of endometrial cancer, deep vein thrombosis and pulmonary embolism in women <50 years given tamoxifen for breast cancer prevention
	Braithwaite 2003	Meta-analysis of English-language RCTs of the use of Tamoxifen in breast cancer treatment and breast cancer risk reduction to determine the relative risk of potentially life-threatening vascular and neoplastic outcomes
NSABP P1, The Italian Study, multiple others	Duffy 2002	Mathematical modelling of the possible effect of tamoxifen in women with BRAC1 or BRAC2 mutations

Cuzick 2013

Publication identifier	Cuzick 2013, Efficacy and safety, Pivotal
Citation	Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 2013;381(9880):1827-34
Study description	Meta-analysis to assess the effectiveness of selective oestrogen receptor modulators (SERMs) on breast cancer incidence
Funding source,	The following statements are provided: • *Funding Source: Cancer Research UK.*

Publication identifier	Cuzick 2013, Efficacy and safety, Pivotal
Conflicts of interest	• *Neither Cancer Research UK nor the funding sources for the individual studies had a role in study design, data collection, data analysis, data interpretation, or writing of the report.* • *Conflicts of interest: JC has received a grant from AstraZeneca for chemoprevention trials. BHM is, and JM was, an employee and shareholder of Eli Lilly. IS, BB, JPC, VV, MD, TP, DLW, LF, SC, JFF, ADC, AZLC, UV declare that they have no conflicts of interest.*
Search Dates	Not described
Study Method	Meta-analysis with individual participant data from nine prevention trials comparing four selective oestrogen receptor modulators (SERMs; tamoxifen, raloxifene, arzoxifene, and lasofoxifene) with placebo, or in one study with tamoxifen. The primary endpoint was incidence of all breast cancer (including ductal carcinoma in situ) during a 10 year follow-up period. Secondary endpoints were incidence in years 0–5 and years 5–10, and all invasive ER-positive or ER-negative cancers, and ductal carcinoma in situ. Other predefined secondary endpoints were incidence of other cancers, venous thromboembolic events, cardiovascular events, fractures, cataract, and all-cause mortality. Comparisons were on an intention-to-treat basis. Fixed-effects and random-effects models assessed.
Search method	The electronic database PubMed was searched using the keywords breast cancer, prevention, selective oestrogen receptor modulator (or SERM), and chemoprevention
Study screening and selection	The method of study selection from search results was not described. Nine randomised trials that compared SERMs with placebo or another drug in women without breast cancer, and had at least 2 years of follow-up were identified. Four trials (Royal Marsden, NSABP P1, IBIS-1, The Italian Prevention Study) assessed 20 mg per day tamoxifen versus placebo for at least 5 years in healthy women who were mostly at increased risk of breast cancer. One trial compared raloxifene to tamoxifen in women at increased risk of developing breast cancer (STAR). Two trials investigated raloxifene versus pla cebo in postmenopausal women who had either osteo porosis, or had risk factors for or established coronary heart disease. One trial18 compared lasofoxifene at two different doses with placebo in postmenopausal women with osteoporosis. One trial20 compared arzoxifene with placebo in post menopausal women with osteoporosis.

	N	Recruitment period	Treatment groups and daily dose	Treatment duration (years)	Entry criteria	Present status	Median follow-up (months)
Marsden[5,6]	2471	1986–96	Placebo (1233) Tamoxifen 20 mg (1238)	5–8	High risk, family history	Blinded, further follow-up	171·6 (153·9–184·0)
IBIS-I[7,8]	7109	1992–2001	Placebo (3566) Tamoxifen 20 mg (3573)	5	Greater than two times relative risk	Blinded, further follow-up	96 (80·1–117·1)
NSABP-P-1[9,10]	13 205	1992–97	Placebo (6707) Tamoxifen 20 mg (6681)	5	>1·6% 5 year risk	Unblinded, no follow-up	57·6 (35·4–64·9)
Italian[11,12]	5408	1992–97	Placebo (2708) Tamoxifen 20 mg (2700)	5	Normal risk, women with hysterectomy	Unblinded, further follow-up	139·6 (122·0–146·1)
MORE[13]/CORE[14]*	7705/6511	1994–98/ 1998–2002	Placebo (2576) Raloxifene 60 mg (2557)/ Placebo (2576) Raloxifene 120 mg (2572)	4/8	Normal risk, postmenopausal women with osteoporosis	Unblinded, no follow-up	71·3 (47·1–95·4)
RUTH[15]	10 101	1998–2000	Placebo (5057) Raloxifene 60 mg (5044)	5	Normal risk, postmenopausal women with established or risk of CHD	Unblinded, no follow-up	66·7 (60·1–72·3)
STAR[16,17]	19 490	1999–2004	Raloxifene 60 mg (9875) Tamoxifen 20 mg (9872)	5	>1·6% 5 year risk, postmenopausal women	Unblinded, no follow-up	81 (60·8–96·6)
PEARL[18,19]	8856	2001–07	Placebo (2852) Lasofoxifene 0·50 mg (2852) Lasofoxifene 0·25 mg (2852)	5	Normal risk, postmenopausal women with osteoporosis	Blinded, no follow-up	59·6 (58·8–60·1)
GENERATIONS[20,21]	9354	2004–09	Placebo (4678) Arzoxifene 20 mg (4676)	4	Normal risk, postmenopausal with low BMD or osteoporosis	Unblinded, no follow-up	54·3 (28·3–56·1)

Data in parenthesis are number of randomised participants. CHD=coronary heart disease. BMD=bone mineral density. *The CORE trial was done in a subset of women originally enrolled in the MORE trial.

Table 1: **Details of breast cancer prevention trials**

Individual participant data for all trials was obtained directly from the trial investigators for the analysis.

Results	Nine trials with 83 399 participants and 306 617 women-years of follow-up were included.

Publication identifier	Cuzick 2013, Efficacy and safety, Pivotal

Median follow-up was 65 months (IQR 54–93).

The overall reduction in all breast cancer (including ductal carcinoma in situ) was 38% (p<0·0001; table 2), with an estimated 10 year cumulative incidence of 6·3% in the control groups and 4·2% in the SERM groups. A reduction was observed in both years 0–5 of follow-up (42%, p<0·0001) and years 5–10 (25%, p=0·007). Despite the smaller effect in years 5–10, there was no evidence of heterogeneity between trials (p=0·3). Random-effects models produced similar HRs to those for the fixed-effects models, but larger 95% Cis. Overall, the frequency of invasive ER-positive cancer was reduced from 4·0% to 2·1% (p<0·0001). This reduction was apparent in years 0–5 (p<0·0001) and in years 5–10 (p<0·0001). The number needed to treat to prevent one diagnosis of breast cancer in the first 10 years was 42; when restricted to invasive ER positive breast cancer the number was 53.

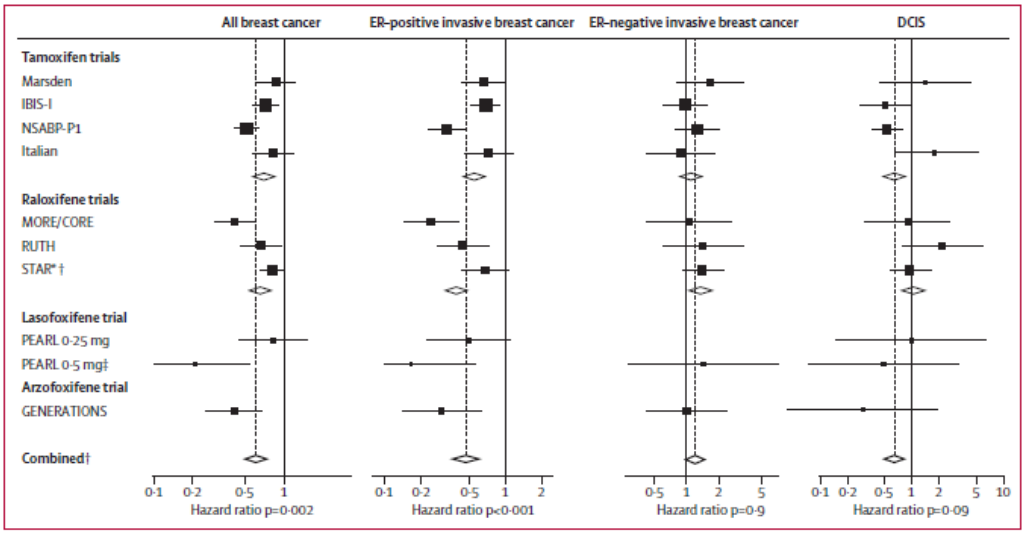


Figure 3: **All breast cancers, invasive breast cancer, and DCIS in years 0–10**
ER=oestrogen receptor. DCIS=ductal carcinoma in situ. *Adjusted by overall tamoxifen effect to give raloxifene versus placebo comparisons. †STAR data not included in comparisons. ‡Data for ER-invasive cancer are pooled.

Comment: the results relevant to tamoxifen will be described below with excerpts from tables provided.

For tamoxifen trials, there was a significant reduction of 33% (p<0·0001) in all breast cancers compared with placebo (see table excerpt below). This reduction was mainly due to a large effect on ER-positive invasive breast cancer, for which there was a reduction of 44% (p<0·0001). There was a significant reduction in DCIS (p=0·009) and a non-significant increase in ER-negative (p=0·4). Significant heterogeneity was shown between trials for all breast cancers (p=0·02) and invasive ER-positive breast cancers (p=0·03).

	Overall*	Annual rates per 1000†	HR (95% CI)	ER-positive invasive	HR (95% CI)	ER-negative invasive	HR (95% CI)	DCIS	HR (95% CI)
Tamoxifen trials									
Marsden	96 vs 114	6·4	0·87 (0·63–1·21)	51 vs 83	0·66 (0·44–0·99)	25 vs 17	1·66 (0·81–3·40)	14 vs 9	1·40 (0·44–4·40)
IBIS-I	143 vs 198	6·7	0·72 (0·58–0·90)	88 vs 131	0·69 (0·52–0·90)	36 vs 38	0·97 (0·62–1·54)	16 vs 27	0·52 (0·27–0·99)
NSABP-P-1	130 vs 248	6·1	0·52 (0·42–0·64)	44 vs 134	0·33 (0·23–0·46)	39 vs 31	1·26 (0·78–2·02)	38 vs 70	0·54 (0·36–0·80)
Italian	62 vs 74	4·2	0·83 (0·58–1·19)	36 vs 48	0·73 (0·45–1·17)	16 vs 17	0·87 (0·43–1·79)	9 vs 6	1·80 (0·60–5·38)
Total (0–10 years)	431 vs 634	–	0·67 (0·59–0·76)	219 vs 396	0·56 (0·47–0·67)	116 vs 103	1·13 (0·86–1·49)	77 vs 112	0·72 (0·57–0·92)
Total (0–5 years)	256 vs 409	–	0·62 (0·53–0·73)	121 vs 235	0·51 (0·41–0·64)	78 vs 76	1·03 (0·75–1·41)	47 vs 83	0·56 (0·39–0·81)
Total (5–10 years)	175 vs 225	–	0·78 (0·62–0·97)	98 vs 161	0·63 (0·47–0·83)	38 vs 27	1·55 (0·88–2·73)	30 vs 29	0·87 (0·49–1·57)

HR=hazard ratio. ER=oestrogen receptor. DCIS=ductal carcinoma in situ. Data are for selective oestrogen receptor modulator versus vs placebo, unless otherwise indicated *All cancers (including DCIS) and those with unknown receptor status. †In control group. ‡STAR data not included for overall effect. §STAR data not excluded for overall effect.

Table 2: **Breast cancer incidence in the chemoprevention trials**

<u>Other end-points (see also table below)</u>

Endometrial cancer: women receiving tamoxifen had a higher rate of endometrial cancer than

Publication identifier	Cuzick 2013, Efficacy and safety, Pivotal

did those given placebo but the increase was confi ned to the first 5 years of follow-up and was not apparent during years 5–10, the period after treatment

Mortality: No trial was designed to look at mortality as an endpoint, and no effect of any SERM was reported for all causes of death. No eff ect on breast cancer death was reported in the tamoxifen trials on the basis of a total of 59 deaths

Other cancers: Cancers other than breast or endometrial cancer were were evenly distributed between the treatment groups (p=0·8) and no heterogeneity between trials was noted (p=0·8).

Venous thromboembolic events: These were significantly increased with tamoxifen (OR 1·60, 1·21–2·12; p=0·001)

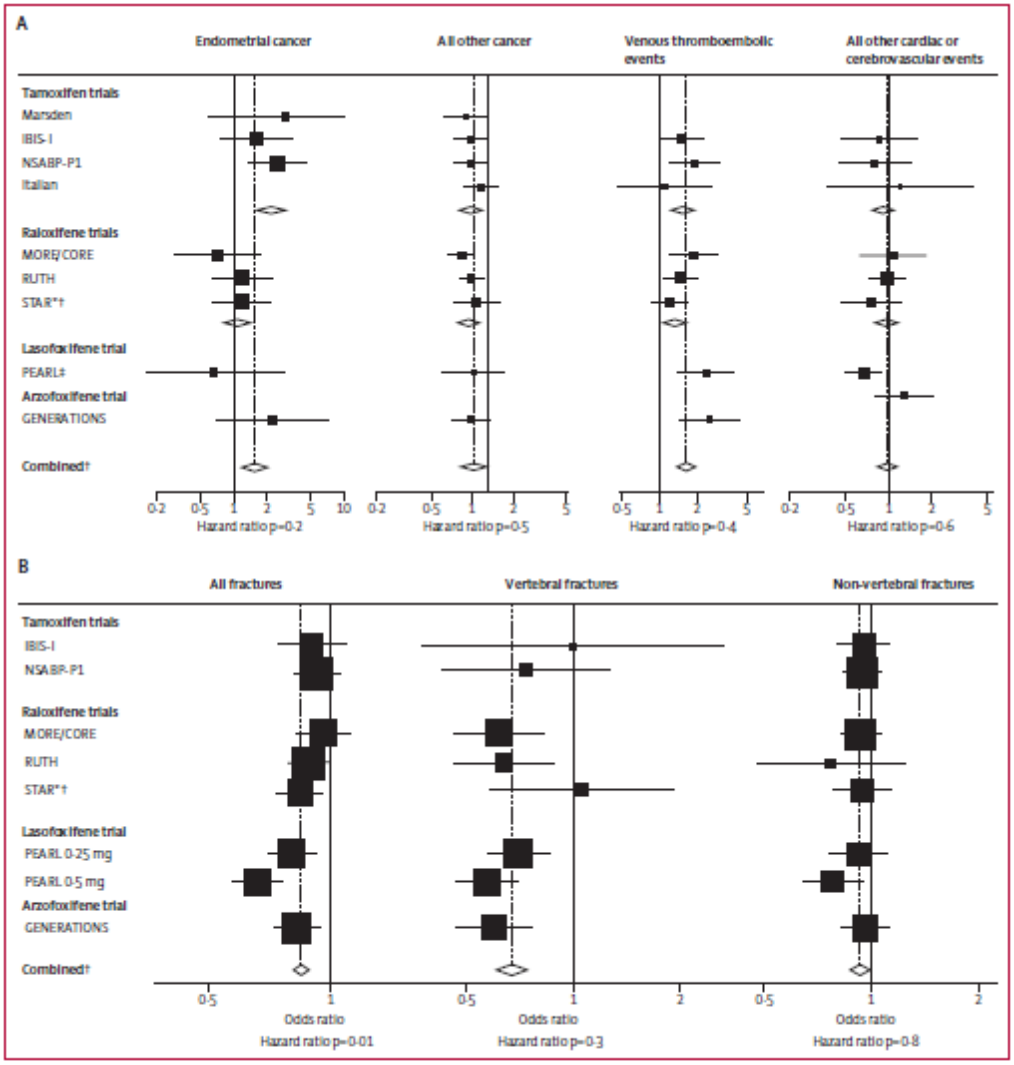
Fractures: No eff ect was seen with tamoxifen (0·92, 0·83–1·02).

Myocardial infarction, stroke, or transient ischaemic attacks: Overall, no eff ect of SERMs was noted and there was no evidence for heterogeneity

	Endometrial cancer	All other cancer*	Any death	Breast cancer death	Venous thrombolic events†	Cardio-vascular events‡	All fractures	Non-vertebral fractures	Vertebral fractures	Cataracts
Marsden	12 vs 5	55 vs 60	54 vs 54	12 vs 9	–	–	–	–	–	–
IBIS-I	19 vs 11	110 vs 112	65 vs 55	10 vs 12	65 vs 43	40 vs 38	229 vs 252	221 vs 244	8 vs 8	76 vs 70
NSABP-P-1	36 vs 15	101 vs 103	59 vs 71	4 vs 6	55 vs 29	90 vs 82	502 vs 539	480 vs 509	22 vs 30	578 vs 513
Italian	–	106 vs 91	36 vs 38	2 vs 2	11 vs 10	14 vs 10	–	–	–	–
MORE/CORE	6 vs 8	112 vs 132	81 vs 84	–	47 vs 25	82 vs 78	353 vs 450	214 vs 225	139 vs 225	275 vs 280
RUTH	21 vs 17	204 vs 203	548 vs 585	2 vs 0	106 vs 73	487 vs 481	529 vs 591	470 vs. 499	59 vs 92	570 vs 561
STAR§ (raloxifene vs tamoxifen)	37 vs 65	354 vs 323	202 vs 236	4 vs 11	154 vs 202	233 vs 220	1272 vs 1364	1195 vs 1299	65 vs 77	603 vs 739
PEARL (0·5 mg vs 0·25 mg vs placebo)	2 vs 2 vs 3	25 vs 20 vs 22	92 vs 73 vs 65	–	48 vs 37 vs 18	47 vs 54 vs 76	359 vs 422 vs 508	203 vs 233 vs 246	156 vs 189 vs 262	320 vs 317 vs 330
GENERATIONS	9 vs 4	74 vs 75	103 vs 98	–	43 vs 17	71 vs 64	426 vs 508	316 vs 327	110 vs 181	382 vs 400
All events	105 vs 63	787 vs 799	1038 vs 1050	30 vs 29	375 vs 215	831 vs 829	2398 vs 2848	1904 vs 2050	494 vs 798	2201 vs 2154
HR or OR (95% CI)	HR 1·56 (1·13–2·14)	HR 0·98 (0·89–1·08)	HR 0·98 (0·90–1·06)	HR 1·03 (0·55–1·92)	OR 1·73 (1·47–2·05)	OR 0·99 (0·91–1·09)	OR 0·85 (0·80–0·89)	OR 0·93 (0·87–0·99)	OR 0·66 (0·59–0·73)	OR 1·01 (0·95–1·06)

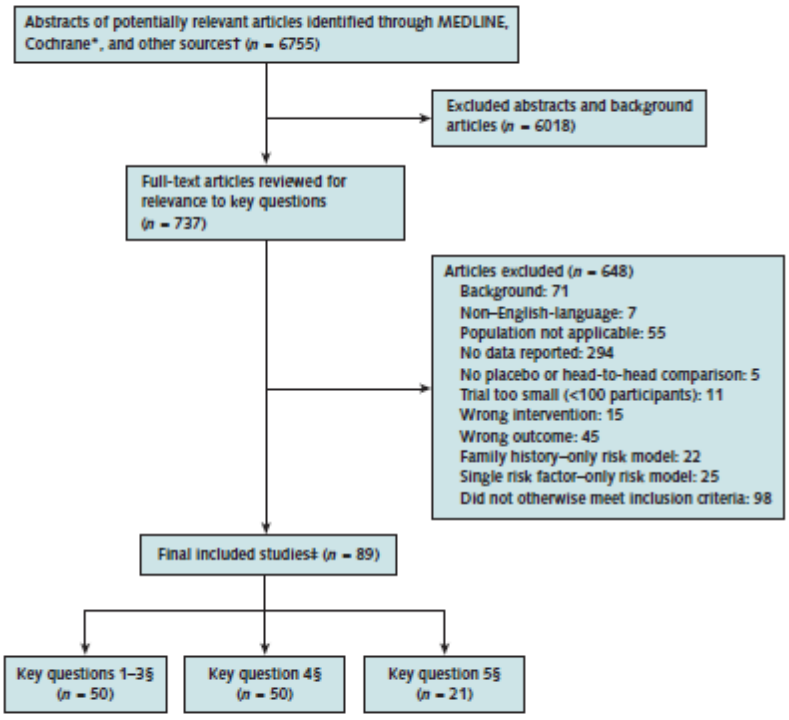
Data are number of patients for selective oestrogen receptor modulator versus vs placebo, unless otherwise indicated. HR=hazard ratio. OR=odds ratio. *Excluding endometrial cancer. †Including deep vein thrombosis, pulmonary embolism, retinal thrombosis, excluding superficial thrombosis. ‡Including myocardial infarction, cerebrovascular accident, and transient ischaemic accident. §STAR data not included for overall effect.

Table 3: Major non-breast cancer events in the prevention trials

Publication identifier	Cuzick 2013, Efficacy and safety, Pivotal
	 *Figure 4:* **Forest plots for adverse events** (A) Endometrial cancer, other cancer, venous thromboembolic events, and cardiac or stroke events. (B) All fractures, vertebral fractures and non-vertebral fractures. *Adjusted by overall tamoxifen effect to give raloxifene versus placebo comparisons. †STAR data not included in comparisons. ‡Data are pooled.
Conclusion	*SERMs significantly reduce the risk of all breast cancer in high-risk and average-risk women who do not have the disease, which is due to a reduction in ER-positive invasive breast cancer*
Allocation by sponsor and Evaluator assessment	This was described as a "pivotal publication" with NHMRC level of evidence I by the sponsor. This is appropriate given that this meta-analysis used individual patient data from the included studies. However, presentation of results was largely for the SERMs as a group rather than for tamoxifen. Important differences in the entry criteria and designs of the tamoxifen trials were alluded to but the possible impact of this on the results was not discussed. This meta-analysis found a considerable reduction in breast cancer incidence (predominately ER +) with the use of tamoxifen with this effect outlasting the treatment period. It also found a significant increase in endometrial cancer and thromboembolic events – these, however, appeared to be limited to the treatment period.

Nelson 2013

Publication identifier	Nelson 2013
Citation	Nelson HD, Smith MEB, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(8):604-14.
Study description	Systematic review to update evidence about the effectiveness and adverse effects of medications to reduce breast cancer risk, patient use of such medications, and methods for identifying women at increased risk for breast cancer for the U.S. Preventive Services Task Force (USPSTF). Comment: This publication was based on an earlier systematic review published in 2002: **Kinsinger LS, Harris R, Woolf SH, Sox HC, Lohr KN.** Chemoprevention of breast cancer: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137:59-69. According to the authors *An updated analysis of STAR with an 81-month median* *follow-up provided most of the new findings for this review*
Funding source, Conflicts of interest	The following statements are provided: • ***Grant Support:*** *By* Agency for Healthcare Research and Quality (AHRQ) *(contract HHSA-290-2007-10057-1-EPC3).* • ***Potential Conflicts of Interest:*** *Dr. Nelson: Grant (money to institution): AHRQ. Support for travel to meetings (money to institution): AHRQ. Dr. Smith: Grant (money to institution): AHRQ. Ms. Griffin: None disclosed. Dr. Fu: Grant (money to institution): AHRQ.* • *The funding source had no role in the selection, critical appraisal, or synthesis of evidence*
Search dates	From database inception to 5 December 2012
Study Method	Randomised trials of medication effectiveness and adverse effects,(IBIS-I, NSABP P1, Royal Marsden, Italianb, STAR) observationalstudies of adverse effects
Search Method	The search method was described: • a search was performed of the MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for relevant English-language studies, systematic reviews, and meta-analyses • a manual search reference lists from articles, citations in Web of Science and Scopus, and clinical trial registries was also performed Comment: details of the search criteria were not described as this “had been described previously”
Study Selection	For benefits: • double-blind, placebo-controlled or head-to-head, randomized, controlled trials (RCTs) of tamoxifen and raloxifene to reduce risk for breast cancer that enrolled women without preexisting breast cancer • included trials that were designed and powered to demonstrate invasive breast cancer incidence as a primary or secondary outcome. For harms: • included RCTs and observational studies of tamoxifen and raloxifene in women without breast cancer that had a nonuser comparison group or direct comparisons between tamoxifen and raloxifene.

Publication identifier	Nelson 2013
	• included all adverse outcomes at all reported follow-up times For concordance, adherence, and persistence of use: • included RCTs, observational studies, and descriptive studies of decisions to use risk-reducing medications Applicability of trials was determined using the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting (PICOTS) format *Appendix Figure.* Summary of evidence search and selection.  * Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. † Identified from reference lists, hand searching, and suggestions by experts. ‡ Studies that provided data and contributed to the body of evidence were considered "included." § Some studies are included in more than 1 key question.
Results	Seven RCTs of tamoxifen or raloxifene in women without preexisting breast cancer were identified. These provided data regarding breast cancer outcomes; mortality; occurrence of fractures, thromboembolic events, cardiovascular disease events, uterine abnormalities, cataracts, and other adverse effects. Trials include • head-to-head comparison of tamoxifen and raloxifene, STAR (Study of Tamoxifen and Raloxifene) • 4 placebo-controlled trials of tamoxifen, including the IBIS-I (International Breast Cancer Intervention Study), NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project) , Royal Marsden Hospital trial, and the Italian Tamoxifen Prevention Study • 2 placebo-controlled trials of raloxifene, MORE (Multiple Outcomes of Raloxifene Evaluation) with long-term follow-up in the CORE (Continuing Outcomes Relevant to Evista) study and the RUTH (Raloxifene Use for the Heart) trial All trials were described as meeting criteria for fair or good quality and high applicability. Comment: only results for the tamoxifen studies will be shown below

Publication identifier	Nelson 2013
	For placebo-controlled trials of tamoxifen • median duration of treatment was approximately 4 years and follow-up was 7 to 13 years • tamoxifen reduced the incidence of invasive breast cancer (risk ratio [RR], 0.70 [95% CI, 0.59 to 0.82]; 4 trials; 7 cases in 1000 women over 5 years) • tamoxifen reduced oestrogen receptor–positive but not oestrogen receptor–negative or noninvasive cancer. In STAR, more women receiving raloxifene had breast cancer than those receiving tamoxifen (RR for raloxifene, 1.24 [CI, 1.05 to 1.47]; 5 cases in 1000 women over 5 years) • tamoxifen did not reduce breast cancer–specific and all-cause mortality rates • tamoxifen reduced incidence of nonvertebral fractures (RR, 0.66 [CI, 0.45 to 0.98]; 1 trial; 3 cases in 1000 women) • tamoxifen increased thromboembolic event incidence (RR, 1.93 [CI, 1.41 to 2.64]; 4 trials; 4 cases in 1000 women) • tamoxifen did not increase coronary heart disease event or stroke incidence • tamoxifen caused more cases of endometrial cancer (RR, 2.13 [CI, 1.36 to 3.32]; 3 trials; 4 cases in 1000 women) and was related to more benign gynaecologic conditions; surgical procedures, including hysterectomy; and uterine bleeding. In STAR, raloxifene caused fewer cases of endometrial cancer (RR, 0.55 [CI, 0.36 to 0.83]; 5 cases in 1000 women), hyperplasia, and procedures than tamoxifen • women receiving tamoxifen had more cataract surgeries than those receiving placebo in NSABP P-1 • The most common side effects were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen Outcomes in sub-groups In STAR, tamoxifen and raloxifene had similar effects on breast cancer outcomes regardless of age and family history of breast cancer. In NSABP P-1, cancer rates were highest and risk reduction greatest among women in the highest modified Gail model risk category (5-year risk >5%) and among women with previous atypical hyperplasia. Thromboembolic events, strokes, and endometrial cancer were more common in older (>50 years) than younger women in NSABP P-1. Adherence and Persistence The seven primary prevention trials of tamoxifen and raloxifene provided limited and heterogeneous data on adherence and persistence. Of trials reporting adherence, at least 70% of participants used the planned treatment dose. In NSABP P-1, 41% of participants took 100% of study medication and 79% took at least 76% of study medication at 36 months. Forgetting was the primary reason for nonadherence for 62% of women at 36 months. In the Royal Marsden Hospital trial, adherence was 8% lower with tamoxifen versus placebo ($P = 0.002$) Persistence was measured as duration of treatment in STAR and 1 placebo-controlled trial of tamoxifen and as completion of the planned course of treatment by 2 placebo-controlled trials of tamoxifen. Completion rates were similar between groups in STAR (71.5% for raloxifene vs. 68.3% for tamoxifen) (48), the Italian Tamoxifen Prevention Study (59.8% for tamoxifen vs. 61.8% for placebo) and IBIS-I (72% overall).

Publication identifier	Nelson 2013

Appendix Table 3. Adherence and Persistence to Medications in Trials of Tamoxifen and Raloxifene

Outcomes	Raloxifene vs. Tamoxifen		Tamoxifen vs. Placebo							
	STAR (48)		NSABP P-1 (11)*		IBIS-I (24)		Royal Marsden (28)		Italian trial (31)	
Adherence	NR	NR	41% full†; 79% adequate		NR	NR	8% less than placebo ($P = 0.002$)		NR	NR
Duration of treatment	46.8 mo	43.5 mo	NR	NR	NR	NR	NR	NR	47.4 mo	48.9 mo
Completion of treatment	71.5%	68.3%	NR	NR	63.9% (2287/3579) for 5 y	71.9% (2574/3579) for 5 y	NR	NR	59.8% (1615/2700) for 5 y	61.8% (1674/2708) for 5 y
Discontinuation due to protocol specified event (major events)	NR	NR	NR	NR	NR	NR	NR	NR	7.6% (206/2700)	6.9% (188/2708)
Discontinuation due to non–protocol-specified event	NR	NR	23.7%	19.7%	NR	NR	NR	NR	26.7% (721/2700)	25.3% (686/2708)
Discontinuation due to adverse event	NR	NR	NR	NR	NR	NR	NR	NR‡	NR	NR

IBIS = International Breast Cancer Intervention Study; MORE = Multiple Outcomes of Raloxifene Evaluation; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; RUTH = Raloxifene Use for the Heart; STAR = Study of Tamoxifen and Raloxifene.
* Adherence was reported in Land et al (81) and discontinuation in Fisher et al (11).
† Adherence at 36 mo was defined as full adherence (taking 100% of medication) and adequate adherence (at least 76% of medication).
‡ An earlier report of the Royal Marsden Hospital trial before enrollment was completed stated that the most frequent side effects leading to discontinuation were hot flashes and gynecologic problems (Powles et al [27]).
§ Includes a treatment group using conjugated equine estrogen.
‖ 3-y study period.
¶ Reported completion of "study" rather than "treatment."
** Includes data relating to lasofoxifene.
†† 1-y study period.
‡‡ 2-y study period.

Surveys of Medication Decisions and Concordance

In 2 similar studies, women reviewed online decision aids that provided their personal 5-year breast cancer risk and information about risk reduction with tamoxifen or tamoxifen and raloxifene. Immediately after viewing the decision aid, 29% of women in the tamoxifen study were likely to seek more information, 30% were likely to discuss it with their physicians, 19% did not believe that tamoxifen would reduce their risk for breast cancer, and 6% were likely to take it in the next year. Three months after viewing the decision aid, 1% of women had started taking tamoxifen, 6% had talked with their physicians, and 5% sought more information.

A study of women with elevated risk scores reported that 12% of women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided. Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining.

Conclusion	*Placebo-controlled primary prevention trials indicate that tamoxifen and raloxifene reduce the incidence of invasive breast cancer by 7 to 9 cases per 1000 women over a 5-year treatment period primarily by reducing estrogen receptor–positive breast cancer. Beneficial effects of risk-reducing medications are countered by more thromboembolic events for both medications, with tamoxifen causing 4 more events per 1000 women than raloxifene in STAR. Tamoxifen also increases incidence of endometrial cancer and related gynecologic outcomes and cataracts compared with placebo and raloxifene.* *Data are lacking for nonwhite, premenopausal, or elderly women who have comorbid conditions or are taking additional medications for other indications*
Allocation by sponsor and Evaluator assessment	This was described as a "primary supportive publication" with NHMRC level of evidence I by the sponsor. This is appropriate. This meta-analysis combines the data from the placebo controlled tamoxifen trials for both the potential benefit of reduction in breast cancer and the potential risks. It found that tamoxifen reduced the risk of ER+ invasive breast cancer but increased the risk of thromboembolic events, endometrial cancer and gynaecologic conditions and cataract surgery. The review attempted to analyse the proportion of women who completed a five year course of treatment but was limited in this due to variable inclusion of such data in the

Publication identifier	Nelson 2013
	publications. The review identified evidence gaps including "*determination of optimal doses, duration, and timing of use; persistence of effects after treatment; and outcomes in population subgroups*". The review provided some other insights. It found that most women at increased risk of breast cancer are unlikely to choose to take tamoxifen. It also found that most of the risk stratification models available "*demonstrated high calibration but low to modest discriminatory accuracy in predicting the probability of breast cancer in a person. Most models performed only slightly better than age alone as a risk predictor*"

1.1.4.1. Iqbal 2012

Publication identifier	Iqbal 2012, primary supportive, safety
Citation	Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, Sestak I, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer Treat Rev. 2012;38(4):318-28.
Study description	Systematic review to determine the risk of endometrial cancer, deep vein thrombosis and pulmonary embolism in women <50 years given tamoxifen for breast cancer prevention in women without pre-existing breast cancer
Funding source, Conflicts of interest	The following statements are provided: *Conflict of interest: None*
Search Dates	January 1970 to December 2010
Study Method	Only randomized controlled studies that enrolled women younger than 50 years without preexisting invasive breast cancer or ductal carcinoma in situ and that randomised participants to either the standard dose of 20 mg per day of tamoxifen or to placebo for at least five years duration with the goal of chemoprevention were included in the review. Studies comprised solely of women greater than 50 years. of postmenopausal women. and which included women with a prior hysterectomy were excluded. The primary outcome measures were the incidence of endometrial cancer. deep vein thrombosis and pulmonary embolism. The mortality data was collected as the secondary outcome. The primary and secondary outcomes were measured as dichotomous data based on the reported frequencies of events. Risk ratios (RR) were calculated by Fisher's exact test. A two sided p-value was calculated for each outcome. Subgroup analyses were performed according to age less than 50 and equal to or greater than 50 years: and menopausal status (premenopausal vs. postmenopausal). A sensitivity analysis was performed on the primary outcome based on the bias assessment.
Search Method	The electronic databases The Cochrane Central Register of Controlled Trials (CENTRAL) and National Library of Medicine (NLM) were searched using the key words: "women younger than 50 years or premenopausal: chemoprevention or tamoxifen: serious adverse-events or endometrial cancer/carcinoma or venous thromboembolism or deep vein thrombosis or pulmonary embolism; and incidence or morbidity or mortality. To avoid language bias, the literature search was expanded to include articles published in languages other than English. The authors also searched the Grey literature for unpublished journal articles and conference

Publication identifier	Iqbal 2012, primary supportive, safety
	proceedings. Clinical Trial Registries were searched for ongoing and unpublished trials. Principal investigators of clinical trials were also contacted for unpublished data and information packets were requested from manufacturers for any additional data. Citations of selected publications were also screened for additional studies
Study and data selection	Studies identified by the search method were screened using the criteria in the table below:

Table 1
Predefined inclusion and exclusion criteria.

Question component	Inclusion criteria	Exclusion criteria
Population	(1) Adult females with either age less than 50 years or premenopausal women (2) No pre-existing breast cancer (3) High risk of breast cancer – (family history of breast cancer in 1st or 2nd degree relatives, Gail's score of 1.6 or more, LCIS or BRCA1 or BRCA2 carrier)	(1) Patients with pre-existing breast cancer (2) Studies that solely included women with age greater than 50 years or postmenopausal women (3) Women with history of Prothrombotic conditions e.g. Factor V Leiden, Protein C & S deficiency etc. (4) Women with hysterectomy
Intervention	Chemoprevention, Placebo-controlled Tamoxifen, 20 mg per day compared with Placebo for at least 5-years	(1) Non-placebo-controlled trials (2) Studies comparing tamoxifen with other SERMs (Raloxifene, Lasofoxifene) (3) Studies comparing tamoxifen with androgens (4) Studies in which any other therapy was offered during intervention period (5) Comparisons that include non-conventional medications
Outcomes	Primary outcomes (1) Incidence of endometrial cancer (2) Incidence of venous thromboembolism (deep vein thrombosis and pulmonary embolism) Secondary outcomes (1) Mortality due to endometrial cancer and venous thromboembolism (deep vein thrombosis and pulmonary embolism)	
Study design	(1) Randomized, double-blind, placebo-controlled trials (2) Experimental studies with Quasi randomization (3) Experimental studies without randomization	(1) Cohort/case control studies (2) Case studies/series and reports (3) Cross over studies (4) Studies with no comparator group (5) Systematic Reviews: meta-analyses

LCIS, lobular carcinoma in situ; SERM, selective estrogen receptor modulator.

The screening process identified seven articles for detailed systematic review. These articles were from three RCTs (the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial; the International Breast Cancer Intervention Study-1 (IBIS-1) and Royal Marsden hospital tamoxifen breast cancer prevention tria1.

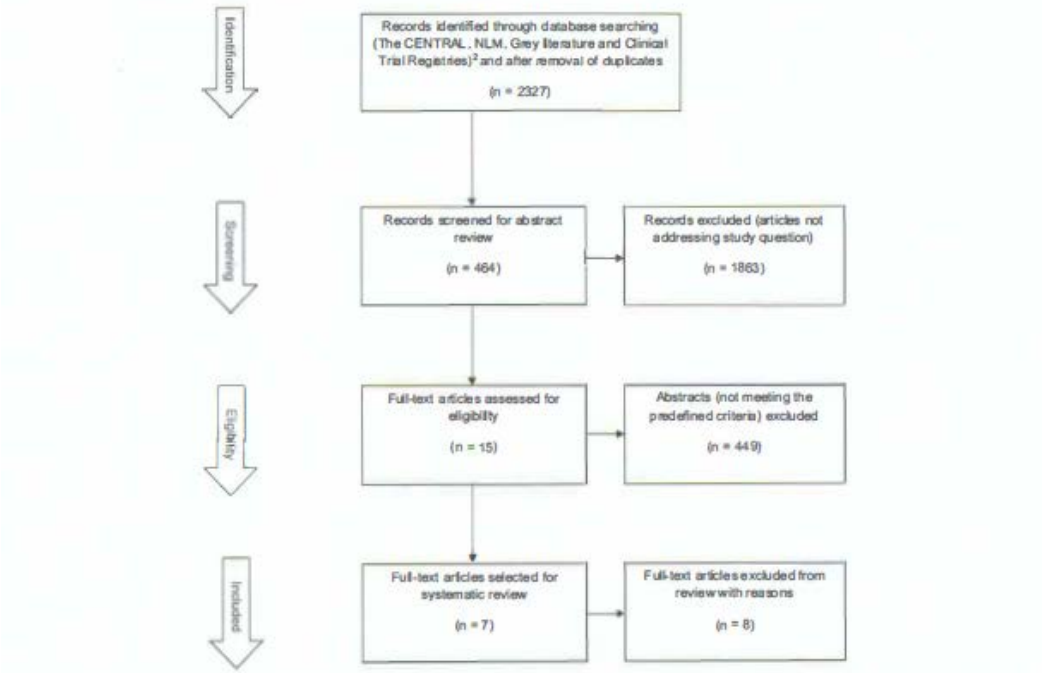


Fig. 1. How diagram 1 of database search. (1) Adopted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(6):e1000097. doi:10.137 1/journal.pmed1000097. (2) The CENTRAL represents The Cochrane's Central Register of Controlled Trials; NLM represents National Library of Medicine.

Data from the included studies was collected using a pre-defined data form. Data items included:

Publication identifier	Iqbal 2012, primary supportive, safety
	study design & methodology; participant characteristics; intervention arms and assigned interventions (dose, timing and duration); compliance and lost to follow-up participants, primary and secondary outcomes; funding sources and disclosures. Possible bias in these publications was assessed using the Cochrane Collaboration's tool and found that in general, all studies met either good or fair criteria

Table 2
Risk of bias assessment of studies.

	NSABP P-1 Risk of bias			IBIS-1 Risk of bias			Royal Marsden trial Risk of bias		
	Yes (low risk)	No (high risk)	Unclear	Yes (low risk)	No (high risk)	Unclear	Yes (low risk)	No (high risk)	Unclear
Adequate sequence generation?	✓			✓			✓		
Adequate allocation concealment?	✓			✓			✓		
Blinding of participants, personnel and outcome assessors	✓			✓			✓		
Incomplete data outcome addressed?	✓				✓[b]			✓[b]	
Free of selective reporting?	✓				✓[b]			✓[b]	
Free of other bias?		✓[a]			✓[b,c]			✓[b,c]	
Overall quality of data (good, fair, and bad)	Good			Fair			Fair		

Abbreviations: NSABP P-1, National Surgical Adjuvant Breast and Bowel Project P-1; IBIS-1, International Breast Cancer Intervention Study-1.
[a] Selection bias for ethnicity.
[b] Inadequate data reporting for according to age or menopausal status.
[c] The use of Hormone replacement therapy (HRT) was permitted during intervention period.

Results	The 3 RCTs were summarised as shown below:

Table 3
Characteristics of Randomized Controlled Trials included in review.

Study	Design	Participants (n) P/T	Inclusion criteria	Exclusion criteria	Treatment
NSABP P-1	RCT Double-blind	n = 13,175 P= 6599 T = 6576 Age <50 years P = 2596 (39.3%) T = 2581 (39.2%) Total = 5177 (39.2%) United States of America Canada	(1) Women with either the age ≥60 years or between 35 and 69 years with a 5-year predicted risk for breast cancer of 1.66[a] (2) LCIS (3) Life expectancy of at least 10 years	(1) Previous breast cancer (2) Previous DVT and PE (3) Estrogen and/or progesterone replacement therapy or oral contraceptives (4) Pregnancy	T vs. P for 5 years T, 20 mg/ day
IBIS-1	RCT Double-blind	n = 7154 P= 3575 T = 3579 Age <50 years: P= 1653 (46.3%) T= 1644 (45.9%) Total = 3297 (46%) United Kingdom and Europe Australia New Zealand	(1) Twofold relative risk (RR) of breast cancer if the age between 45 and 70 years (2) Fourfold RR of breast cancer if the age between 40 and 44 years (3) Tenfold RR of breast cancer if the age between 35 and 39 years[b]	(1) Previous invasive cancer (2) Previous deep vein thrombosis or pulmonary embolism (3) Users of anticoagulants (4) Pregnancy	T vs. P for 5 years T, 20 mg/ day
Royal Marsden trial	RCT Double-blind	n = 2471 P = 1233 T = 1238 Age <50 years: P = 749 (60.7%) T= 774 (62.5%) Total = 1523 (61.6%) United Kingdom	Women between ages 30-70 years and with family history of breast cancer[c]	(1) Previous cancer (2) Previous DVT and PE (3) Oral contraceptives (4) Pregnancy	T vs. P for 8 years T, 20 mg/ day

Abbreviations: P, placebo; T, tamoxifen; LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ; EC, endometrial cancer; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; NSABP P-1, National Surgical Adjuvant Breast and Bowel Project P-1; IBIS-1, International Breast Cancer Intervention Study-1.
[a] NSABP P-1 participant's risk assessment: participants were enrolled on the basis of breast cancer risk assessment. A modified Gail's model was used to assess the risk. The model incorporates the age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche.
[b] IBIS-1 participant's risk assessment: participants were enrolled on the basis of family history of breast cancer and presence of LCIS. Specifically, the eligibility criteria from age 45 years include (1) breast cancer in mother or sister before the age of 50 years, (2) breast cancer in 2 first- or second-degree relatives at any age, or (3) breast cancer in first-degree relative at any age. were nulliparous or had previous hyperplastic benign lesion. Eligibility criteria from age 40 years include (1) history of atypical ductal or lobular hyperplasia, (2) one first-degree relative with bilateral breast cancer at any age, or (3) one of the two first- or second-degree relatives with breast cancer diagnosed before age 50 years. Eligibility criteria from age 35 years include (1) lobular carcinoma in situ or (2) two first-degree relatives with breast cancer, both diagnosed before age 50 years. Also, any women with a 10-year risk of 5% or more based on a complex model were also included in the study.
[c] Royal Marsden trial participant's risk assessment: participants were enrolled on the basis of family history of breast cancer including (1) one first-degree relative with breast cancer diagnosed at the age younger than 50 years, (2) one first-degree relative with bilateral breast cancer, (3) one first-degree relative with breast cancer diagnosed at any age and one other first- or second-degree relative with breast cancer and 4) women with benign breast biopsy and a first-degree relative with breast cancer.

Because NSABP P-1 study was unblinded in 1998, only the results prior to unblinding (active treatment phase) were included.

The included studies differed in:

- Enrollment criteria - the risk assessment of breast cancer in the NSABP P-1 study was determined either by age, benign high risk breast lesion or modified Gail's model. The lBIS-1 and Royal Marsden studies used family history of breast cancer as the major determinant of risk. This resulted in about 25% of the women in the NSABP Pl study having no family history of breast cancers whereas 97% women in the IBIS-1 and 99%

Publication identifier	Iqbal 2012, primary supportive, safety

women in the Royal Marsden study reported a family history of breast cancer.

- Menopausal status - the NSABP P1 study, unlike in the IBIS-1 and the Royal Marsden study, did not define menopausal status. This review, therefore, categorized all participants according to age: less than 50 years, or equal to or greater than 50 years.
- Use of HRT - The IBIS-1 and Royal Marsden studies permitted the use of hormone replacement therapy during the intervention periods, the NSABP P1 did not
- Frequency of follow-up, study duration and treatment compliance - in the NSABP P-1 study, 21.6% women stopped their assigned treatment (19.7% in placebo and 23.7% in tamoxifen) and additional 2.3% were lost to followup. In the IBIS-1 study, the follow-up was available on 85% women and the data on lost to follow-up women was not reported. In the Royal Marsden study, about 35% women stopped their assigned treatment (30.8% in placebo and 40% in tamoxifen group) and additional 11 % participants were lost to follow-up. The median follow-up time was 54.6 months in NSABP P-1 study, while it was 96 months in the IBIS-1 study and 13 years in the Royal Marsden study.
- Age related outcome data - The NSABP-Pl was the only study which reported each outcome measure (endometrial cancer. deep vein thrombosis and pulmonary embolism) according to different age groups. In the IBIS-1 study, only endometrial cancer events were reported according to age. In the Royal Marsden study, none of the outcome measures were reported according to age or menopausal status

The results for each outcome measure are described for each of the individual trials, with this broken down by age group where the data was available.

Table 5
Summary of events in randomized controlled trials[b] according to age and phase of treatment (active phase, follow-up phase and overall events).

	NSABP-P1			IBIS-1		
Phase of treatment	Active phase	Follow-up phase[c]	Overall events[c]	Active phase	Follow-up phase	Overall events[c]
Number analyzed (P vs. T)	6599 vs. 6576	6610 vs. 6597	6610 vs. 6597	3566 vs. 3573	3575 vs. 3579	3575 vs. 3579
Endometrial cancer[a]	P vs. T	P vs. T	P vs. T	P vs. T	P vs. T	P vs. T
Age < 50	2596 vs. 2581	2600 vs. 2589	2600 vs. 2589	1826 vs. 1812	1653 vs. 1644	1653 vs. 1644
Total events	8 vs. 9	1 vs. 3	9 vs. 12	2 vs. 1		2 vs. 1
Rate (per 1000 women)[d]	1.09 vs. 1.32	0.06 vs. 0.19	0.56 vs. 0.75	0.26 vs. 0.13	No new cases of endometrial cancer	0.15 vs. 0.08
RR (95% CI)	1.13 (0.44–2.93)	3.01 (0.31–28.95)	1.34 (0.57–3.17)	0.50 (0.05–5.55)		0.50 (0.05–5.54)
p-value	0.9	0.6	0.6	0.9		0.9
Age ⩾ 50	1598 vs. 1561	1600 vs. 1522	1600 vs. 1522	457 vs. 529	639 vs. 703	639 vs. 703
Total events	7 vs. 27	1 vs. 14	8 vs. 41	3 vs. 10	6 vs. 6	9 vs. 16
Rate (per 1000 women)[d]	0.76 vs. 3.05	0.1 vs. 1.5	0.81 vs. 4.38	1.5 vs. 5.6	1.11 vs. 0.85	1.67 vs. 2.28
RR (95% CI)	3.86 (1.69–8.86)	14.7 (1.94–111.7)	5.39 (2.53–11.45)	3.05 (0.98–12.82)	0.7 (0.25–2.36)	1.77 (0.78–3.99)
p-value	0.0002	0.001	0.00002	0.07	0.8	0.2
Deep vein thrombosis						
Age < 50						
Total events	8 vs. 11	4 vs. 5	12 vs. 16	6 vs. 21	4 vs. 3	10 vs. 24
Rate (per 1000 women)	0.78 vs. 1.08	0.25 vs. 0.31	0.75 vs. 1.0	0.79 vs. 2.79	0.30 vs. 0.23	0.77 vs. 1.85
RR (95% CI)	1.13 (0.44–2.93)	1.26 (0.34–4.67)	1.34 (0.63–2.82)	3.53 (1.43–8.72)	0.75 (0.17–3.36)	2.41 (1.16–5.03)
p-value	0.9	0.9	0.5	0.006	0.9	0.02
Age ⩾ 50						
Total events	14 vs. 24	8 vs. 9	22 vs. 33	13 vs. 26	15 vs. 14	28 vs. 40
Rate (per 1000 women)	0.88 vs. 1.55	0.32 vs. 0.37	0.89 vs. 1.34	1.80 vs. 3.55	0.98 vs. 0.91	1.84 vs. 2.62
RR (95% CI)	1.72 (0.89–3.32)	1.13 (0.43–2.91)	1.50 (0.88–2.57)	1.98 (1.02–3.83)	0.93 (0.45–1.92)	1.42 (0.88–2.29)
p-Value	0.1	0.9	0.1	0.05	0.9	0.1
Pulmonary embolism						
Age < 50						
Total events	1 vs. 2	1 vs. 2	2 vs. 4	8 vs. 10	3 vs. 1	11 vs. 11
Rate (per 1000 women)	0.1 vs. 0.2	0.02 vs. 0.05	0.13 vs. 0.25	1.05 vs. 1.33	0.44 vs. 0.15	0.84 vs. 0.84
RR (95% CI)	2.01 (0.18–22.17)	2.0 (0.10–22.70)	2.01 (0.37–10.96)	1.26 (0.50–3.18)	0.34 (0.03–3.22)	1.01 (0.44–2.31)
p-Value	0.9	0.9	0.6	0.8	0.6	0.8
Age ⩾ 50						
Total events	5 vs. 16	6 vs. 8	11 vs. 24	10 vs. 11	11 vs. 12	21 vs. 23
Rate (per 1000 women)	0.3 vs. 1.0	0.24 vs. 0.32	0.45 vs. 0.97	1.38 vs. 1.50	0.72 vs. 0.78	1.37 vs. 1.49
RR (95% CI)	3.21 (1.18–8.74)	1.33 (0.46–3.84)	2.19 (1.08–4.46)	1.09 (0.46–2.55)	1.08 (0.48–2.45)	1.09 (0.60–1.96)
p-Value	0.02	0.7	0.04	0.9	0.9	0.8

Abbreviations: NSABP-P1, National Surgical Adjuvant Breast and Bowel Project-P1; IBIS-1, International Breast Cancer Intervention Study-1; P, placebo; T, tamoxifen; RR, risk ratio; CI, confidence interval.

[a] Data calculated in women with intact uterus.
[b] The Royal Marsden Study is not included because the data is not reported according to age for all primary outcome measures (endometrial cancer, deep vein thrombosis and pulmonary embolism).
[c] Because NSABP-P1 study was unblinded in 1998; the follow-up phase of NSABP-P1 is not included in the primary analysis of this review.
[d] Rate= Annual rate per 1000 women per year.
[e] Overall events include events in both active and follow-up phases of treatment.

Estimates of risk based on combined data (the NSABP-Pl and IBIS-1 trials) are also provided. Women less than 50 years of age who receive tamoxifen for breast cancer chemoprevention do not have a significantly increased risk of endometrial cancer as compared to women given placebo (risk ratio, I.I 9: 95% Cl, 0.53-2.65; p < 0.6). The risk is significantly higher in women greater than 50 years who are given tamoxifen (risk ratio. 3.32: 95% Cl. 1.95-5.67; p = < 0.0001).

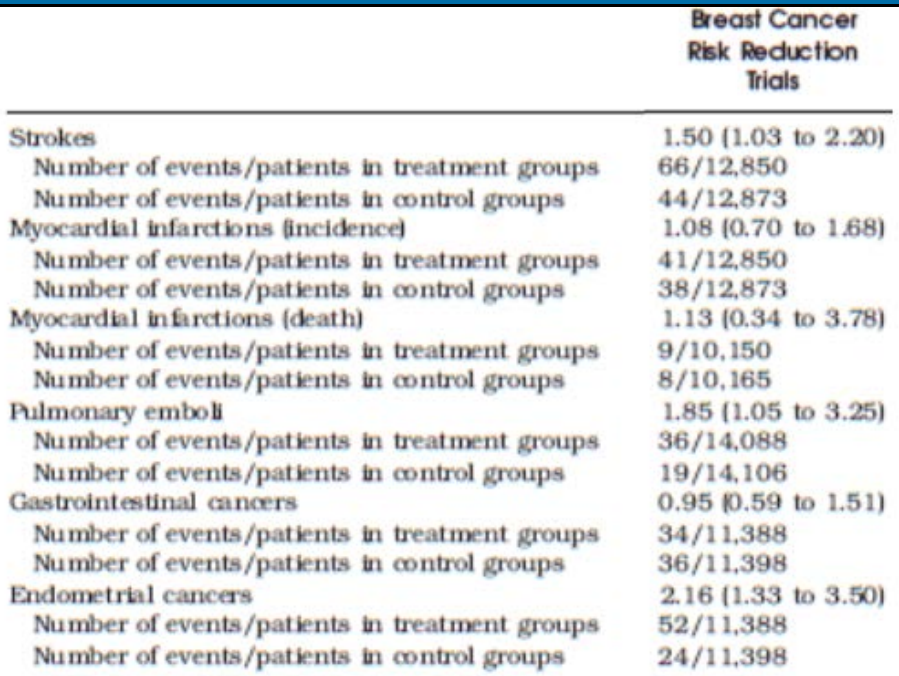
The overall risk (active and follow-up phases of treatment) of deep vein thrombosis with

Publication identifier	Iqbal 2012, primary supportive, safety
	tamoxifen is significant in women less than 50 years (risk ratio. 1.45; 95% Cl. 1.09-3.07; p = 0.02): however, it is only during the active phase that the risk is higher (risk ratio, 2.30; 95% Cl. 1.23-4.31; p = 0.009). There was no excess of deep vein thrombosis in the follow-up phase of treatment (risk ratio. 1.00; 95% Cl, 0.38-2.67; p = 0.9). The difference in risk of pulmonary embolism was not significant in women less than 50 years (risk ratio. 1.16; 95% Cl. 0.55-2.43; p = 0.6) or in women equal to or greater than 50 years (risk ratio, 1.46; 95% Cl, 1.46 (0.94-2.29): p = 0.1).
Conclusion	The risk of endometrial cancer and VTE varies with the age of the women receiving tamoxifen for breast cancer chemoprevention. The risks appear to be largely limited to the active period of treatment.
Allocation by sponsor and Evaluator assessment	This was described as a "primary supportive publication" with NHMRC level of evidence I by the sponsor. This is appropriate. This meta-analysis provides a discussion of the differences between the tamoxifen breast cancer risk reduction trials and summarises the key results from each trial. It also pools data from comparable trials to demonstrate that the adverse event of endometrial cancer Is less common in women aged < 50 years but that the adverse events of DVT and PE are not affected by age.

Braithwaite 2003

Publication identifier	Braithwaite 2003
Citation	Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med. 2003;18(11):937-
Study description	Meta-analysis of English language RCTs assessing breast cancer risk reduction and treatment to estimate the effects of tamoxifen on potentially lifethreatening vascular and neoplastic outcomes.
Funding source, Conflicts of interest	The following statements are provided: • *This research was supported by National Library of Medicine grant # T15-LM07092-09, the Pharmaceutical Research and Manufacturers' Association, the Robert Wood Johnson Foundation, and AHRQ grant #R25-HS09796.* • *The study sponsors had no role in the study design, collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication. All authors were asked to disclose apparent or real conflicts of interest that may have influenced their interpretation of the results. One author (RTC) has acted as a consultant for Astra Zeneca, a pharmaceutical company that manufactures hormonal chemotherapy for breast cancer. None of the other authors reported any conflicts of interest.*
Search Dates	1966 to November 2002
Study Method	A random effects meta-analysis of data from all published randomised controlled trials (published in English) involving the use of tamoxifen - both breast cancer risk reduction and treatment trials were included. Results were separately analysed for patients receiving tamoxifen for different indications and for different patient subgroups. Risks were reported as relative risk (RR) - relative risks and 95% confidence intervals (CI) were calculated for each trial by comparing the incidence rate among tamoxifen users to nonusers. Both fixed-effects models and random-effects models were used to combine the risk ratios across studies.

Publication identifier	Braithwaite 2003
Search Method	The search method was described: • a search was performed of the MEDLINE and CANCERLIT computerized databases (1966 to November 2002) using the medical subject headings *tamoxifen* and *estrogen antagonists*, and textwords *tamoxifen*, *selective estrogen receptor modulator*, and *SERM* and restricted to randomised controlled trials that were published in English and conducted on human subjects. • a manual search using the authors' reference files, reference lists from original communications, and experts in the field was also performed
Study and Data Selection	Abstracts or full-text articles that were identified by the search method were screened in duplicate. Articles were excluded if they did not report on clinical outcomes of interest or if the treatment arm did not differ from the control arm solely by the presence of tamoxifen or if enrollees had had previous exposure to tamoxifen or if , the treatment and control groups were not randomised For data from the eligible publications, outcomes were only used if they were labelled precisely; cancers-in-situ were grouped with invasive cancers; age >50 was used as a proxy for postmenopausal status; median values were used as an approximation for mean values when the latter were not reported; outcomes among breast cancer patients with tumour recurrence were not distinguished from outcomes among patients with no known recurrence; .where more than one article was published from a single trial, the latest report with information on the outcome of interest was used
Results	Thirty-two separate randomized controlled trials with data for 52,929 patients reported on at least one neoplastic or vascular outcome. Four trials (NSABP 1 – Fisher 1998, Royal Marsden – Powles 1998, The Italian Study – Veronesi 1998 & 2002, IBIS-1 – Cozick 2002) investigated breast cancer risk reduction (28,193 participants), 25 trials (24,373 participants) investigated breast cancer treatment, and 3 trials (363 participants) were unrelated to breast cancer. Comment: Results are presented as they pertain to breast cancer risk reduction Table 1. Characteristics of Tamoxifen Trials Included in Meta-analysis Trial / Number of Patients Analyzed / White, % / Postmenopause, % / Age / Dose (mg/day) / Duration of Exposure / Follow-up Interval Risk reduction trials NSABP P-1[8] / 13,175 / 96.5 / 60.7 / NR / 20 / 4.0 / 4.0 Royal Mars[9] / 2471 / NR / 33.6 / 47 / 20 / 5.8 / 5.8 Italian[10,11] / 5408 / NR / NR / 51 / 20 / 5.0 / 6.8 IBIS-I[12] / 7139 / NR / 49.1 / 51 / 20 / 5.0 / 4.2 Subtotal / 28,193 / 96.5 / 54.1 / 50.3 / 20 / 4.6 / 4.7 Increased risk of stroke, pulmonary emboli and endometrial cancer were found in women receiving tamoxifen for reduction in t eh risk of breast cancer – see table below. **Excerpt from Table 2 - Relative Risks (95% CI) Associated with Tamoxifen Use for Selected Vascular and Neoplastic Outcomes**

Publication identifier	Braithwaite 2003
	

	Breast Cancer Risk Reduction Trials
Strokes	1.50 (1.03 to 2.20)
Number of events/patients in treatment groups	66/12,850
Number of events/patients in control groups	44/12,873
Myocardial infarctions (incidence)	1.08 (0.70 to 1.68)
Number of events/patients in treatment groups	41/12,850
Number of events/patients in control groups	38/12,873
Myocardial infarctions (death)	1.13 (0.34 to 3.78)
Number of events/patients in treatment groups	9/10,150
Number of events/patients in control groups	8/10,165
Pulmonary emboli	1.85 (1.05 to 3.25)
Number of events/patients in treatment groups	36/14,088
Number of events/patients in control groups	19/14,106
Gastrointestinal cancers	0.95 (0.59 to 1.51)
Number of events/patients in treatment groups	34/11,388
Number of events/patients in control groups	36/11,398
Endometrial cancers	2.16 (1.33 to 3.50)
Number of events/patients in treatment groups	52/11,388
Number of events/patients in control groups	24/11,398

Conclusion	*If all adverse outcomes with statistically significant risk increases in the present analysis are considered together (pulmonary emboli, stroke, gastrointestinal cancers, endometrial cancers), the absolute risk for any event after 5 years of tamoxifen treatment is 0.84%, corresponding to one adverse outcome for every 118 patients treated. In comparison, the number needed to treat to prevent one breast cancer in a woman with the minimum risk for which tamoxifen is indicated (1.66% after 5 years) is 159, assuming a risk reduction of 38%. For a higher risk woman (5% 5-year risk), the number needed to treat would be 53.*
Allocation by sponsor and Evaluator assessment	This was described as a "primary supportive publication" with NHMRC level of evidence I by the sponsor. This is appropriate. Use of this meta-analysis is, however, limited as much of the analysis and discussion uses data abstracted from both breast cancer treatment and breast cancer risk reduction publications. Despite this, a significant increase in risk of stroke, pulmonary emboli and endometrial cancer was found in women receiving tamoxifen for reduction in the risk of breast cancer

Duffy 2002

Publication identifier	Duffy 2002, primary supportive, efficacy
Citation	Duffy SW, Nixon RM. Estimates of the likely prophylactic effect of tamoxifen in women with high risk BRCA1 and BRCA2 mutations. Br J Cancer. 2002;86(2):218-21.
Included trials	NSABP P1, Italian, multiple others
Study description	The oestrogen-receptor specific effects of tamoxifen from randomized preventive or therapeutic trials were combined with the oestrogen receptor status of tumours in BRCA1 and BRCA2 mutation positive women from published tumour surveys to obtain estimates of the likely effect of tamoxifen administration in mutation carriers.

Publication identifier	Duffy 2002, primary supportive, efficacy
Funding source, Conflicts of interest	The following statements are provided: Nil
Study Method	Three groups of publications were identified (method not described): • surveys of ER status in breast cancer patients with a high risk mutation in the BRCA1 or BRCA2 gene (17 publications) • randomised trials of tamoxifen administration for at least 3 years for primary prevention of breast cancer, with published results stratified by ER status (two publications – Fisher 1998 for the NSABP P1 trial and Veronesi 1998 for the Italian study) • randomised trials of tamoxifen administration for at least 3 years in breast cancer patients for prevention of recurrences or new primary breast cancers, with published results stratified by ER status (5 publications) Results of each of the above three types of study were first synthesized using random effects meta-analysis methods, and then combined with those of the BRCA1 and BRCA2 tumour surveys in turn, to model the effect of tamoxifen in prevention of ER+ and ER- breast cancer in women with BRAC1 or BRAC2 mutations..
Results	For BRAC1 mutations: **Table 5** Synthesized estimates of preventive effect of tamoxifen in BRCA1 positive women **Method** / **Type of prevention** / **RR (tamoxifen vs control)** / **95% CI** Two-stage / Primary / 0.95 / 0.51 – 1.76 Both / 0.87 / 0.68 – 1.11 Simultaneous / Primary / 0.95 / 0.53 – 1.65 Both / 0.87 / 0.68 – 1.10 For BRAC2 mutations: **Table 6** Synthesized estimates of preventive effect of tamoxifen in BRCA2 positive women **Method** / **Type of prevention** / **RR (tamoxifen vs control)** / **95% CI** Two-stage / Primary / 0.63 / 0.34 – 1.15 Both / 0.73 / 0.59 – 0.90 Simultaneous / Primary / 0.64 / 0.40 – 1.08 Both / 0.73 / 0.57 – 0.88
Conclusion	*The above suggests that any preventive benefit of tamoxifen in women positive for the high risk BRCA1 mutation is likely to be modest, but that a larger benefit of the order of a 25 – 35% reduction in incidence may be conferred in BRCA2 mutation carriers. This finding stems from the lesser effect of tamoxifen in prevention or treatment of ER- cancers, which are more common in BRCA1 mutation carriers.*
Allocation by sponsor and Evaluator assessment	This was described as a meta-analysis that was a "primary supportive publication" with NHMRC level of evidence I by the sponsor. The publication refers to a combination of surveys and publications of "randomised" studies (published between 1986 and 2001) and does not fit neatly in the NHMRC classification which describes level I as "Evidence obtained from a systematic review of all relevant randomised controlled trials". .The mathematical modelling in this publication of the possible benefits of tamoxifen in women with BRAC1 and BRAC2 mutations is

Publication identifier	Duffy 2002, primary supportive, efficacy
	speculative only and the publication may be better characterised as “secondary supportive”

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