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Medication Use for the Risk Reduction of Primary Breast Cancer in Women: A Systematic Review for the U.S. Preventive Services Task Force

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www.ahrq.gov

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Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
Mail Code: BICC
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Heidi D. Nelson, MD, MPH
Rongwei Fu, PhD
Bernadette Zakher, MBBS
Marian McDonagh, PharmD
Miranda Pappas, MA
L.B. Miller, BA
Lucy Stillman, BS

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Structured Abstract

Background: Medications to reduce breast cancer risk are an effective prevention intervention for women at increased risk, although medications also cause adverse effects.

Purpose: To update the 2013 U.S. Preventive Services Task Force (USPSTF) systematic review on the use of medications to reduce the risk of primary breast cancer.

Data Sources: Searches included the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, EMBASE, and MEDLINE (January 1, 2013 to July 21, 2018); and manual review of reference lists.

Study Selection: Discriminatory accuracy studies of breast cancer risk assessment methods; double-blind, placebo-controlled or head-to-head randomized controlled trials (RCT) of tamoxifen, raloxifene, and aromatase inhibitors for primary prevention of breast cancer that enrolled women without preexisting breast cancer; and RCTs and observational studies of harms of medications.

Data Extraction: One investigator abstracted data on study methods; setting; population characteristics; eligibility criteria; interventions; numbers enrolled and lost to followup; method of outcome ascertainment; and results for each outcome and a second investigator checked abstractions for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Seventeen risk models evaluated in 24 studies had generally low discriminatory accuracy in predicting the probability of breast cancer in an individual (c-statistics 0.55 to 0.65). Most models performed only slightly better than age alone as a risk predictor. No studies evaluated optimal ages or frequencies of risk assessment.

In placebo-controlled trials, tamoxifen (risk ratio [RR] 0.69; 95 percent confidence interval [CI] 0.59 to 0.84; 7 fewer cases per 1000 women over 5 years of use [95 percent CI 4 to 12]; 4 trials), raloxifene (RR 0.44; 95 percent CI 0.24 to 0.80; 9 fewer cases [95 percent CI 3 to 15]; 2 trials), and the aromatase inhibitors exemestane and anastrozole (RR 0.45; 95 percent CI 0.26 to 0.70; 16 fewer cases [95 percent CI 8 to 24]; 2 trials) reduced invasive breast cancer. Risk for invasive breast cancer was higher for raloxifene than tamoxifen in the STAR head-to-head trial (RR, 1.24; 95% CI, 1.05-1.47) after long-term followup. Effects did not differ by age of initiation or duration of use (3 to 5 years), although these effects were not directly compared. Risk reduction persisted at least 8 years after discontinuation in tamoxifen trials with long-term followup. All medications reduced estrogen receptor positive, but not estrogen receptor negative invasive breast cancer; tamoxifen reduced noninvasive cancer in two trials; and breast-cancer specific and all-cause mortality were not reduced.

In placebo-controlled trials, raloxifene (RR 0.61; 95 percent CI 0.53 to 0.73; 2 trials) reduced vertebral fractures; tamoxifen reduced nonvertebral fractures in the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) trial (RR 0.66; 95 percent CI 0.45 to 0.98); while the aromatase inhibitors had no effect on fractures. Tamoxifen and raloxifene had similar effects on

reducing fractures at multiple vertebral and nonvertebral sites in the STAR head-to-head trial.

In placebo-controlled trials, tamoxifen (RR 1.93; 95 percent CI 1.33 to 2.68; 4 trials) and raloxifene (RR 1.56; 95 percent CI 1.11 to 2.60; 2 trials) increased thromboembolic events, while aromatase inhibitors did not. Raloxifene caused fewer thromboembolic events (RR 0.75; 95 percent CI 0.60 to 0.93) than tamoxifen in the STAR head-to-head trial. Tamoxifen, raloxifene, and aromatase inhibitors did not increase coronary heart disease events or strokes.

In placebo-controlled trials, tamoxifen increased endometrial cancer (RR 2.25; 95 percent CI 1.17 to 4.41; 3 trials), while raloxifene and aromatase inhibitors did not. In the STAR head-to-head trial, raloxifene caused fewer cases of endometrial cancer (RR 0.55; 95 percent CI 0.36 to 0.83) and endometrial hyperplasia (RR 0.19; 95 percent CI 0.12 to 0.29), and fewer hysterectomies (RR 0.45; 95 percent CI 0.37 to 0.54) than tamoxifen. Tamoxifen increased cataracts (RR 1.22; 95 percent CI 1.08 to 1.48; 3 trials) and cataract surgery compared with placebo, while raloxifene and aromatase inhibitors did not. Risks for thromboembolic events and endometrial cancer with tamoxifen were higher for older compared with younger women and returned to normal after discontinuation. All medications caused adverse side effects, such as vasomotor or musculoskeletal symptoms, that varied by medication.

Risks for invasive cancer were generally reduced in all population subgroups evaluated based on menopausal status (pre and postmenopausal); family history of breast cancer; body mass index categories; modified Gail model risk categories; and age at menarche, parity, or age at first live birth. Tamoxifen and anastrozole had larger effects in reducing invasive breast cancer in women with previous breast lesions (lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia).

Limitations: Trials were limited by clinical heterogeneity related to different medications, exposure durations, eligibility criteria, adherence, and ascertainment of outcomes. No trials compared timing and duration directly. Long-term followup data were lacking from most trials, and followup was particularly short for the aromatase inhibitors. Trials were not designed for subgroup comparisons and analysis of differences may be underpowered.

Conclusions: Tamoxifen, raloxifene, and the aromatase inhibitors exemestane and anastrozole reduce invasive breast cancer in women without preexisting breast cancer, but also cause adverse effects that vary by medication. Tamoxifen and raloxifene increase thromboembolic events and tamoxifen increases endometrial cancer and cataracts. Identifying candidates for therapy is complicated by risk stratification methods that demonstrate low accuracy.

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Chapter 1. Introduction and Background

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update the 2013 recommendation on the use of medications to reduce risk for primary breast cancer in women.[1,2]

Condition Background

Condition Definition

Breast cancer is a malignancy that develops in breast tissue beginning in the lining of the lactation ducts or lobules of the breast.[3] Invasive breast cancer has the potential to spread into surrounding tissue, while noninvasive or in situ breast cancer is confined to the ducts or lobules.[3] Estrogen receptor positive (ER+) breast cancer, approximately 75 percent of cases, describes cells that have a receptor protein that binds estrogen. ER+ cells may need estrogen to grow, and may stop growing when treated with substances that block the binding and actions of estrogen. Estrogen receptor negative (ER-) cells do not respond to estrogen. Ductal carcinoma in situ (DCIS) may be a precursor form of breast cancer, while lobular carcinoma in situ (LCIS) serves as a marker for increased risk of developing invasive cancer.[4]

Prevalence and Burden of Disease/Illness

Breast cancer is the second most commonly diagnosed cancer among women in the United States after nonmelanoma skin cancer, and is the second leading cause of cancer death after lung cancer. In 2018, an estimated 266,120 women will be diagnosed with breast cancer and 40,920 women will die from the disease.[5] Based on data from 2011 to 2015, 70 percent of female breast cancer cases occurred in women aged 45 to 74 years (median age of diagnosis was 62 years).[6] White and black women have similar rates of breast cancer incidence (128.6 and 126.9 per 100,000 persons respectively) and are more likely to be diagnosed with breast cancer compared with other races. In 2018, breast cancer accounted for 15.3 percent of all new cancer diagnoses in the United States. In 2015, approximately 3,418,124 women were living with breast cancer in the United States.[6]

Etiology and Natural History

Based on data from 2013 to 2015, 12.4 percent of women will be diagnosed with breast cancer at some point in their lives.[6] The 5-year relative survival rate in the United States for any breast cancer diagnosis is 91 percent, which improves to 99 percent with localized disease. Five-year relative survival rates for women with regional and distant disease are 85 percent and 27 percent, respectively.[7] Older women are more likely to die of the disease compared with younger women,

and 81 percent of female breast cancer deaths occurred in women over the age of 54 years between 2011 and 2015 (median age of death was 68 years).[6] Black women are more likely to die of breast cancer (28.7 deaths per 100,000 persons) compared with other races.

Risk Factors

Several factors are associated with increased risk for breast cancer. The strongest predictors are female sex and increasing age. Other important risk factors include previous diagnosis of high-risk breast lesions (DCIS, LCIS, atypical ductal or lobular hyperplasia [ADH, ALH], and others), first degree relatives with breast cancer, presence of breast cancer susceptibility mutations, previous breast biopsy, increased breast density, and previous radiation therapy to the chest (e.g., treatment for Hodgkin lymphoma).[8] While many other risk factors have been associated with breast cancer in epidemiologic studies, their effects are lower or inconsistent.[2,9]

Rationale for Screening/Screening Strategies

Periodic mammography screening is the current approach to early detection. Prevention strategies include use of risk-reducing medications and surgeries (i.e., mastectomy, oophorectomy) for women identified at increased risk. This review focuses on risk-reducing medications.

Candidates for risk-reducing medications need to be accurately identified to optimize potential benefits and minimize harms. The goal of clinical assessment for breast cancer risk is to stratify women into average and above average risk groups. Some of the clinical trials established inclusion criteria based on individual risk factors, while others set risk thresholds of at least 1.67 percent 5-year risk of breast cancer as determined by the modified Gail model, a clinical model to predict individualized probability of developing breast cancer. The previous USPSTF recommendation indicated 3 percent 5-year risk of breast cancer.[1] Clinical tools to assess individual risks for breast cancer in primary care settings, such as the Gail model, incorporate information about specific risk factors to estimate the likelihood of future breast cancer.[2,9] However, risk assessment tools were developed from population-level data and have only a low degree of discriminatory accuracy when used to determine risk for individual women. In the previous systematic review, c-statistic scores ranged from 0.55 to 0.65 among 13 models tested.[2,9]

Interventions/Treatment

Medications used in the United States to reduce the risk of breast cancer in women at increased risk include raloxifene,[10] tamoxifen,[11] and aromatase inhibitors.[12-14] Only raloxifene and tamoxifen are approved by the U.S. Food and Drug Administration (FDA) for this indication, and raloxifene is only approved for use in postmenopausal women.[10,11] Raloxifene and tamoxifen are selective estrogen receptor modulators (SERMs) that act by blocking the response of estrogen receptors in breast tissue, limiting breast tissue proliferation and subsequent cancer. The previous review reported that the degree of risk reduction from use of these medications ranged from 30 percent to 68 percent compared with placebo, predominantly reducing incidence of ER+

invasive breast cancer.[2] A subsequent meta-analysis of individual participant data from nine trials of SERMs, including tamoxifen and raloxifene, reported a 38 percent risk reduction in breast cancer incidence over 10 years of followup.[15] Both SERMs increase risk of thromboembolism and tamoxifen increases risk of endometrial cancer.[2]

Aromatase inhibitors, including exemestane[16-18] and anastrozole,[17] have been evaluated for breast cancer risk reduction in postmenopausal women in clinical trials, although they are primarily used to treat breast cancer. These medications act by blocking aromatase, the enzyme responsible for converting androgen to estrogen, thereby decreasing the production of estrogen in tissue.

Current Clinical Practice/Recommendations of Other Groups

Use of medications for breast cancer risk reduction has been limited in clinical practice. The uptake of risk-reducing medications among 21,423 women in 26 studies was 16.3 percent in a recent meta-analysis.[19] However, use among clinical populations is much lower, with estimates ranging from approximately 4 percent of women at increased risk to less than 1 percent of eligible women overall.[20,21] Women's concerns about adverse effects and their beliefs that benefits are not worth the harms are important factors in their decisions to decline use of these medications.[2] In addition, many primary care physicians are unfamiliar with tamoxifen and aromatase inhibitors because they are primarily used for breast cancer treatment.[22]

The National Comprehensive Cancer Network (NCCN) Breast Cancer Risk Reduction Panel recommends tamoxifen (20 mg/day) as an option to reduce breast cancer risk in healthy pre and postmenopausal women 35 years of age or older, whose life expectancy is 10 years or more, and who have at least 1.7 percent 5-year risk of breast cancer as determined by the modified Gail Model, or who have had LCIS.[23] The NCCN recommends tamoxifen over raloxifene for most postmenopausal women desiring non-surgical risk reduction therapy because it is more effective. However, consideration of toxicity may still lead to the choice of raloxifene in some women. If raloxifene is chosen, the NCCN Breast Cancer Risk Reduction Panel recommends use of 60 mg/day.[23]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF, [24] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**).

Key Questions

1. In adult women without preexisting breast cancer, what is the accuracy of risk assessment methods to identify women who could benefit from medications to reduce risk for primary breast cancer (e.g., clinical risk assessment models)?
    a. What is the optimal age at which to begin risk assessment to identify women who could benefit from medications to reduce risk for primary breast cancer?
    b. What is the optimal frequency of risk assessment to identify women who could benefit from medications to reduce risk for primary breast cancer?
2. In adult women without preexisting breast cancer, what is the effectiveness and comparative effectiveness of medications to reduce risk for primary breast cancer on improvement in short- and long-term health outcomes, including invasive breast cancer, noninvasive breast cancer (including DCIS), breast cancer mortality, all-cause mortality, and other beneficial outcomes (such as reduced fractures caused by certain medications and improved quality of life)?
    a. Does the effectiveness of risk-reducing medications vary by timing of initiation or duration of use?
    b. Does the effectiveness of risk-reducing medications persist beyond discontinuation of use?
3. What are the harms of using medications to reduce risk for primary breast cancer?
    a. Do the harms of risk-reducing medications vary by timing of initiation or duration of use?
    b. Do the harms of risk-reducing medications persist beyond discontinuation of use?
4. Do the outcomes of using medications to reduce risk for primary breast cancer vary by population subgroups?

Contextual Questions

Contextual questions provide additional information for the USPSTF, but are not systematically reviewed or represented in the Analytic Framework.

1. What are current clinician and patient attitudes and practices regarding use of medications to reduce risk for primary breast cancer? Do they vary by population subgroups, including nonwhite women; premenopausal women; women with comorbid conditions; and women with lower educational levels, socioeconomic status, and access to care?

2. How well do statistical models inform the practice of identifying and treating women with medications to reduce risk for breast cancer?

Search Strategies

A research librarian searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Ovid EMBASE and MEDLINE (January 1, 2013 to July 21, 2018) for relevant English-language studies, systematic reviews, and meta-analyses. Search strategies are available in **Appendix A1**. Investigators reviewed reference lists of relevant articles.

Study Selection

Selection criteria for studies based on the patient populations, interventions, outcome measures, and types of evidence were developed for each key question (**Appendix A2**). After an initial review of citations and abstracts, investigators retrieved full-text articles of potentially relevant material and conducted a second review to determine inclusion. A second reviewer confirmed results of the initial reviewer, and discrepancies were resolved by team consensus. For Key Question 1, studies of clinical risk assessment models that could be used in primary care settings to identify women at higher than average risk for breast cancer were included. Only studies reporting discriminatory accuracy of the models were included. Discriminatory accuracy is a measure of how well the model can correctly classify persons at higher risk from those at lower risk and is measured by the model's concordance statistic or c-statistic. The c-statistic is determined by the area under the receiver-operating characteristic curve (AUC), a plot of sensitivity (true-positive rate) versus 1 – specificity (false-positive rate). Perfect discrimination is a c-statistic of 1.0, whereas a c-statistic of 0.5 would result from chance alone. An acceptable level of discrimination is between 0.70 and 0.79, excellent is between 0.80 and 0.89, and outstanding is 0.90 or greater,[25] although these thresholds vary depending on the clinical condition and purpose of the test. Studies of individual risk factors or laboratory tests as well as models designed primarily to evaluate risk for pathogenic mutations in breast cancer susceptibility genes (e.g. *BRCA1/2*) were excluded.

For Key Question 2, only double-blind, placebo-controlled or head-to-head randomized controlled trials (RCT) of tamoxifen, raloxifene, or aromatase inhibitors for primary prevention of breast cancer that enrolled women without preexisting breast cancer were included. These trials reported breast cancer incidence as a primary or secondary outcome of the study. For Key Question 3, RCTs and observational studies of tamoxifen, raloxifene, or aromatase inhibitors in women without preexisting breast cancer that had a nonuser comparison group or direct comparisons between the medications were included. All adverse outcomes at all reported followup times were considered to capture potential short- and long-term adverse effects. Studies reporting only intermediate outcomes rather than health outcomes, such as cholesterol levels rather than cardiovascular disease events, were not included.

The selection of literature is summarized in the literature flow diagram (**Appendix A3**).

Appendix A4 lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

For the included RCTs and observational studies, investigators abstracted the following data: study design; setting; population characteristics (including age, ethnicity, diagnosis); eligibility criteria; interventions (dose and duration); numbers enrolled and lost to followup; method of outcome ascertainment; and results for each outcome. For studies of risk models, investigators abstracted: study design; population characteristics; eligibility criteria; reference standards; risk factors included in the models; and performance measures of the models.

Two investigators independently applied criteria developed by the USPSTF[24] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process.

Data Synthesis

For all key questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[24] Evidence was rated good, fair, or poor, based on study quality, consistency of results between studies, precision of estimates, study limitations, risk of reporting bias, and applicability, and summarized in a table.[24]

Statistical Analysis

Meta-Analysis

Results of the placebo-controlled primary prevention trials were combined using meta-analyses to obtain more precise estimates of clinical outcomes for the target population (Key Questions 2, 3 and 4). To determine the appropriateness of meta-analysis, investigators considered clinical and methodological differences and assessed statistical heterogeneity.

Estimates of risk ratios (RR; rate ratio, hazard ratio [HR], or relative risk) and their standard errors were abstracted or estimated from each study and used as the effect measure. For each outcome, the following steps were adopted to obtain the RR and to account for the varying followup periods of the trials:

1. If a study reported a rate ratio based on a Poisson model, where women-years of followup was incorporated in the estimates, or a HR from a Cox regression model, the reported estimate was used.
2. If not, but the study reported the number of events and women-years of followup, or women-years of followup could be estimated from the reported data, the biostatistician estimated the rate ratio based on a Poisson distribution using the number of events and women-years of followup.
3. If both 1) and 2) were not possible, the reported or estimated relative risk was used, which

does not account for the women-years of followup. However, the estimate of relative risk would be expected to be very close to the estimate of rate ratio since the mean or median followup time was similar between the treatment and control arms in the trials.

The presence of statistical heterogeneity among the studies was assessed using Cochran's χ^2 tests, and the magnitude of heterogeneity using the I^2 statistic.[26] The RRs were combined by using a profile likelihood random effects model to account for variation among studies.[27] When there is no variation among studies, the random effects model yields the same results as a fixed effects model.

To explore whether the combined estimate differed among subpopulations, subgroup analysis was performed by age (≤50; > 50 years), family history of breast cancer (yes; no), use of menopausal hormone therapy (yes; no), menopausal status (pre; post), and body mass index (BMI; ≤25; >25), when at least two studies reported results. For outcomes of major adverse events, the analyses were stratified by active versus posttreatment periods, although the tamoxifen trials were the only trials to report data by treatment periods.

For all above analyses, results were combined separately for tamoxifen, raloxifene, and the aromatase inhibitors. All analyses were performed by using STATA® 13.1 (StataCorp, College Station, TX), and all results were provided with 95 percent confidence intervals (CIs).

Event Rates

To facilitate the evaluation of benefits and harms across trials, event rates for both treatment and placebo groups, along with combined estimates of RRs, were provided in the forest plots for each meta-analysis. Using steps similar to those for RRs, event rates per 1000 women-years were presented if the study reported such data. Otherwise, if the study reported the number of events and women-years of followup, or women-years of followup could be estimated from the reported data, the event rates per 1000 women-years were estimated by the biostatistician. When the event rates were not reported or estimated, they were shown as NR (not reported) in the plots.

Estimation of the Number of Events Reduced or Increased

To interpret the clinical impact of the risk-reducing medications, the biostatistician estimated the number of events reduced for benefits or increased for harms compared with placebo per 1000 women assuming 5 years of medication use, when the meta-analysis indicated a significant difference between the treatment and the placebo groups. These numbers and the corresponding 95 percent CIs were estimated using the combined RRs from the meta-analyses and the combined event rates from the placebo groups of included trials. The combined event rates were estimated from a meta-analysis of the placebo event rates from each trial by using a random effects Poisson model and raw data of the number of events and women-years of followup. This analysis was performed using PROC NLMIXED, SAS 9.4. (SAS Institute Inc., Cary, NC). The 95 percent CIs for the number of events reduced or increased were obtained using a simulation method that assumed that both the logs of the RRs and event rates have normal distributions, and then drew 10,000 random samples from these normal distributions. The numbers of events reduced or increased were then estimated from each sample, and the 95 percent CIs were

obtained by computing the 2.5 percent and 97.5 percent quantiles of the full sample.

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners and will be posted for public comment. The report will be revised based on reviewer comments prior to finalization.

Chapter 3. Results

Key Question 1. In Adult Women Without Preexisting Breast Cancer, What Is the Accuracy of Risk Assessment Methods to Identify Women Who Could Benefit From Medications to Reduce Risk for Primary Breast Cancer?

Summary

The goal of clinical assessment for breast cancer risk is to stratify women into average and above average risk groups to determine candidates for risk reduction therapy. Current U.S. clinical recommendations indicate at least a 1.67 percent or 3 percent 5-year risk of breast cancer threshold as determined by the modified Gail model. Seventeen models incorporating risk factors for breast cancer to predict a woman's risk for developing breast cancer have been evaluated for use in clinical settings. Risk models demonstrate good calibration, with the expected number of breast cancer cases in a study population closely matching the number of breast cancer cases observed. However, most models have low discriminatory accuracy in predicting the probability of breast cancer in an individual with c-statistics generally ranging from 0.55 to 0.65, performing only slightly better than age alone as a risk predictor.

Evidence

A total of 24 studies reporting results of evaluations of 17 risk models met inclusion criteria (**Table 1**).[28-51] Of these, 14 were rated good-quality because they met quality criteria, adequately described methods, used appropriate reference standards, and included large sample sizes (**Appendix B1**).[28,31,34-39,41,43-47] Nine studies were rated fair-quality because they inadequately met some of the criteria or methods were not well-described.[29,30,32,33,40,42,48-50] One study rated poor-quality[51] was excluded from the results.

Three new studies enhanced existing models with new data by adding breast density to the Gail and Tyrer-Cuzick models;[33] modifying the Gail model for Asian Americans;[42] and adding benign breast disease to the Breast Cancer Surveillance Consortium (BCSC) model.[48]

Risk Models

The Gail model was the first major breast cancer risk model to be used clinically.[41] The current version is referred to as the Breast Cancer Risk Assessment Tool and is provided on a publicly accessible National Cancer Institute website.[52] This model was derived from multivariate logistic regression analysis of identified risk factors for breast cancer.[41] In the original version of the Gail model, breast cancer incidence rates and baseline hazard rates were determined for invasive cancer, DCIS, and LCIS from a cohort of women in the Breast Cancer Detection and Demonstration Project (BCDDP). The model was subsequently modified by using U.S. national data for invasive cancer from the Surveillance, Epidemiology, and End Results (SEER)

program.[38] From these data, the model was developed to allow the prediction of individualized absolute risk (probability) of developing breast cancer in women undergoing annual screening mammography. The Gail model has been tested in large populations of white women, data from the Women's Health Initiative (WHI) for black women, and Asian and Pacific Islander women in the WHI and data from SEER, but needs further validation for Hispanic women and other subgroups. The Breast Cancer Risk Assessment Tool is updated periodically as new data or research becomes available, and the algorithm was last updated in 2011.[52]

Subsequent risk models use a similar approach as the Gail model, however, they vary in their use of reference standards. Age-specific breast cancer rates and attributable risk estimates to determine baseline age-specific hazard ratios should ideally be obtained from an applicable population reference standard, such as SEER data in the United States. Several studies of subsequent models do not provide information about their reference standards.[35-37,40,42,44,45]

Models also vary by the variables they include (**Table 2**). The original Gail model included age, age at menarche, age of first birth, family history of breast cancer in first degree relatives, number of previous breast biopsies, and history of atypical hyperplasia.[41] Subsequent models include one or more of these variables in addition to other factors. These include race,[30,35,47,53] BMI or height,[30,32,34-36,49] estrogen and progestin use,[30,32,35,36] parity,[35,36] history of breast feeding,[35] menopause status or age,[30,36,49] smoking,[35] alcohol use,[32,35,36] physical activity,[32,35] breast density,[30,33,34,47] benign breast disease,[48] and diet.[32] Some variations have been developed for specific populations, such a Asian American,[42] African Americans,[28,40] and Italian[32,39,43] women.

Calibration is a measure of how well predicted probabilities agree with actual observed risk. The calibration of a model refers to its ability to predict the average risk in a subset of the population. When the predicted risk matches the proportion that actually develops disease, a model is considered to be well calibrated. In a perfect prediction model, the predicted risk in a population (percent expected) would equal the observed number of cases (percent observed) such that the percent expected/percent observed (E/O) equals 1.0. For most models, the expected numbers of cases of breast cancer closely matched the observed numbers.[1,30,32,34-36,38,39,47,49,53]

Studies of Discriminatory Accuracy

In prognostic modeling, discriminatory accuracy is the ability to correctly classify individuals at higher risk from those at lower risk, and is measured by the model's c-statistic (AUC). Studies indicate that discriminatory accuracy for most of the models ranges from 0.55 to 0.65 (**Table 2**).[28-50] Only one study reported levels above 0.70 for both the Gail-2 and the Tyrer-Cuzick models, with a c-statistic of 0.74 (95 percent CI 0.67 to 0.80) and 0.76 (95 percent CI 0.70 to 0.82), respectively.[29] However, this study was small (<100 cases) and did not include a primary care population, limiting its clinical applicability. The BCSC-Tice model, drawing from large U.S. national populations, provided the next highest discriminatory accuracy, with a c-statistic of 0.66 (95 percent CI 0.65 to 0.66).[47] The model with the lowest level of discrimination was the African American Gail model, with a c-statistic of 0.56 in two studies.[28,53] The discriminatory accuracies of age[30,44] or breast density alone[30] as a predictor of breast cancer risk ranged from 0.55 to 0.57 and 0.55 to 0.56, respectfully.

In most of the primary prevention trials, women were assessed for their individual risks for developing breast cancer, and only those meeting established risk thresholds were eligible to participate. One study evaluated this approach to risk stratification by determining discriminatory accuracy based on a low (<1.67 percent) versus high (≥1.67 percent) risk threshold.[47] This threshold was used as inclusion criteria in the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) and the Study of Tamoxifen And Raloxifene (STAR) trials, and is included in the FDA's approval of the use of SERMS for risk reduction. In this study, the BCSC-Tice model demonstrated high calibration (E/O 0.99 to 1.03), and consistent, although low, discriminatory accuracy across quintiles (c-statistic 0.61 to 0.64).[47]

Key Question 1a. What Is the Optimal Age at Which to Begin Risk Assessment to Identify Women Who Could Benefit From Medications to Reduce Risk for Primary Breast Cancer?

No studies were identified that addressed this question.

Key Question 1b. What Is the Optimal Frequency of Risk Assessment to Identify Women Who Could Benefit From Medications to Reduce Risk for Primary Breast Cancer?

No studies were identified that addressed this question.

Key Question 2. In Adult Women Without Preexisting Breast Cancer, What Is the Effectiveness and Comparative Effectiveness of Medications to Reduce Risk for Primary Breast Cancer on Improvement in Short- and Long-Term Health Outcomes, Including Invasive Breast Cancer, Noninvasive Breast Cancer (Including DCIS), Breast Cancer Mortality, All-Cause Mortality, and Other Beneficial Outcomes?

Overview of the Primary Prevention Trials

Ten large RCTs of tamoxifen, raloxifene, and the aromatase inhibitors anastrozole and exemestane enrolled women without breast cancer and reported breast cancer outcomes. These trials provide the main results for Key Questions 2, 3, and 4 in this systematic review. The primary prevention trials include one head-to-head trial of tamoxifen and raloxifene, STAR;[54-56] five placebo-controlled trials of tamoxifen, including the International Breast Cancer Intervention Study (IBIS-I),[57-59] NSABP P-1,[60-62] Royal Marsden Hospital Trial,[63,64] Italian Tamoxifen Prevention Study,[65-69] and the Hormone Replacement Therapy Opposed by Low-dose

Tamoxifen (HOT) study;[70] two placebo-controlled trials of raloxifene, the Multiple Outcomes of Raloxifene Evaluation (MORE) with long-term followup in the Continuing Outcomes Relevant to Evista (CORE) study,[71-85] and the Raloxifene Use for the Heart (RUTH) trial;[86,87] and two placebo-controlled trials of aromatase inhibitors, the International Breast Cancer Intervention Study II (IBIS-II) of anastrozole,[17,88,89] and the Mammary Prevention.3 trial (MAP.3) of exemestane.[90,91] The newest placebo-controlled tamoxifen trial, HOT, uses a lower dose than the other trials (5 mg/day vs. 20 mg/day) and was considered separately. Details of individual trials are provided in **Table 3**. The trials met criteria for fair- or good-quality (**Appendix B2**).

The trials included large numbers of women, ranging from the HOT study[70] enrolling 1,884 women to the STAR trial enrolling 19,747.[54] Participants were recruited from clinics and communities located in several countries, with North America, Europe, and the United Kingdom most represented. The majority of participants were white and none of the trials provided outcomes specific to racial or ethnic groups. Participants ranged in age from 30s to 80s at baseline.

Inclusion criteria for trials are described in **Table 3** and **Appendix C1**. All trials enrolled women who would be considered candidates for risk reduction medications in the intended target population, although participant characteristics varied across trials. The tamoxifen trials enrolled both pre and postmenopausal women, while the raloxifene and aromatase inhibitor trials enrolled only postmenopausal women. The Italian trial of tamoxifen exclusively enrolled women who had undergone prior hysterectomy including some with oophorectomy,[65] representing only a subgroup of the target population. Several trials enrolled women using exogenous estrogen including the Italian (14 percent of women), Royal Marsden (15 to 27 percent), IBIS-I (40 percent), and HOT (100 percent) tamoxifen trials. Estrogen use could modify or confound breast cancer risk, as well as other outcomes, such as thromboembolic events.

The tamoxifen trials, including STAR, were designed to determine invasive breast cancer incidence as the primary outcome.[54,57,58,61-66,68-70] As such, inclusion criteria considered breast cancer risk in all trials except the Italian[65] and HOT[70] trials. Two trials, STAR and NSABP P-1, used the modified Gail model[41,92] to identify participants at increased risk. In STAR, women were eligible for the trial if they were postmenopausal and had a Gail model 5-year predicted breast cancer risk of 1.67 percent or greater.[54] The NSABP P-1 trial used this same threshold as well as additional criteria, such as age 60 years and older, or a history of LCIS.[62] The IBIS-I and Royal Marsden trials defined risk based on numbers of relatives with breast cancer as well as personal history of prior benign breast biopsies.[57,63]

For the raloxifene trials, breast cancer incidence was one of two primary outcomes in RUTH and was a secondary outcome in MORE. The MORE trial enrolled women with osteoporosis in order to determine the efficacy of raloxifene in preventing fractures.[71,73] Eligibility criteria included bone mineral density (BMD) T-score of -2.5 or less at the femoral neck or lumbar spine, or low BMD with pre-existing vertebral fractures at baseline. The RUTH trial was designed to determine the efficacy of raloxifene in preventing coronary events and enrolled women with coronary heart disease or multiple risk factors for heart disease.[86] Participants were required to have a cardiovascular risk score of 4 or greater according to a point system that assigned values for specific conditions.

The aromatase inhibitor trials enrolled postmenopausal women with risk factors for breast cancer. The IBIS-II trial of anastrozole based inclusion criteria on age and estimated breast cancer risk from a list of risk factors (age 40 to 44 years with risk 4 times higher than the general population; age 45 to 60 years with risk ≥2 times higher; age 60 to 70 years with risk 1.5 times higher).[17] The MAP.3 trial of exemestane used risk criteria based on age 60 years and older, Gail risk score of 1.67 percent or greater, and prior DCIS or high-risk breast lesion on biopsy.[90]

Differences in inclusion criteria across the trials led to the enrollment of dissimilar groups of women (**Appendix C2**). The mean age of participants at entry ranged from 47[63] to 53[70] years in the tamoxifen trials, 67[73] to 68[73,86] years in the raloxifene trials, 58.5 years in STAR,[54] and 60[17] to 63[90] years in the aromatase inhibitor trials. Risks for most outcomes measured in these trials increase with age, including risks for breast cancer and adverse events such as thromboembolic events and strokes. The 15- to 20-year age difference between participants in the different trials would be expected to influence results and limit comparisons across trials. Although the head-to-head design of the STAR trial allows direct comparisons between tamoxifen and raloxifene, there are no head-to-head comparison trials that include the aromatase inhibitors or alternative dosing regimens.

Trials also varied by treatment duration and followup times. These variations could influence results because participants with short exposures may not attain the optimal benefits or experience the adverse effects that would accrue for those with longer exposures. Also, short followup times may not allow conditions with slower progression, such as breast cancer, to be detected during the course of the trial. The STAR trial reported a mean treatment duration of 3.6 to 3.9 years and mean followup of 3.9 years for initial results, and 6.8 years for long-term results.[54-56] Median treatment duration in the placebo-controlled trials of tamoxifen were approximately 4 to 5 years,[62,66] while median followup times ranged from 6 years in the HOT[70] trial to 16 years in IBIS-I.[59] The Royal Marsden[64] and IBIS-I[58] trials provided some results by active versus posttreatment periods, while other trials did not. Absolute risk reduction depends on followup time and trials with longer followup provide better estimates, such as the IBIS-I trial with16 years and Royal Marsden with 13 years.

In the raloxifene trials, results of the MORE trial were reported after 3 and 4 years of treatment.[71-80,83] The CORE study is a continuation of MORE that follows a subset of MORE participants in order to further examine raloxifene's effect on breast cancer incidence. Although participants continued their randomized assignment to raloxifene or placebo in CORE, all had a gap in use. Median time between participation in MORE and CORE was 10.6 months (2.6 to 62 months).[93] Results of CORE were reported for 4-year and combined 8-year outcomes (MORE + CORE).[81,82,84] For RUTH, the median treatment duration was 5.1 years and followup 5.6 years.[86] The aromatase inhibitor trials are the most recent and have the shortest followup times. The median treatment duration and followup was 5 years for IBIS-II[17] and 3 years for MAP.3.[90]

Adherence and completion rates varied across trials and treatment groups. In the STAR trial, the mean duration of treatment was similar for raloxifene and tamoxifen (3.2 vs. 3.1 years, respectively).[54] In IBIS-I, adherence after 4.5 years was 65.2 percent for tamoxifen versus 74.0 percent for placebo ($P < 0.001$).[94] In the Italian trial, designed for 60 months of treatment, women using tamoxifen had lower completion rates than placebo (59.8 vs. 61.8 percent, respectively).[66]

In the Royal Marsden trial, adherence was 8 percent lower with tamoxifen compared with placebo (p=0.002).[64] In RUTH, 70 percent of raloxifene versus 71 percent of placebo groups took at least 70 percent of the study medication.[86] Also, women using raloxifene had slightly higher completion rates than placebo (80 vs. 79 percent; p=0.02), although the median duration of treatment was 5.05 years for both groups.[86] Adherence was not reported by group in MORE; 92 percent of the entire study population took at least 80 percent of the assigned study medication.[73] In IBIS-II, 5-year adherence was 68 percent for anastrozole and 72 percent for placebo (p=0.0047),[17] while for MAP.3, 3-year adherence was 67 percent for exemestane and 71 percent for placebo.[90]

Protocol specified and non-protocol specified events affecting adherence were reported by some of the trials. Protocol specified events are outcomes explicitly stated in the protocol requiring that a participant discontinue the study medication. In the NSABP P-1 trial, discontinuation related to non-protocol specified events was 23.7 percent of tamoxifen versus 19.7 percent of placebo groups.[62] In the Italian trial, 7.6 percent of tamoxifen versus 6.9 percent of placebo groups experienced protocol specified events and withdrew from treatment; 26.7 percent of tamoxifen versus 25.3 percent of placebo groups experienced non-protocol specified events and withdrew from treatment.[66] In RUTH, 22 percent of raloxifene and 20 percent of placebo groups experienced adverse events and discontinued study medications (p=0.01); specific adverse events were not described.[86] In the MORE trial, significantly more women receiving raloxifene than placebo reported hot flashes and withdrew from treatment.[73] Early discontinuation in IBIS-II was related to toxic effects (20 percent anastrozole vs. 15 percent placebo) and patient refusal (5 percent in each group).[17] In MAP.3, early discontinuation was also related to toxic effects (15.4 percent exemestane vs. 10.8 percent placebo; p<0.001) and patient refusal (6.9 percent exemestane vs. 6.0 percent placebo; p=0.22).[90]

Although most trials reported similar outcomes (**Table 4**), the ascertainment of outcomes varied by trial. While diagnostic criteria for primary outcomes were generally well-defined and diagnoses were determined by blinded adjudication committees, ascertainment of additional outcomes was not well described. For these outcomes, it is likely that differences in results between trials may be due, at least in part, to how the outcomes were determined. All of the primary prevention trials reported incidence of invasive, ER+, ER-, and noninvasive breast cancer. All-cause mortality was provided in all of the trials, and breast cancer specific mortality in all but RUTH, however a review reported results of MORE, CORE, and RUTH combined.[95] Fracture outcomes were more comprehensively evaluated in the MORE trial[71,73,76,84] that evaluated fractures at multiple anatomic sites, such as the hip and wrist specifically, and detected rigorously defined radiographic vertebral fractures. The NSABP P-1, RUTH, STAR, HOT, MAP.3, and IBIS-II trials included clinical vertebral fractures[17,54,61,70,86,90] identified by physical findings or symptoms. Most trials reported various categories of nonvertebral fractures including all types or those specific to osteoporosis (hip, vertebral, wrist).

All trials reported thromboembolic events, and some provided specific results for deep vein thrombosis (DVT),[62,69,79,86] pulmonary embolus (PE),[62,69,79,86] and superficial phlebitis.[17,58,69] Coronary heart events were described in all trials and generally included myocardial infarction, angina, acute ischemic syndrome, and other cardiac events. However, specific outcomes included in this broad category varied and were often not well specified. The RUTH trial,

designed primarily to measure coronary outcomes, provided the most comprehensive measures.[86] Stroke was measured in all trials and transient ischemic attack in six.[17,54,58,62,66,70,73,90] Endometrial cancer, hysterectomy, endometrial hyperplasia, uterine fluid, and vaginal bleeding were determined in various ways in most trials. While seven trials reported cataracts,[17,54,58,62,64,79,86] most of these were self-reported. Descriptions of other outcomes, such as vasomotor symptoms, edema, pain, for example, varied by trial.

Summary

Ten large randomized controlled trials provide data on breast cancer risk reduction in women without pre-existing breast cancer. These include one good-quality head-to-head trial of tamoxifen and raloxifene and nine fair- and good-quality placebo-controlled trials (five tamoxifen, two raloxifene, and two aromatase inhibitors). The HOT trial of low-dose tamoxifen indicated no statistically significant differences in outcomes compared with placebo and was not included in the meta-analyses of tamoxifen trials. Results of placebo-controlled trials cannot be directly compared between types of medications because of important differences between study participants, especially differences in age.

Tamoxifen 20 mg/day (RR 0.69; 95 percent CI 0.59 to 0.84; 4 trials), raloxifene (RR 0.44; 95 percent CI 0.24 to 0.80; 2 trials), and aromatase inhibitors (RR 0.45; 95 percent CI 0.26 to 0.70; 2 trials) reduced the incidence of invasive breast cancer in midlife and older women by approximately 31 to 56 percent in placebo-controlled trials. These estimates are comparable to 7 (4 to 12) fewer events per 1000 women over 5 years of use for tamoxifen, 9 (3 to 15) for raloxifene, and 16 (8 to 24) for aromatase inhibitors. Tamoxifen reduced invasive breast cancer more than raloxifene in the STAR head-to-head trial (RR 1.24; 95 percent CI 1.05 to 1.47) after long-term followup comparable to 5 (1 to 9) fewer events with tamoxifen per 1000 women over 5 years of use. Tamoxifen (RR 0.58; 95 percent CI 0.42 to 0.81; 4 trials), raloxifene (RR 0.33; 95 percent CI 0.15 to 0.70; 2 trials), and aromatase inhibitors (RR 0.37; 95 percent CI 0.19 to 0.63; 2 trials) reduced ER+ invasive breast cancer, but not ER- invasive breast cancer, in placebo-controlled trials. Raloxifene and tamoxifen had similar effects on ER+ and ER- invasive breast cancer in the STAR head-to-head trial while on active treatment.

For noninvasive cancer, risks were reduced only in the NSABP P-1[61] (RR 0.63; 95 percent CI 0.45 to 0.89) and IBIS-I[59] (RR 0.65; 95 percent CI 0.43 to 1.00) tamoxifen trials. Meta-analyses of trials of tamoxifen, raloxifene, and aromatase inhibitors indicated no reduction in noninvasive cancer. The STAR head-to-head trial indicated no differences between raloxifene and tamoxifen in reducing noninvasive breast cancer (RR 1.22; 95 percent CI 0.95 to 1.59).

All-cause mortality was similar for women using raloxifene compared with tamoxifen; or tamoxifen, raloxifene, or aromatase inhibitors compared with placebo, although followup times in trials varied. Tamoxifen did not reduce breast cancer mortality compared with raloxifene or placebo, while few cases of breast cancer mortality were reported in placebo-controlled trials of raloxifene and aromatase inhibitors.

Tamoxifen and raloxifene had similar effects on fractures at multiple vertebral and nonvertebral sites in the STAR head-to-head trial. In placebo-controlled trials, raloxifene (RR 0.61; 95 percent

CI 0.53 to 0.73; 2 trials) reduced vertebral fractures, tamoxifen reduced nonvertebral fractures in the NSABP P-1 trial (RR 0.66; 95 percent CI 0.45 to 0.98), while the aromatase inhibitors had no effect on fractures.

Evidence

The ten randomized controlled trials described above and in **Table 3**, **Table 4**, and **Appendix B3** provide data for Key Question 2. Trials are reported in 32 publications, of which seven are new and 25 were cited in the 2013 review. The new studies include updated long-term results of the IBIS-I trial of tamoxifen,[59] a placebo-controlled trial of low-dose tamoxifen,[70] and placebo-controlled trials of anastrozole[17,88,89] and exemestane.[90,91] Results are summarized in **Tables 5** and **6**. The HOT trial of low-dose tamoxifen indicated no statistically significant differences in outcomes compared with placebo and was not included in the meta-analyses of tamoxifen trials discussed in this section.[70]

Invasive Breast Cancer

Tamoxifen vs. Raloxifene

Risk for invasive breast cancer was higher for raloxifene than tamoxifen in the STAR head-to-head trial (RR, 1.24; 95% CI, 1.05-1.47) after long-term followup, comparable with 5 (1 to 9) fewer events with tamoxifen per 1000 women over 5 years of use.[56] Differences for ER+ and ER- subtypes were not statistically significant.[54]

Tamoxifen vs. Placebo

Tamoxifen (20 mg/day) reduced invasive breast cancer in all four prevention trials compared with placebo using long-term followup data (7 to 16 years).[59,61,64,66] Reductions ranged from 20 to 43 percent with the biggest effect from the largest trial, the NSABP P-1 trial (RR 0.57; 95 percent CI 0.46 to 0.70).[61] Combined results indicate a summary RR of 0.69 (95 percent CI 0.59 to 0.84; 4 trials; **Figure 2**), comparable to 7 (4 to 12) fewer cases per 1000 women over 5 years of use. Tamoxifen reduced risks for ER+ (RR 0.58; 95 percent CI 0.42 to 0.81; 4 trials; **Figure 3**), but not ER- breast cancer (RR 1.18; 95 percent CI 0.93 to 1.53; 4 trials; **Figure 4**).[58,61,64,66]

Raloxifene vs. Placebo

Raloxifene reduced invasive breast cancer by 44 percent and 66 percent in the MORE[93] and RUTH[86] trials, respectively. Combined results indicate a RR of 0.44 (95 percent CI 0.24 to 0.80; 2 trials; **Figure 2**), comparable to 9 (3 to 15) fewer cases per 1000 women over 5 years of use. Raloxifene also reduced risk for ER+ (RR 0.33; 95 percent CI 0.15 to 0.70; 2 trials; **Figure 3**), but not ER- breast cancer (RR 1.25; 95 percent CI 0.60 to 2.58; 2 trials; **Figure 4**).

Aromatase Inhibitors vs. Placebo

Anastrozole[17] and exemestane[90] reduced invasive breast cancer compared with placebo (RR 0.45; 95 percent CI 0.26 to 0.70; 2 trials; **Figure 2**), comparable to 16 (8 to 24) fewer cases per

1000 women over 5 years of use. The aromatase inhibitors reduced risk for ER+ (RR 0.37; 95 percent CI 0.19 to 0.63; 2 trials; **Figure 3**), but not ER- breast cancer (RR 0.79; 95 percent CI 0.35 to 1.79; 2 trials; **Figure 4**) similar to tamoxifen and raloxifene.

Noninvasive Breast Cancer, Including Ductal Carcinoma In Situ

Tamoxifen vs. Raloxifene

STAR reported no statistically significant difference between tamoxifen and raloxifene for noninvasive breast cancer (RR 1.22; 95 percent CI 0.95 to 1.59), although the point estimate is favorable for tamoxifen.[56]

Tamoxifen vs. Placebo

All four tamoxifen trials reported noninvasive cancer outcomes, although specific definitions of noninvasive cancer varied between trials. Risks were reduced in the NSABP P-1[61] (RR 0.63; 95 percent CI 0.45 to 0.89) and IBIS-I[59] (RR 0.65; 95 percent CI 0.43 to 1.00) trials, but not in the Royal Marsden[64] and Italian[66] trials. When trials were combined, the risk of noninvasive breast cancer was not significantly reduced (RR 0.72; 95 percent CI 0.56 to 1.41; 4 trials; **Figure 5**).

Raloxifene vs. Placebo

Both the MORE[93] and RUTH[86] trials indicated increased point estimates for noninvasive breast cancer, although results were not statistically significant (RR 1.47; 95 percent CI 0.61 to 3.85; 2 trials; **Figure 5**).

Aromatase Inhibitors vs. Placebo

Risk for noninvasive breast cancer was reduced in the IBIS-II[17] trial (RR 0.30; 95 percent CI 0.12 to 0.74), but not in the MAP.3 trial.[90] When trials were combined, the risk of noninvasive breast cancer was not significantly reduced (RR 0.46; 95 percent CI 0.16 to 1.42; 2 trials; **Figure 5**).

Breast Cancer Mortality

Tamoxifen vs. Raloxifene

STAR reported no statistically significant difference between tamoxifen and raloxifene for breast cancer mortality (RR 0.36; 95 percent CI 0.08 to 1.21).[56]

Tamoxifen vs. Placebo

All four tamoxifen trials reported breast cancer specific mortality using long-term followup data (7 to 16 years).[58,61,64,66] None of these results were significantly different for tamoxifen versus placebo (RR 1.20; 95 percent CI 0.79 to 1.79; 4 trials; **Figure 6**).

Raloxifene vs. Placebo

In a review that reported results of MORE, CORE, and RUTH combined, there were two breast cancer deaths in the raloxifene group and none reported in the placebo group.[95]

Aromatase Inhibitors vs. Placebo

Very few breast cancer deaths occurred in the IBIS-II[17] and MAP.3[90] trials and no relative risks were reported.[90]

All-Cause Mortality

Tamoxifen vs. Raloxifene

All-cause mortality in the STAR trial was similar for women treated with tamoxifen or raloxifene (RR 0.84; 95 percent CI 0.70 to 1.02).[56]

Tamoxifen vs. Placebo

All four tamoxifen trials reported all-cause mortality using long-term followup data (7 to 16 years), and none were significantly different for tamoxifen compared with placebo (RR 1.07; 95 percent CI 0.91 to 1.23; 4 trials; **Figure 7**).[59,61,64,66]

Raloxifene vs. Placebo

All-cause mortality was similar between raloxifene and placebo in the RUTH and MORE trials (RR 0.90; 95 percent CI 0.63 to 1.05; 2 trials; **Figure 7**).[86,93]

Aromatase Inhibitors vs. Placebo

All-cause mortality was similar between aromatase inhibitors and placebo in the IBIS II[17] and MAP.3[90] trials (RR 1.02; 95 percent CI 0.58 to 1.82; 2 trials; **Figure 7**).

Osteoporotic Fractures

Tamoxifen vs. Raloxifene

Results of the STAR trial indicate no differences between tamoxifen and raloxifene for clinical vertebral (RR 0.98; 95 percent CI 0.65 to 1.46), hip, wrist, or total fractures, although all rates were slightly less for raloxifene.[54]

Tamoxifen vs. Placebo

The NSABP P-1,[61] IBIS-I,[58] and Royal Marsden[64] trials reported fractures as secondary outcomes. In the NSABP P-1 trial, tamoxifen did not significantly reduce clinical vertebral fractures compared with placebo (RR 0.75; 95 percent CI 0.48 to 1.15; **Figure 8**). Combined

outcomes of hip and wrist fractures were significantly reduced with tamoxifen compared with placebo (RR 0.66; 95 percent CI 0.45 to 0.98; **Figure 9**),[61] comparable to 3 (0.2 to 5) fewer cases per 1000 women over 5 years of use. Point estimates of RRs were also reduced for these fractures in the IBIS-I[58] and Royal Marsden trials,[64] however, results were not statistically significant.

Raloxifene vs. Placebo

The MORE trial recruited women with low BMD (T-score ≤ -2.5) and/or prior vertebral fractures.[76,84] At baseline, 37 percent of women had prior radiographically defined vertebral fractures. In MORE, raloxifene reduced radiographically defined vertebral fractures (RR 0.60; 95 percent CI 0.53 to 0.69),[76] but not nonvertebral or hip fractures compared with placebo.[84] Results were similar for women with and without prior vertebral fractures and for women using two different doses of raloxifene (60 or 120 mg/day).

The RUTH trial measured fractures as secondary outcomes.[86,96] RUTH reported reduced clinical vertebral fractures (RR 0.65; 95 percent CI 0.47 to 0.89), but not nonvertebral fractures (RR 0.96; 95 percent CI 0.84 to 1.10) among raloxifene users compared with placebo, consistent with results of MORE.[86] Combining results of MORE and RUTH indicates a vertebral fracture RR of 0.61 (95 percent CI 0.53 to 0.73; 2 trials; **Figure 8**) comparable to 7 (4 to 12) fewer cases per 1000 women over 5 years of use, and a nonvertebral fracture RR of 0.97 (0.86 to 1.12; 2 trials; **Figure 9**).

Aromatase Inhibitors vs. Placebo

The IBIS-II[17] and MAP.3[90] trials reported fractures as secondary outcomes. Clinical vertebral (RR 1.28; 95 percent CI 0.59 to 2.75; 2 trials; **Figure 8**) and nonvertebral fractures (RR 1.05; 95 percent CI 0.87 to 1.28; 2 trials; **Figure 9**) were not significantly reduced in either trial or when combined in meta-analysis.

Key Question 2a. Does the Effectiveness of Risk-Reducing Medications Vary by Timing of Initiation or Duration of Use?

Summary

Eight trials reported no significant differences in breast cancer outcomes by age, although age categories varied by trial. No studies specifically compared shorter versus longer regimens of medication use or initiation based on time since menopause. While most trials intended 5 years of use, mean exposure times varied across the trials from 3 to 5 years. Despite these variations, comparisons across similar medications indicate general consistency in risk reduction for invasive breast cancer.

Evidence

Timing of Initiation

The STAR,[54] IBIS-I,[58] Italian,[66] NSABP P-1,[61] RUTH,[87] MORE,[81] IBIS-II,[17] and MAP.3[90] trials reported no significant differences in breast cancer outcomes by age, although age categories varied by trial. Initiation based on time since menopause was not reported. In STAR, invasive breast cancer outcomes did not differ for women using raloxifene compared with tamoxifen in the three age categories evaluated (≤49; 50 to 59; ≥60 years), and results were similar across categories.[54] In the three tamoxifen placebo-controlled trials, combined risk estimates for invasive or all breast cancer outcomes were significantly reduced and similar for women age 50 years and younger (RR 0.65; 95 percent CI 0.54 to 0.85; 3 trials) and women over 50 years (RR 0.68; 95 percent CI 0.50 to 0.94; 3 trials; **Figure 10**).[17,58,61,66] The raloxifene placebo-controlled trials showed similar results for invasive breast cancer across different age categories (MORE <65 years; RUTH <60 years) that were not combined in a meta-analysis (**Figure 10**).[81,87] Risk reduction was similar regardless of age (<60; >60 years) in the aromatase inhibitor trials as well (**Figure 10**).[17,90]

Duration of Use

Although most trials intended 5 years of medication use, mean exposure times varied across the trials from 3 years in MAP.3[90] to 5 years in IBIS-I,[58] Royal Mardsen,[64] RUTH,[87] and IBIS-II.[17] No studies specifically compared shorter versus longer regimens. Despite these variations, comparisons across similar medications indicate general consistency in risk reduction for invasive breast cancer. Among the four tamoxifen placebo-controlled trials, risk reduction was similar regardless of exposures of 4 (NSABP P-1,[61] Italian[66]) or 5 years (IBIS-I,[58] Royal Marsden[64]). Notably, the tamoxifen trial with the shortest mean exposure time resulted in the largest risk reduction (NSABP P-1 RR 0.57; 95 percent CI 0.46 to 0.70).[61] Slight differences between risk reduction estimates across the trials may relate to additional factors leading to heterogeneity in addition to duration of use, especially variations in participant eligibility criteria.

Key Question 2b. Does the Effectiveness of Risk-Reducing Medications Persist Beyond Discontinuation of Use?

The IBIS-I[58] and Royal Marsden[64] trials provided results for invasive and ER+ breast cancer for both active treatment (mean duration 5 years) and posttreatment periods (median followup 13 and 16 years, respectively). These results indicate continued risk reduction after discontinuation of tamoxifen, providing point estimates of even larger reductions in invasive and ER+ breast cancer during the posttreatment period. For IBIS-I, risk reduction for invasive breast cancer was 0.74 (95 percent CI 0.60 to 0.93) for the 0 to 10 year followup period, and 0.70 (95 percent CI 0.52 to 0.95) for the greater than 10 year followup period,[17] although the difference between periods was not statistically significant.

Key Question 3. What Are the Harms of Using Medications to Reduce Risk for Primary Breast Cancer?

Summary

Raloxifene caused fewer thromboembolic events (RR 0.75; 95 percent CI 0.60 to 0.93) than tamoxifen in the STAR head-to-head trial, comparable to 4 (1 to 7) fewer events per 1000 women over 5 years of use. Tamoxifen (RR 1.93; 95 percent CI 1.33 to 2.68; 4 trials) and raloxifene (RR 1.56; 95 percent CI 1.11 to 2.60; 2 trials) increased thromboembolic events compared with placebo, while aromatase inhibitors did not. These estimates are comparable to 5 (2 to 9) more events per 1000 women over 5 years of use for tamoxifen and 7 (0.3 to 17) for raloxifene. Tamoxifen, raloxifene, and aromatase inhibitors did not increase coronary heart disease events or strokes.

In the STAR head-to-head trial, raloxifene caused fewer cases of endometrial cancer (RR 0.55; 95 percent CI 0.36 to 0.83) and endometrial hyperplasia (RR 0.19; 95 percent CI 0.12 to 0.29), and fewer hysterectomies (RR 0.45; 95 percent CI 0.37 to 0.54) than tamoxifen. Tamoxifen increased endometrial cancer compared with placebo (RR 2.25; 95 percent CI 1.17 to 4.41; 3 trials); while risks for endometrial cancer were not increased with raloxifene and aromatase inhibitors.

Raloxifene caused fewer cataracts (RR 0.80; 95 percent CI 0.72 to 0.95) and cataract surgeries (RR 0.79; 95 percent CI 0.70 to 0.90) than tamoxifen in the STAR head-to-head trial. Tamoxifen increased cataracts compared with placebo (RR 1.22; 95 percent CI 1.08 to 1.48; 3 trials). Raloxifene and aromatase inhibitors did not increase risks for cataracts or cataract surgery in trials.

In head-to-head comparisons, women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using tamoxifen had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms. Compared with placebo, the most commonly reported side effects for tamoxifen were hot flashes and other vasomotor symptoms, vaginal discharge, and other vaginal symptoms such as itching or dryness; for raloxifene, vasomotor symptoms and leg cramps; and for aromatase inhibitors, arthralgia, carpal tunnel syndrome, joint stiffness, vasomotor symptoms, dry eyes, and hypertension.

Evidence

A total of 19 studies (in 44 publications) met inclusion criteria for Key Question 3 including seven new publications and 37 cited in the prior review. The new studies include updated long-term results of the IBIS-I trial of tamoxifen,[59] a placebo-controlled trial of low-dose tamoxifen,[70] and placebo-controlled trials of anastrozole[17,88,89] and exemestane.[90,91] Details of studies are provided in **Table 3**, **Table 7**, and **Appendix B3**.

For tamoxifen, information on adverse effects was confined to the five large placebo controlled primary prevention trials,[57-66,68-70,97-100] and the STAR head-to-head trial.[54-56,101] No other

randomized controlled trials or observational studies evaluated adverse effects of tamoxifen in women without breast cancer. Trials ascertained and reported adverse effects in different ways, although most evaluated them at clinic visits using either self or staff administered questionnaires and checklists. The HOT trial of low-dose tamoxifen indicated no statistically significant differences in outcomes compared with placebo and was not included in the meta-analyses of tamoxifen trials discussed in this section.[70]

For raloxifene, adverse effects were reported from the two large placebo-controlled trials, MORE/CORE and RUTH,[71-87,96] the STAR head-to-head trial,[54-56] eight smaller trials (in 11 publications) evaluating either bone density, biochemical profiles, or fractures (**Appendix B3**),[102-112] and one observational study.[113] Of the smaller raloxifene trials, six reported thromboembolic events;[105-107,109,110,112] four uterine outcomes;[102,103,107,108] one urinary outcomes;[104] one cognitive function;[111] and none reported cardiovascular events. The most commonly reported adverse events were hot flashes and vasomotor symptoms reported in eight trials.[103,105,106,108-112] The one observational study evaluated the effect of raloxifene on vaginal bleeding and endometrial thickness.[113] These studies contribute little to the evaluation of harms because they involve so few women relative to the large primary prevention trials, although they are generally consistent with the results of the larger trials. Consequently, they were not included in the meta-analyses of raloxifene trials discussed in this section.

For anastrozole and exemestane, information on adverse effects was confined to the two large placebo-controlled primary prevention trials.[17,90] Similar to tamoxifen, no other RCT or observational studies evaluated adverse effects of aromatase inhibitors in women without breast cancer.

Thromboembolic Events

Tamoxifen vs. Raloxifene

In the STAR trial, raloxifene caused fewer thromboembolic events (DVT + PE) than tamoxifen (RR 0.75; 95 percent CI 0.60 to 0.93), comparable to 4 (1 to 7) fewer events per 1000 women over 5 years of use (**Table 5**).[56] Separate estimates for DVT (RR 0.72; 95 percent CI 0.54 to 0.95), and PE (RR 0.80; 95 percent CI 0.57 to 1.11) indicated reduced events with raloxifene.[56]

Tamoxifen vs. Placebo

The four tamoxifen prevention trials identified thromboembolic complications as an adverse effect of active treatment, although the definition of this outcome varied by trial.[58,62,64,69] All trials included DVT and PE outcomes, the IBIS-I trial also included superficial thrombophlebitis and retinal vein thrombosis,[58] and the Italian trial included visceral, retinal, and superficial thrombophlebitis.[69] All of these trials excluded women with either a history of prior thromboembolic events or one within 10 years prior to study enrollment.

Active treatment with tamoxifen increased composite measures of thromboembolic events in all four prevention trials resulting in a RR of 1.93 (95 percent CI 1.33 to 2.68; 4 trials; **Figure 11**),[58,62,64,69] comparable to 5 (2 to 9) more events with tamoxifen per 1000 women over 5 years

of use. The IBIS-I[59] and Royal Marsden[64] trials provided results for both active and posttreatment periods indicating no increased risk after discontinuation of active treatment (RR 0.98; 95 percent CI 0.48 to 1.80; 2 trials; **Figure 11**).

Only the NSABP P-1[62] and Italian trials[69] evaluated DVT and PE separately. In the NSABP P-1 trial, tamoxifen increased risks for PE (RR 3.01; 95 percent CI 1.15 to 9.27); but risk was not statistically significantly increased for DVT (RR 1.60; 95 percent CI 0. 91 to 2.86).[62] In the Italian trial, risks were not elevated.[69] Combining results, RRs are 2.69 (95 percent CI 0.54 to 8.13; 2 trials) for PE and 1.45 (95 percent CI 0.73 to 2.59; 2 trials) for DVT (**Figure 12**).

Tamoxifen increased superficial thrombophlebitis in the Italian (RR 1.96; 1.10 to 3.51)[69] and IBIS-I trials (RR 2.84; 95 percent CI 1.07 to 8.78),[58] with a combined RR of 2.14 (95 percent CI 1.17 to 4.42; 2 trials; **Figure 12**). The Italian trial also reported one retinal vein thrombosis in each arm of the trial and one visceral thrombosis in the placebo group.[69]

Raloxifene vs. Placebo

Raloxifene increased thromboembolic events in both the MORE (RR 2.10; 95 percent CI 1.20 to 3.80)[79] and RUTH (RR 1.44; 95 percent CI 1.06 to 1.95)[86] trials. Further analysis of the MORE trial by year of treatment indicated the highest risks during the first 2 years of therapy (RR ≥6 in years 1 and 2 vs. 0.9 in year 4).[79] Combining results of both trials in a meta-analysis results in a RR of 1.56 (95 percent CI 1.11 to 2.60; 2 trials; **Table 8** and **Figure 11**), comparable to 7 (0.3 to 17) more events with raloxifene per 1000 women over 5 years of use.[56] Both trials also reported elevated risks for PE (combined RR 2.11; 95 percent CI 0.82 to 6.12; 2 trials) and DVT separately (combined RR 1.66; 95 percent CI 0.79 to 5.14; 2 trials; **Figure 12**) that did not reach statistical significance.

Aromatase Inhibitors vs. Placebo

In contrast to tamoxifen and raloxifene, anastrozole[17] and exemestane[90] did not increase thromboembolic events compared with placebo (RR 1.24; 0.65 to 2.61; 2 trials; **Table 8** and **Figure 11**). The aromatase inhibitor trials did not report DVT or PE separately; risk for superficial thrombophlebitis was not increased in IBIS-II.[17]

Cardiovascular Events

Tamoxifen vs. Raloxifene

The STAR trial reported no differences between raloxifene and tamoxifen for a composite measure of ischemic coronary heart disease events (RR 1.10; 95 percent CI 0.85 to 1.43; **Table 5**).[54] Specific events, such as myocardial infarction, severe angina, and acute ischemic syndrome, were also not significantly different between medications.[54] Stroke and transient ischemic attacks were also similar for raloxifene and tamoxifen in STAR (RR 0.96; 95 percent CI 0.64 to 1.43 and 1.21; 95 percent CI 0.79 to 1.88, respectively; **Table 5**).[54]

Tamoxifen vs. Placebo

Although the four prevention trials evaluated cardiovascular events,[58,62,64,69] definitions of outcomes, and the quality and detail of reporting varied across trials. Only the Italian trial indicated that they excluded women with a history of cardiovascular disease other than stable angina.[69]

The NSABP P-1 trial provided the most detailed information on cardiovascular outcomes, although it did not explicitly describe how these events were defined or adjudicated.[62] In this trial, rates of a composite measure of coronary heart disease, myocardial infarction, acute coronary syndrome, and severe angina were similar for tamoxifen and placebo.[62] The IBIS-I trial reported no increase in a composite measure of "all cardiac problems," including myocardial infarction, angina and other cardiac problems, as well as myocardial infarction specifically for both active treatment and posttreatment periods.[58] Definitions for these outcomes were not provided. The Italian trial indicated no increase in myocardial infarction but identified an elevated rate of atrial fibrillation (RR 1.73; 95 percent CI 1.02 to 2.98) among women randomized to tamoxifen,[66] however, this is the only trial reporting atrial fibrillation specifically. The Royal Marsden trial reported no differences in "cardiovascular problems."[64]

Since tamoxifen showed no differential effects on multiple specific coronary heart disease outcomes, results of composite measures of coronary heart disease were combined in meta-analysis, resulting in a summary RR of 1.00 (95 percent CI 0.75 to 1.30; 4 trials; **Table 8** and **Figure 13**).[58,62,64,66] The combined RR for myocardial infarction specifically is 1.01 (95 percent CI 0.45 to 1.70; 3 trials; **Figure 14**).[58,62,66]

All four prevention trials evaluated stroke outcomes, and stroke was a predefined outcome in the IBIS-I trial. None of the trials indicated how stroke was defined or whether it was adjudicated. Tamoxifen did not increase stroke in either the active or posttreatment periods of the Royal Marsden[64] and IBIS-I[59] trials. The Italian[66] and NSABP P-1[62] trials reported elevated RRs for stroke during active treatment that did not reach statistical significance. In meta-analysis, the combined RR for stroke is 1.36 (95 percent CI 0.78 to 2.20; 4 trials; **Table 8** and **Figure 15**). After discontinuation of treatment in the IBIS-I[58] and Royal Marsden[64] trials, tamoxifen had no effect on stroke (RR 0.92; 95 percent CI 0.25 to 2.09; 2 trials; **Figure 15**).

Tamoxifen did not increase risk for transient ischemic attack in the trials evaluating this outcome (RR 0.77; 95 percent CI 0.42 to 1.42; 3 trials; **Figure 16**).[58,62,66]

Raloxifene vs. Placebo

Cardiovascular outcomes were extensively evaluated in the MORE and RUTH trials.[75,86] In the MORE trial, raloxifene did not increase risk for a composite measure of coronary heart disease, including myocardial infarction, coronary death, silent myocardial infarction, sudden death, unstable angina, coronary ischemia, and acute coronary syndrome (RR 0.92; 95 percent CI 0.66 to 1.27).[75] Results using a more narrow definition of coronary heart disease events, including coronary death, myocardial infarction, and unstable angina, were similar between raloxifene and placebo. Followup in the CORE trial also showed no relationship between the use of raloxifene

for 8 years and major cardiovascular events (HR 1.16; 95 percent CI 0.86 to 1.56) or coronary events (RR 1.22; 95 percent CI 0.82 to 1.83).[96] The RUTH trial was designed to determine whether raloxifene prevented coronary heart disease among women at high risk for heart disease or with existing heart disease. In RUTH, raloxifene showed no benefit in reducing composite coronary heart disease outcomes including coronary heart disease death, non-fatal myocardial infarction, and acute coronary syndrome (RR 0.95; 95 percent CI 0.84 to 1.07) or myocardial infarction specifically.[86] Combining coronary heart disease composite measures from MORE and RUTH provides a RR of 0.95 (95 percent CI 0.80 to 1.10; 2 trials; **Figure 13**).

Raloxifene did not increase risk of stroke in the MORE[75] or RUTH[86] trials (RR 1.04; 95 percent CI 0.64 to 1.36; 2 trials; **Figure 15**). In CORE, raloxifene did not increase risk of stroke after 8 years of followup.[96] None of the raloxifene trials evaluated transient ischemic attacks.

Aromatase Inhibitors vs. Placebo

Anastrozole[17] and exemestane[90] showed no differences compared with placebo for coronary heart disease events (combined RR 0.76; 95 percent CI 0.41 to 1.49; 2 trials; **Figure 13**) or stroke (combined RR 0.98; 95 percent CI 0.27 to 2.56; 2 trials; **Figure 15**).

Genitourinary Outcomes

Tamoxifen vs. Raloxifene

Raloxifene caused fewer cases of endometrial cancer (RR 0.55; 95 percent CI 0.36 to 0.83) than tamoxifen, comparable to 5 (2 to 9) more cases with tamoxifen per 1000 women over 5 years of use[56] (**Table 5**). Raloxifene was also associated with less endometrial hyperplasia (RR 0.16; 95 percent CI 0.09 to 0.29) and fewer hysterectomies (RR 0.44; 95 percent CI 0.35 to 0.56) than tamoxifen.

Tamoxifen vs. Placebo

Three prevention trials reported data on endometrial cancer;[58,62,64] the Italian trial included only women with prior hysterectomies.[65] Trials evaluated endometrial changes in different ways. The Royal Marsden trial evaluated endometrial thickness with ultrasound, although the protocol was not reported.[114] The IBIS-I trial included endometrial cancer as a predefined outcome. The NSABP P-1 trial included endometrial sampling prior to randomization for women enrolled later in the trial,[62] and monitored gynecologic conditions and procedures during the course of the trial.[99]

All three trials reported increased risks for endometrial cancer with tamoxifen, although only results from the NSABP P-1 trial reached statistical significance (RR 3.28; 95 percent CI 1.87 to 6.03).[61,62] Combining results from the three trials provides a RR of 2.25 (95 percent CI 1.17 to 4.41; 3 trials; **Table 8** and **Figure 17**), comparable to 4 (1 to 8) more events with tamoxifen per 1000 women over 5 years of use.[56,61,64]

In the NSABP P-1 trial, tamoxifen increased rates of endometrial hyperplasia without atypia (RR

2.06; 95 percent CI 1.64 to 2.60)[99] and other benign gynecologic conditions for both pre and postmenopausal women. For premenopausal women, these included endometrial polyps (RR 1.9; 95 percent CI 1.55 to 2.41), leiomyomas (RR 1.3; 95 percent CI 1.14 to 1.55), endometriosis (RR 1.9; 95 percent CI 1.35 to 2.70), and ovarian cysts (RR 1.5; 95 percent CI 1.2 to 1.78), as well as gynecologic surgical procedures including hysterectomy (RR 1.6; 95 percent CI 1.88 to 11.29).[99] For postmenopausal women, these included endometrial polyps (RR 2.4; 95 percent CI 1.65 to 3.24), leiomyomas (RR 1.4; 95 percent CI 1.04 to 1.80), endometriosis (RR 1.9; 95 percent CI 1.29 to 5.58), and gynecologic procedures (RR 2.2; 95 percent CI 1.6 to 3.13).[99] Tamoxifen had similar effects in the IBIS-I trial increasing rates of gynecologic procedures including hysterectomy, abnormal bleeding, endometrial polyps, and ovarian cysts.[57] Tamoxifen was associated with higher rates of hysterectomy than placebo in the Royal Marsden trial (177 vs. 96 per 1000 women years, respectively; $p<0.001$).[64] None of the tamoxifen trials reported rates of ovarian cancer.

Tamoxifen increased vaginal symptoms, including dryness, discharge, and other types, in all of the prevention trials.[58,62,64,66] Over twice as many women using tamoxifen versus placebo reported vaginal discharge ($p<0.001$) or vaginal symptoms ($p=0.008$) in the Royal Marsden trial.[64] In the NSABP P-1 trial, 13 percent of women taking placebo and 29 percent taking tamoxifen reported vaginal discharge that was at least moderately bothersome.[62] Tamoxifen increased risks for vaginal dryness (RR 1.14; 95 percent CI 0.97 to 1.34) and discharge (RR 3.44; 95 percent CI 2.9 to 4.09) in the Italian trial.[66] Tamoxifen increased symptoms of cystitis and incontinence in the Italian trial (RR 1.52; 95 percent CI 1.23 to 1.89),[66] but not similar symptoms during and after active treatment in the Royal Marsden trial.[64]

Raloxifene vs. Placebo

The raloxifene trials differed in their methods of ascertaining endometrial cancer outcomes. In the MORE trial, 17 clinical centers performed annual transvaginal ultrasonography in all participants with a uterus, carefully monitoring uterine pathology.[79] In the RUTH trial, endometrial cancer was determined on the basis of unsolicited reporting by the participant.[86] In neither trial were the risks of endometrial cancer elevated (combined RR 1.14; 95 percent CI 0.54 to 2.17; 2 trials; **Figure 17**).[79,86]

Raloxifene increased rates of endometrial cavity fluid, as determined by periodic transvaginal ultrasound in the MORE trial ($p<0.009$).[72] Raloxifene did not increase rates of ovarian cancer in RUTH, the only trial reporting this outcome.[86] Raloxifene increased urinary symptoms in the CORE trial (2.1 percent raloxifene vs. 1.2 percent placebo; $p=0.041$).[93]

Aromatase Inhibitors vs. Placebo

Anastrozole did not increase endometrial cancer compared with placebo (RR 0.60; 95 percent CI 0.09 to 3.07) in IBIS-II.[17] This outcome was not reported in MAP.3.[90]

Ophthalmologic Disorders

Tamoxifen vs. Raloxifene

In the STAR trial, women on raloxifene had fewer cataracts (RR 0.80; 95 percent CI 0.72 to 0.95) and cataract surgeries than women on tamoxifen, comparable to 15 (8 to 22) more cases with tamoxifen (**Table 5**).[56]

Tamoxifen vs. Placebo

All four prevention trials evaluated ocular outcomes,[58,62,64,66] although the Italian trial reported data on the composite category of "ophthalmologic diseases."[66] None of the trials described how women were evaluated for ophthalmologic outcomes. The NSABP P-1,[62] Royal Marsden,[64] and IBIS-I[58] trials reported increased cataracts with tamoxifen, although results for the IBIS-I trial did not reach statistical significance. The combined RR for cataracts is 1.22 (95 percent CI 1.08 to 1.48; 3 trials), comparable to 26 (5 to 50) more events with tamoxifen per 1000 women over 5 years of use (**Table 8** and **Figure 18**).[58,61,64] Cataract surgery was also more common with tamoxifen in the NSABP-1 trial during the initial (RR 1.57; 95 percent CI 1.16 to 2.14)[62] and followup (RR 1.21; 95 percent CI 1.10 to 1.34)[61] phases.

Raloxifene vs. Placebo

Raloxifene did not cause more cataracts than placebo in the MORE and RUTH trials (combined RR 0.93; 95 percent CI 0.82 to 1.06; 2 trials; **Figure 18**).[79,86]

Aromatase Inhibitors vs. Placebo

Anastrozole did not increase cataracts compared with placebo (RR 0.94; 95 percent CI 0.70 to 1.27) in IBIS-II.[17] This outcome was not reported in MAP.3.[90]

Other Adverse Effects

Tamoxifen vs. Raloxifene

In STAR, mean scores on quality of life instruments (health survey, depression scale, sexual questionnaire) did not differ between women using tamoxifen versus raloxifene, except sexual function was slightly better for tamoxifen (odds ratio [OR] 1.22 percent; 95 percent CI 1.01 to 1.46).[55] Women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using tamoxifen reported more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms.[55]

Tamoxifen vs. Placebo

Tamoxifen increased vasomotor symptoms in the four prevention trials.[58,62,64,66] In the Royal Marsden trial, 32 percent of women taking placebo reported hot flashes versus 48 percent of women taking tamoxifen ($p<0.001$).[64] In the NSABP P-1 trial, 29 percent of placebo and 46

percent of tamoxifen users reported hot flashes.[62] Hot flashes were also increased with tamoxifen in the Italian trial (RR 1.78; 95 percent CI 1.57 to 2.0).[66]

Two studies from the NSABP P-1 trial evaluated depression and other symptoms and identified no increased depression with tamoxifen.[60,115] Women randomized to tamoxifen reported 4 percent more sexual side effects than women randomized to placebo, although women on tamoxifen were slightly more sexually active (p=0.031).[115] Tamoxifen caused weight gain in the Royal Marsden trial,[64] but not in the Italian trial.[66] Tamoxifen did not increase headaches in the IBIS-I or Royal Marsden trials.[58,64]

Raloxifene vs. Placebo

Raloxifene increased vasomotor symptoms in both the MORE and RUTH trials.[72,86] In MORE, 7 percent of women using placebo, 11 percent using raloxifene 60 mg/day, and 12 percent using raloxifene 120 mg/day reported vasomotor symptoms (p<0.05).[72] In the RUTH trial, comprised of older women, the rates of vasomotor symptoms were lower in general than in MORE, but higher for women taking raloxifene compared with placebo (8.0 vs. 4.8 percent, respectively; p<0.001).[86]

Raloxifene caused leg cramps[72,86] and peripheral edema in the MORE (6.1 percent placebo vs. 7.1 percent raloxifene 60 mg vs. 7.9 percent raloxifene 120 mg; p=0.026)[72] and RUTH trials (12.1 percent placebo vs. 14.4 percent raloxifene; p<0.001).[86] Influenza syndrome symptoms occurred at a higher rate among women taking raloxifene in MORE (16.2 percent raloxifene 60 mg vs. 16.7 percent raloxifene 120 mg vs. 14 percent placebo),[72] but not in RUTH.[86] In RUTH, raloxifene caused joint pain, but had no effect on mood, depression, and anxiety symptoms.[86]

Aromatase Inhibitors vs. Placebo

Anastrozole is associated with increased moderate arthralgia, carpal tunnel syndrome, joint stiffness, vasomotor symptoms, dry eyes, and hypertension.[17] Exemestane is associated with fatigue, sweating, insomnia, and arthralgia.[90] Increased menopause-related vasomotor symptoms, sexual symptoms, and pain were more common with exemestane compared with placebo mainly during the first 6 months to 2 years of the study.[91]

Key Question 3a. Do Harms of Risk-Reducing Medications Vary by Timing of Initiation and/or Duration of Use?

The NSABP P-1 tamoxifen placebo-controlled trial suggested higher risks for DVT, PE, and stroke for women age 50 years and older compared with women younger than 50 years, although results were not statistically significant.[62] Results of the NSABP P-1 trial also indicated that the risk of thromboembolic events was elevated only during the first 3 years of tamoxifen use.[116] Age over 60 years was also an important risk factor for venous thrombosis in the Italian trial.[69] The NSABP P-1 trial found that endometrial cancer was more common among women age 50 years and older compared with women younger than 50 years (RR 4.01; 95 percent CI 1.70 to 10.90 vs. RR 1.21; 95 percent CI 0.41 to 3.60; respectively).[62] Initiation based on time since

menopause was not reported.

Key Question 3b. Do Harms of Risk-Reducing Medications Persist Beyond Discontinuation of Use?

Summary

While tamoxifen increased thromboembolic events compared with placebo in trials, risk returned to normal after discontinuation of tamoxifen in the two trials providing posttreatment data. Risk for endometrial cancer also diminishes after discontinuation of tamoxifen.

Evidence

Long-term followup of the IBIS-I[58] and Royal Marsden[64] trials provide results for thromboembolic outcomes for both active treatment (mean duration 5 and 8 years, respectively) and posttreatment periods (median followup 16 and 13 years, respectively). Similar followup results are not available for raloxifene or the aromatase inhibitors. During active treatment, tamoxifen significantly increased venous thromboembolic events compared with placebo (RR 1.93; 95 percent CI 1.33 to 2.68; 4 trials).[58,62,64,69] After discontinuation of tamoxifen, risk returned to normal (RR 0.98; 95 percent CI 0.48 to 1.80; 2 trials; **Figure 11**).[59]

The IBIS-I trial also provided long-term data on risk of endometrial cancer. During the 0 to 5 year followup period, risk increased for tamoxifen compared with placebo (RR 3.76; 95 percent CI 1.20 to 15.56), while risk declined after discontinuation (5 to 10 year followup RR 0.64; 95 percent CI 0.21 to 1.80; ≥10 year followup RR 1.40; 95 percent CI 0.38 to 5.61).[59]

Key Question 4. How Do Outcomes Vary by Population Subgroups?

Summary

Trials of risk-reducing medications provide data for specific population subgroups, although outcomes are predominantly confined to breast cancer and most estimates are not statistically significant because of smaller numbers of participants in the comparison groups. Subgroups are based on menopausal status, hysterectomy status, estrogen use, family history of breast cancer, BMI, history of breast abnormalities, predicted breast cancer risk,[54,61,87] and reproductive factors. No trials reported outcomes by race or ethnic groups.

Tamoxifen and raloxifene had similar effects on breast cancer outcomes regardless of family history of breast cancer in the head-to-head STAR trial. Tamoxifen reduced breast cancer outcomes in subgroups evaluated in placebo-controlled trials based on menopausal status, estrogen use, family history of breast cancer, and history of LCIS or atypical hyperplasia. In the NSABP P-1 trial, cancer rates were highest and risk reduction greatest among women in the

highest modified Gail model risk category and among women with prior atypical hyperplasia. Raloxifene reduces breast cancer outcomes in subgroups evaluated in placebo-controlled trials based on age at menarche, parity, age at first live birth, and BMI. Aromatase inhibitors have similar effects regardless of BMI or Gail risk score, but risk reduction was greatest for women with LCIS, ADH, or ALH compared with women without these breast lesions for anastrozole. Estimates from subgroups based on prior estrogen use, family history of breast cancer, and prior hysterectomy or oophorectomy were limited by smaller numbers of participants.

Evidence

Some trials of risk-reducing medications provide data for population subgroups, although outcomes are predominantly confined to breast cancer (all breast cancer, invasive, and ER+). Data are available for subgroups based on menopausal status,[58,64,66,81] hysterectomy status,[87] estrogen use,[58,61,66,81,87] family history of breast cancer,[54,61,66,81,87] BMI,[81,87,116] history of breast abnormalities,[54,61] predicted breast cancer risk,[54,61,87] and reproductive factors.[87] No trials reported outcomes by race or ethnic groups.

Menopausal Status

The IBIS-I[58] and Italian[66] tamoxifen trials evaluated breast cancer outcomes by menopausal status (pre vs. post). Point estimates indicated similar risk reduction with tamoxifen for both pre and postmenopausal women, although results were of borderline statistical significance for postmenopausal women in both trials (**Figure 19**). In the MORE/CORE studies, raloxifene had less effect on invasive cancer outcomes among women with estradiol levels less than 5 pmol/L (RR 0.52; 95 percent CI 0.26 to 1.06) than women with higher levels (5 to 10 pmol/L, RR 0.33; 95 percent CI 0.13 to 0.84; >10 pmol/L, RR 0.25; 95 percent CI 0.14 to 0.47).[81]

Hysterectomy Status

In RUTH, raloxifene did not significantly reduce risk for invasive cancer for women with prior hysterectomies or oophorectomies, while risk reduction was significant in women without these prior surgeries.[87] However, these differences could reflect the smaller numbers of women in the surgical subgroups.

Use of Exogenous Estrogen

The IBIS-I,[58] Royal Marsden,[64] Italian,[66] RUTH,[87] MORE,[81] IBIS-II,[17] and MAP.3[90] trials evaluated breast cancer outcomes by use of menopausal hormone therapy (estrogen with or without progestin). In the IBIS-I, Royal Marsden, and Italian tamoxifen trials, women were allowed to use hormones during the trial, and use rates varied from 14 percent in the Italian trial[66] to 40 percent in IBIS-I.[57] Women in the raloxifene and aromatase inhibitor trials were not allowed to use hormones during the trial and hormone use status represented prior use. For all medications, risk reduction improved for hormone nonusers compared with users (**Figure 20**). However, these findings may reflect the smaller numbers of hormone users in the trials.

Family History of Breast Cancer

The STAR,[54] Italian,[66] NSABP P-1,[61] RUTH,[87] and MORE[81] trials evaluated breast cancer outcomes by family history of breast cancer, most commonly referring to the number of first-degree relatives with breast cancer. In STAR, invasive breast cancer did not differ significantly for women using raloxifene compared with tamoxifen in the three family history categories evaluated (0 to 1; >2), and results were similar across categories.[54] Tamoxifen reduced invasive and all breast cancer for women without a family history in the two tamoxifen placebo-controlled trials, but had dissimilar results for women with a family history. In the NSABP P-1 trial, risk was similar for women in both family history groups;[61] while in the Italian trial,[66] risks were reduced for women with no family history and increased for women with family history, although results were not statistically significant (**Figure 21**). The raloxifene trials indicate similar significantly reduced risk estimates for women without family history and dissimilar results for women with family history (**Figure 21**).[81,87] These results may reflect the smaller numbers of women with positive family history for breast cancer in these trials rather than true medication effects.

Body Mass Index

The RUTH and MORE trials evaluated invasive breast cancer by BMI (≤25 vs. >25 kg/m^2).[81,87] While MORE indicated similar significantly reduced risk estimates for women with low and high BMI, RUTH reported lower risk estimates for women with high BMI (**Figure 22**), although estimates were not significantly different between women with low or high BMI. The aromatase inhibitors reduced invasive breast cancer in all BMI groups evaluated in the IBIS-II[17] and MAP.3[90] trials (BMI <25, 25-30, <30 kg/m^2; **Figure 22**).

A nested case-control analysis of data from the NSABP P-1 trial indicated that increased BMI is associated with higher risk of thromboembolic events among women in both the placebo and control groups (RR 3.69; 95 percent CI 2.09 to 6.65).[116]

History of Breast Abnormalities

Breast cancer risk reduction was similar regardless of history of LCIS or atypical hyperplasia for tamoxifen and raloxifene in STAR,[54] tamoxifen in IBIS-I,[58] and exemestane in MAP.3.[90] In NSABP P-1, tamoxifen reduced invasive cancer compared with placebo regardless of history of LCIS or atypical hyperplasia, although reduction was greatest among women with prior atypical hyperplasia (RR 0.25; 95 percent CI 0.10 to 0.52).[61] Risk reduction was also greatest for women with LCIS, ADH, or ALH for anastrozole in IBIS-II (HR 0.32; 95 percent CI 0.13 to 0.79).[17]

Predicted Breast Cancer Risk

In STAR, tamoxifen and raloxifene had similar effects on invasive breast cancer for women in all risk categories determined by the modified Gail model (5-year predicted risk ≤3.00; 3.01 to 5.00; ≥5.01).[54] In NSABP P-1, tamoxifen reduced risk for invasive cancer compared with placebo for women in all modified Gail model risk categories (5-year predicted risk ≤2.00; 2.01 to 3.00; 3.01 to 5.00, ≥5.01).[61] Cancer rates were highest and risk reduction greatest among

women in the highest risk group in this trial. In RUTH, raloxifene reduced risk for invasive cancer compared with placebo for women in all modified Gail model risk categories (5-year predicted risk ≤2.00; 2.01 to 3.00; 3.01 to 5.00), although results were statistically significant only for the large number of women in the lowest risk group.[87] Exemestane had similar effects in reducing invasive breast cancer for women with high and low Gail risk scores (≤2.0 percent; >2.0 percent).[90]

Reproductive Factors

Raloxifene reduced risk for invasive cancer regardless of age at menarche (<11, ≥11 years), parity (0, 1 to 2, ≤3), or age at first live birth (<20, ≥20 years) in the RUTH trial.[87]

Contextual Question 1. What Are Current Clinician and Patient Attitudes and Practices Regarding Use of Medications to Reduce Risk for Primary Breast Cancer?

Patient Perspectives

Three systematic reviews examined factors related to patient uptake of risk-reducing medications for breast cancer.[19,117,118] Although reviews included several of the same studies, each had a different focus. Two reviews used criteria to critically appraise included studies,[19,118] while the other did not.[117] Most studies were conducted in the United States or similar countries and are applicable to primary care practice.

Use of risk-reducing medications was 16.3 percent (95 percent CI 13.6 to s19.0, I^2 = 98.9 percent, p <0.001) in a meta-analysis of 26 studies of women at increased risk for breast cancer and without previous breast cancer diagnosis.[19] Uptake ranged from 0 to 54.9 percent, with significantly higher uptake in trials (25.2 percent; 95 percent CI 18.3 to 32.2, 13 trials) compared with non-trials (8.7 percent; 95 percent CI 6.6 to 10.9, 13 studies). Uptake was not affected by study location or type of medication (tamoxifen, raloxifene, aromatase inhibitors). Predictors of uptake include having an abnormal breast biopsy, receiving a physician recommendation for medication, and higher clinically assessed or perceived risk for breast cancer, although no factor was consistently associated with uptake across studies. Lower uptake was associated with concerns about adverse effects and contraindications with estrogen. No patient or demographic factors were associated with uptake across studies in this review.

Motivators and barriers to both hypothetical and actual uptake rates in women at increased risk for breast cancer were examined in a systematic review of 31 observational and qualitative studies (**Table 9**),[117] including 13 studies not included in the previous review.[19] Uptake was increased among women who had higher perceived risk of breast cancer, were more worried about breast cancer, had received a recommendation for use from their health care provider, and had a positive perception of drug effectiveness. Barriers to uptake included concerns about side effects, not wanting to take a medication regularly or as a preventive measure, and not wanting a daily reminder of their risk. Four studies demonstrated that women who were better informed of

the benefits and risks of tamoxifen were less likely to use it.[119-122] A study of *BRCA1/2* mutation carriers found that women preferred mastectomy or bilateral oophorectomy rather than tamoxifen to reduce their risks for breast cancer.[123]

A review of similar studies reported findings by hypothetical versus real decisionmaking about the use of risk-reducing medications.[118] In regression analysis controlling for intervention and breast cancer risk, studies of women making hypothetical decisions reported significantly higher mean uptake (24.7 percent, 9 studies) compared with studies of real decisions (14.8 percent, 5 studies), as defined by participants taking tamoxifen and raloxifene or being enrolled in the STAR trial (OR 1.65; 95 percent CI 1.26 to 2.16). Uptake varied widely in both settings (real, 0.5 to 51.2 percent; hypothetical, 5.7 to 60.0 percent). Notably, mean uptake for real decisions was skewed by one study with high uptake;[124] the mean rate of uptake among the remaining four studies was 5.8 percent. One study that reported both hypothetical and real uptake rates in the same cohort described rates of 5.7 percent compared with 0.5 percent, respectively.[119] Furthermore, studies that included an educational or decision-support intervention had lower mean uptake rates than those that did not in both real (4.1 vs. 31.0 percent) and hypothetical situations (11.7 vs. 31.2 percent). Studies of high-risk women making hypothetical decisions demonstrated lower uptake than studies that were not limited to high-risk women (22.3 vs. 29.6 percent, respectively).

Six recent observational studies not included in systematic reviews reported use of SERMS for breast cancer risk reduction among high-risk women ranging from 5.5 to 54.4 percent.[125-130] Similar to findings from systematic reviews, recurrent themes among individual studies included interest in risk reduction, but concerns about side effects. Notably, a study of high-risk women in Australia (median age 39 years) reported that 87 percent of eligible women (n=168; 95 percent premenopausal) declined therapy, and of these, 28 percent were not able to provide a specific reason for declining even when probed.[125]

The importance of risk in clinical decisionmaking is supported by several studies. In a study of high-risk women attending a breast center in the United States (n=189; 51.5 percent postmenopausal; 57.7 percent white), for every 1 percent increase in 5-year Gail risk score, use of risk-reducing medications (tamoxifen, raloxifene, aromatase inhibitors) increased by 17 percent (RR 1.17; 95 percent CI 1.03 to1.33).[129] Similarly, in a multivariable analysis of high-risk women attending a clinic in the United States (69.1 percent postmenopausal; 88.5 percent white), the odds of accepting risk-reducing medications increased 4 percent for every 1 percent increase in lifetime risk.[128] In addition, odds increased with diagnoses of LCIS (OR 7.65; 95 percent CI 1.48 to 39.5) and atypical hyperplasia (OR 2.76; 95 percent CI 1.37 to 5.54) in this cohort.[128] Risk reduction was also the most important factor in hypothetical decisions about medication use in a discrete-choice experiment among 622 women with *BRCA1/2* mutations in Australia.[127] However, few women who said that they would take a risk-reducing medication in theory (28 percent) followed through with this decision in practice (5.5 percent). Reasons for declining medications in this study included the lack of a physician recommendation (52 percent) and concerns for side effects (39 percent).

Provider recommendation was the most influential independent factor for risk-reducing medication uptake among predominantly postmenopausal women surveyed in one large U.S.

study (n=795; 88 percent white).[126] Other factors that increased the likelihood of use included a positive attitude toward taking risk-reducing SERMs compared with a negative attitude; higher levels of worry about breast cancer in the next 5 years; knowing others who had a good experience with a SERM; having considered taking a SERM in the past; having a positive perception of SERM users as being brave, smart, or healthy; having atypical hyperplasia on prior biopsy, and having a discussion of test results with a health care provider. Factors that decreased the likelihood of use included knowing someone with a bad experience with SERMs, and family members with thromboembolic conditions or endometrial cancer. Familial considerations were also important in a survey of 258 high-risk women in England (mean age 45.4 years; 96.5 percent white), in which women who had children were significantly more likely to have initiated tamoxifen for risk-reduction compared with their nulliparous counterparts (17.6 percent vs. 3.8 percent; OR 5.26; 95 percent CI 1.13 to 24.49).[130] Furthermore, qualitative themes in this study suggested that women not only considered their children when assessing the risks and benefits of risk-reducing medication, they were also influenced by their familial network's views and experience of taking medications more generally.

Few studies focused on decisionmaking about risk-reducing medications for breast cancer in the context of race/ethnicity. A study of racially diverse women (n=417; mean age 59 years; 28.5 percent white; 14.6 percent black; 20.6 percent Latina; 36.2 percent Asian) recruited from primary care community clinics found that willingness to take risk-reducing medications varied considerably, and was not based only on risk perception or understanding the risks and benefits of the medications.[131] After receiving brief information about tamoxifen, 40 percent of women reported they would be willing to take tamoxifen if considered high-risk. In this sample, characteristics of women more likely to take tamoxifen included being Asian, uninsured, having less than a high school education, higher numeracy, and greater breast cancer knowledge. However, women with higher knowledge about tamoxifen were less willing to use it for breast cancer risk reduction. In another study of 1094 racially diverse women surveyed from the general population (mean age 54 years; 79.1 percent white; 15.6 percent Hispanic; 15.3 percent black), interest in risk-reducing medications was low, even when presented in a scenario of maximum benefit with fewest risks.[132] Time needed to take the medication for effect and 5-year risk of breast cancer were the most important drivers of tradeoff preferences between different scenarios in this study.

Provider Perspectives

Prescribing risk-reducing medications is an uncommon practice among primary care physicians surveyed in three U.S. studies.[133-135] In a cross-sectional survey of 316 primary care physicians (34 percent with >20 years attending experience) at an academic health center, only 13 percent of physicians had ever prescribed a risk-reducing medication for breast cancer risk reduction in a high-risk patient.[134] In adjusted analysis, there were no significant differences in prescribing practices across specialties; internal medicine (8.5 percent), family medicine (8.0 percent) and gynecology (30 percent). Among prescribers, 65 percent had prescribed risk-reducing medications only one to five times.

Among 822 physicians (mean age 47 years; 92 percent board-certified) surveyed in California, only 10.6 percent had prescribed tamoxifen and 30.7 percent had prescribed raloxifene for breast

cancer risk reduction in the past year.[133] In this sample, obstetrician/gynecologists were significantly more likely than their internal medicine and family medicine counterparts to prescribe tamoxifen or raloxifene to reduce breast cancer risk (tamoxifen: 15 vs. 9.0 and 7.5 percent, p=0.01; raloxifene: 43.2 vs. 23.3 and 21.9 percent, p<0.001). Factors significantly associated with low prescribing included practice in Health Management Organization or academic settings, and physicians who were foreign-born. Raloxifene prescribing was more common among physicians who were female and had more breast cancer diagnoses per year in their practices; while tamoxifen prescribing was more common among physicians who had more breast cancer diagnoses per year in their practices and those with personal experience of breast cancer themselves or among relatives.

In an additional survey of U.S. primary care physicians (n=350; mean age 46 years), 27.4 percent had prescribed tamoxifen for breast cancer prevention in the past year.[135] However, the vast majority (85.4 percent) of prescribers had prescribed tamoxifen for breast cancer risk reduction only one to six times. Prescribers tended to be older, were less likely to be female, and more likely to have a family member with breast cancer.

Responses from physicians in U.S. studies described several key considerations when prescribing risk-reducing medications for breast cancer. These include comfort with medications, perceived evidence of benefit and harm, patient interest, and perceived role in prescribing risk-reducing medications. Among primary care physicians at an academic health center, the main reasons for not prescribing risk-reducing medications included discomfort with medications (79.8 percent), not identifying candidates for risk-reducing medications (60.7 percent), not enough time to discuss medications with patients (32.1 percent), and not believing that these medications were of benefit for most eligible women (10.7 percent).[134] Additionally, California-based physicians reported that factors relating to training and role (i.e. not my role to prescribe, not sufficiently trained/informed to prescribe) were barriers to prescribing tamoxifen and raloxifene for breast cancer risk reduction.[133] Patient factors (i.e. lack of patient interest, patient would not understand) were additional barriers.

In a cohort of U.S. primary care physicians, factors related to prescribing included having a family member with breast cancer, physician belief that benefits outweigh risks, considering it easy to determine eligibility, and patients asking for more information.[135] Employing hypothetical vignettes of a 55-year old woman with varied family history and hysterectomy status, physicians were more likely to recommend tamoxifen to a women who had a mother with breast cancer than to a woman with no family history of breast cancer; and also more likely to recommend tamoxifen if a women had a mother and a sister with breast cancer compared with only a mother with breast.[135]

Contextual Question 2. How Well Do Statistical Models Inform the Practice of Identifying and Treating Women With Medications to Reduce Risk for Breast Cancer?

One statistical model estimated the benefits and harms of tamoxifen and raloxifene for breast cancer risk reduction to identify candidates for therapy.[136] This model was used by the USPSTF

in its previous recommendation that set a 5-year breast cancer risk threshold of 3 percent to select candidates for medications to reduce breast cancer risk.[1] The model uses risk/benefit indices developed from weighting various health outcomes; estimating baseline incidence of health outcomes from breast cancer risk-reducing medication trials, the SEER, and the WHI; and calculating relative risk estimates for health outcomes in the presence of tamoxifen or raloxifene from the NSABP P-1 and STAR trials.

In the model, life-threatening events (invasive breast cancer, hip fracture, endometrial cancer, stroke, and PE) were weighted as 1.0; severe events (situ breast cancer and DVT) were weighted as 0.5; while other events (wrist and spine fractures and cataracts) were weighted as 0.0. The net benefit index was estimated using the expected number of life-threatening equivalent events in 5 years without risk-reducing medication in 10,000 women minus the expected number of life-threatening equivalent events if risk-reducing medication is used.

Results of the model suggested that the benefits and harms of tamoxifen and raloxifene for breast cancer risk reduction in postmenopausal women varied by age, race, risk for invasive breast cancer, and history of hysterectomy. These estimates were described in tables that could be used to guide decisionmaking [137] For women age 50 to 59 years with 5-year Gail model risks of 4.5 to 6.5 percent or higher, tamoxifen had moderate to strong net positive benefit in the model. However, for older women, harms outweighed benefits regardless of risk level. Raloxifene had strong net benefit for women age 50 to 59 years with 5-year risks of 3.5 percent or higher, and for older women with 5-year risks of 6.5 percent or higher. For postmenopausal black and Hispanic women with a uterus, raloxifene demonstrated a better risk/benefit profile compared with tamoxifen, similar to that seen in white women. Net benefit indices were typically larger in Hispanic compared with white women, and smaller in black versus white women. Also, over a 5-year period, postmenopausal women with a uterus had a better risk/benefit ratio for raloxifene than for tamoxifen, whereas for women without a uterus the risk/benefit ratio of raloxifene and tamoxifen was similar.

Chapter 4. Discussion

Summary of Review Findings

Table 10 summarizes the evidence reviewed for this update. New studies include updated long-term results from the placebo-controlled IBIS-I trial of tamoxifen[59] and two placebo-controlled trials of aromatase inhibitors, IBIS-II of anastrozole[17,88,89] and the MAP.3 trial of exemestane.[90,91] A new placebo-controlled tamoxifen trial, HOT, used a lower dose than the other trials (5 mg/day vs. 20 mg/day), and indicated no differences between tamoxifen and placebo.[70] In addition, four new studies expand existing risk prediction models with new data. These include two studies that added breast density to the Gail and Tyrer-Cuzick models;[33,51] a study modifying the Gail model for Asian Americans;[42] and a study that added benign breast disease to the BCSC model.[48]

Seventeen risk models have been evaluated in 24 studies including various modifications of the original Gail model, a model developed from the BCSC, the Tyrer-Cuzick model developed from the IBIS-I trial, models developed for specific populations (Italian, African American, Asian American), and others (Chlebowski, Rosner-Colditz). While most models share common risk factor variables, they differ by including additional variables and using different reference populations. Regardless of their complexity, models have low discriminatory accuracy in predicting the probability of breast cancer in an individual woman (c-statistics 0.55 to 0.65). Isolated studies demonstrating higher c-statistics were methodologically limited, or inconsistent with other studies of the same model. Models that include breast density, postmenopausal hormone use, and a more extensive family history minimally improve predictive estimates. Most models performed only slightly better than age alone as a risk predictor. No studies evaluated optimal ages or frequencies for risk assessment.

A modified 5-year Gail score of 1.67 percent or higher has been used as a risk threshold in primary prevention trials and in FDA approval of tamoxifen and raloxifene for reducing risk for primary breast cancer. However, thresholds based on tools with low discriminatory accuracy may not be clinically useful in selecting candidates for therapy. Most women age 60 and older without other risk factors would meet this threshold by age alone.

Tamoxifen, raloxifene, and aromatase inhibitors (anastrozole, exemestane) reduce risk for invasive breast cancer in women without preexisting breast cancer after 3 to 5 years of use. Placebo-controlled trials indicated clinically significant reductions for tamoxifen (RR 0.69; 95 percent CI 0.59 to 0.84; 7 fewer cases per 1000 women over 5 years of use [95 percent CI 4 to 12]; 4 trials), raloxifene (RR 0.44; 95 percent CI 0.24 to 0.80; 9 fewer cases [95 percent CI 3 to 15]; 2 trials), and aromatase inhibitors (RR 0.45; 95 percent CI 0.26 to 0.70; 16 fewer cases [95 percent CI 8 to 24]; 2 trials). Risk for invasive breast cancer was higher for raloxifene than tamoxifen in the STAR head-to-head trial (RR, 1.24; 95% CI, 1.05-1.47) after long-term followup. Effects did not differ by age of initiation (before or after age 50 years) or duration of use (3 to 5 years), although this effect was not directly compared. Risk reduction persisted at least 8 years after discontinuation in the two tamoxifen trials providing long-term followup data. All medications reduced ER+, but not ER- invasive breast cancer; tamoxifen reduced

noninvasive cancer in two trials. Breast-cancer specific and all-cause mortality were not reduced, although statistical power and followup of trials were insufficient for mortality outcomes.

In placebo-controlled trials, raloxifene (RR 0.61; 95 percent CI 0.53 to 0.73; 2 trials) reduced vertebral fractures; tamoxifen reduced nonvertebral fractures in the NSABP P-1 trial (RR 0.66; 95 percent CI 0.45 to 0.98); while the aromatase inhibitors had no effect on fractures. Tamoxifen and raloxifene had similar effects on fractures at multiple vertebral and nonvertebral sites in the STAR head-to-head trial.

In placebo-controlled trials, tamoxifen (RR 1.93; 95 percent CI 1.33 to 2.68; 4 trials) and raloxifene (RR 1.56; 95 percent CI 1.11 to 2.60; 2 trials) increased thromboembolic events while aromatase inhibitors did not. Raloxifene caused fewer thromboembolic events (RR 0.75; 95 percent CI 0.60 to 0.93) than tamoxifen in the STAR head-to-head trial. Tamoxifen, raloxifene, and aromatase inhibitors did not increase risk for coronary heart disease events or strokes.

Tamoxifen increased endometrial cancer compared with placebo (RR 2.25; 95 percent CI 1.17 to 4.41; 3 trials), while endometrial cancer were not increased with raloxifene and aromatase inhibitors. In the STAR head-to-head trial, raloxifene caused fewer cases of endometrial cancer (RR 0.55; 95 percent CI 0.36 to 0.83) and endometrial hyperplasia (RR 0.19; 95 percent CI 0.12 to 0.29), and fewer hysterectomies (RR 0.45; 95 percent CI 0.37 to 0.54) than tamoxifen. Tamoxifen increased cataracts (RR 1.22; 95 percent CI 1.08 to 1.48; 3 trials) and cataract surgery compared with placebo, while raloxifene and aromatase inhibitors did not. Risks for thromboembolic events and endometrial cancer with tamoxifen were higher for older compared with younger women (<50 or ≥50 years) and returned to normal after discontinuation. All medications caused nuisance effects that impact quality of life and could lead to discontinuation,[94,138] such as vasomotor or musculoskeletal symptoms, that varied by medication. Symptoms such as arthralgia often occurred at high rates in both treatment and placebo groups.

Risks for invasive cancer were reduced in all population subgroups evaluated based on menopausal status (pre and postmenopausal); family history of breast cancer; BMI categories; modified Gail model risk categories; and age at menarche, parity, or age at first live birth. Tamoxifen and anastrozole had more effects on women with previous breast lesions (LCIS, ADH, or ALH). Trials were not designed for subgroup comparisons and analysis of differences may be underpowered.

Regarding treatment choice, small descriptive studies indicate that women make decisions to use medications to reduce breast cancer risk based on their concern for adverse effects as well as their risks of breast cancer informed by an abnormal breast biopsy or risk assessment. They weigh their physicians' recommendations highly in their decisions. Physicians are more likely to prescribe medications if they believe benefits outweigh risks, they consider determining eligibility for medication is easy, and their patients ask for more information.

Limitations

While most discriminatory accuracy studies of risk assessment methods met criteria for good-

quality, others inadequately met criteria or methods were not well-described. These studies varied in size, study populations, and methods and results may not be directly comparable. Studies primarily reported c-statistics as accuracy measures, however, other approaches may be better suited for predicting relatively rare events such as breast cancer. For example, a longitudinal cohort study of 132,139 women in a breast registry found that women with 10-year risk for breast cancer of 8 percent or higher determined by the Tyrer-Cuzick model with and without breast density had statistically significantly elevated hazards ratios for breast cancer.[139] An approach targeting higher risk women would be relevant to identifying candidates for risk reducing medications in primary care practice.

Primary prevention trials are limited by clinical heterogeneity related to different medications, exposure durations, eligibility criteria, adherence, and ascertainment of outcomes. Trials were not designed for subgroup comparisons and analysis of differences may be underpowered. No trials compared timing and duration directly and long-term followup data were lacking from most trials.

The aromatase inhibitor prevention trials particularly lack followup data, however, these data are important to understand harms that have been demonstrated in trials of breast cancer treatment. While treatment trials do not meet inclusion criteria for this evidence review, they provide additional insight on potential harms that have not yet been adequately studied in prevention trials (**Appendix C3**). A multicenter RCT of 2,980 women with locally excised ER+ DCIS compared 1 mg/day of oral anastrozole with 20 mg/day of oral tamoxifen for 5 years with median followup of 7.2 years.[140] Results indicated increased fractures (9 percent anastrozole vs. 7 percent tamoxifen; OR 1.36, 95 percent CI 1.03 to 1.80) and stroke (OR 3.36, 95 percent CI 1.04 to 14.18) with anastrozole; increased venous thromboembolic events with tamoxifen; and no differences in coronary heart disease. A meta-analysis of individual-level data from 31,920 postmenopausal women with ER+ early breast cancer in treatment RCTs of aromatase inhibitors versus tamoxifen also indicated increased fractures for aromatase inhibitors, but showed no differences for coronary heart disease, venous thromboembolic events, or stroke outcomes.[141] Also, seven RCTs that compared extended aromatase inhibitor treatment with treatment followed by placebo or no treatment also showed increased fractures and stroke for extended aromatase inhibitors.[142] It is unclear how well the results of treatment trials of women with early breast cancer translate to women without cancer, particularly in the absence of true placebo comparison groups. For example, does the increase in fractures reflect the direct harm of aromatase inhibitors or the protective effect of tamoxifen?

Many issues outside the scope of this systematic review influence the decision to use medications to reduce risk of breast cancer. These issues need to be considered when applying the results of this review to health policy, insurance coverage, or patient decisions. Research is lacking in many essential areas including optimal doses, duration of use, persistence of effects after treatment, and outcomes in population subgroups. Data are lacking for nonwhite women, premenopausal women, and women with co-morbidities or taking additional medications for other indications.

Emerging Issues/Next Steps

Studies of emerging medications and other types of interventions to reduce breast cancer risk are under investigation. Ongoing NCI-funded studies of topical tamoxifen metabolites that maintain the preventive benefits of tamoxifen while decreasing systemic harms are in early phases. Research on mechanisms and intermediate markers would be useful. Well designed and powered head-to-head trials of different medications and regimens could contribute much needed information on outcomes, duration and timing of treatment, and identification of optimal candidates. Controlled trials of lifestyle modification interventions to reduce risk for breast cancer, such as weight loss and exercise, could also be explored. These interventions could be incorporated into comparative trials that also include medications.

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities

While priority populations were not explicitly excluded from studies in this systematic review, results were not reported specifically by population.

Future Research

The efficacy of tamoxifen, raloxifene, and aromatase inhibitors to reduce risk for invasive breast cancer has been demonstrated for women without preexisting cancer in RCTs, however, it is not clear which women in clinical practice would optimally benefit from risk reducing medications. Inclusion criteria for three of the placebo-controlled tamoxifen trials (NSABP P-1, IBIS, Royal Marsden), STAR, and the aromatase inhibitors included assessments of risk for breast cancer and only women meeting criteria were enrolled. However, for the other trials, no breast cancer risk assessment was performed and women of all risk groups were included. Despite these differences, trials of all the medications demonstrated efficacy in reducing invasive breast cancer. Further analysis comparing various subgroups, such as by age and risk factors, also indicated no major differences, suggesting that most women could benefit. Future research to determine the optimal candidates for these medications and the effects of risk reducing therapy on them would focus risk-reducing efforts. Applying these findings to clinical selection criteria would improve identification of candidates in practice settings.

No new studies and no studies in the 2013 review evaluated risk reducing medications specifically in *BRCA1/2* mutation carriers. However, mutation testing was not a common practice when most of the trials were conducted and it is not known how many *BRCA1/2* carriers were enrolled. The NSABP P-1 trial of tamoxifen described results for 288 mutation carriers who developed breast cancer during the trial.[143] Of the eight women with breast cancer who had *BRCA1* mutations, five received tamoxifen and three placebo (RR 1.67; 95 percent CI 0.32 to 10.70). Of 11 women with breast cancer and *BRCA2* mutations, three received tamoxifen and eight placebo (RR 0.38; 95 percent CI 0.06 to 1.56). Also, 86 percent (6/7) of women with *BRCA1* mutations had ER- breast cancer, and 67 percent (6/9) with *BRCA2* mutations had ER+.

Tamoxifen is only effective in reducing risk for ER+ breast cancer. Additional research on benefits and harms of risk reducing medications for *BRCA1/2* mutation carriers would guide their clinical decisions, particularly as mutation testing becomes more widespread. In addition to improving our understanding of optimal candidates for therapy, research is needed to further evaluate clinical risk instruments to identify women who are most likely to benefit from risk-reducing interventions. Current research indicates that prediction models that include breast density offer marginal improvement in diagnostic accuracy. Addition of other factors such as diet, alcohol use, physical activity, smoking status, and height offer little improvement in diagnostic accuracy. New methods need to build on current research findings, and research needs to expand beyond diagnostic accuracy studies. Methods need to be evaluated in relevant clinical settings and populations to determine their effectiveness in identifying high-risk women for clinical decisionmaking. Effective methods should also be validated in various racial and ethnic populations, among non-English speakers, and across multiple age groups. This work should include research regarding optimal methods for communicating risks and benefits to women[144] and lead to the development of effective patient decision aids.

The results of current trials indicate that adverse effects differ between medications and may drive decisions for risk-reducing medications as much or more than benefits. Further research to more clearly identify characteristics of individuals experiencing specific adverse effects would guide physicians and patients to regimens that cause the least harm. Strategies could be tested that optimize benefits and minimize harms. For example, the effects of adding aspirin in conjunction with tamoxifen or raloxifene could improve the benefit/harm balance for women by reducing risks of thromboembolic adverse events, stroke, and possibly breast cancer itself.[145] Further analysis of data from the MORE and RUTH trials could address this question because a large proportion of subjects were using aspirin in these trials. Future trials could evaluate the benefits and harms of using tamoxifen or raloxifene with an anticoagulant such as warfarin, heparin, or low molecular weight heparin.

Primary prevention trials need to be continually evaluated for long-term and unanticipated outcomes. Many questions remain regarding the persistence of beneficial and harmful effects of medications. For example, tamoxifen users in the NSABP P-1 trial who developed ER- breast cancer had shorter times to diagnosis and were more likely to be detected by routine mammograms than placebo users who developed ER- breast cancer.[146]

Evaluating the timing of medication use may also lead to effective clinical strategies. Results of current trials suggest that breast cancer risk reduction persists after treatment while some harms diminish. It is important to understand these changes over time. Use of medication for risk reduction at younger ages (45 to 55 years) could provide better long-term benefit and short-term harm for individuals at lower risk of thromboembolism or stroke than use at older ages (over age 60 years). Placebo-controlled trials of raloxifene in younger postmenopausal women selected for breast cancer risk would be more comparable to trials of other risk reducing medications and could provide more accurate estimates of benefits and harms for raloxifene. Also, further analysis of data from currently available trials could compare risk/benefit profiles for women of various ages and risk groups. Additional analysis could also indicate optimal treatment durations. Shortening treatment duration would reduce harms, but also could compromise efficacy.

Despite prior recommendations to identify women at high-risk for breast cancer and offer medications to reduce their risks,[1] and the availability of effective medications for this purpose, use is low in the United States.[20,21,135] Understanding this experience requires additional research regarding the attitudes of physicians toward recommending 3 to 5 years of medication therapy to reduce risk as well as attitudes of patients regarding receptivity to this recommendation and adherence over time. Research on the physician and patient decisionmaking process could identify factors important for selecting use of medications to reduce breast cancer risk beyond empirical risk and lead to the development of effective clinical decision aids.

Conclusions

Tamoxifen, raloxifene, and aromatase inhibitors reduce invasive breast cancer for women without preexisting breast cancer, but also cause adverse effects that vary by medication. Tamoxifen and raloxifene increase thromboembolic events and tamoxifen increases endometrial cancer and cataracts. Identifying candidates for therapy is complicated by risk stratification methods that demonstrate low accuracy.

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Figure 1. Analytic Framework

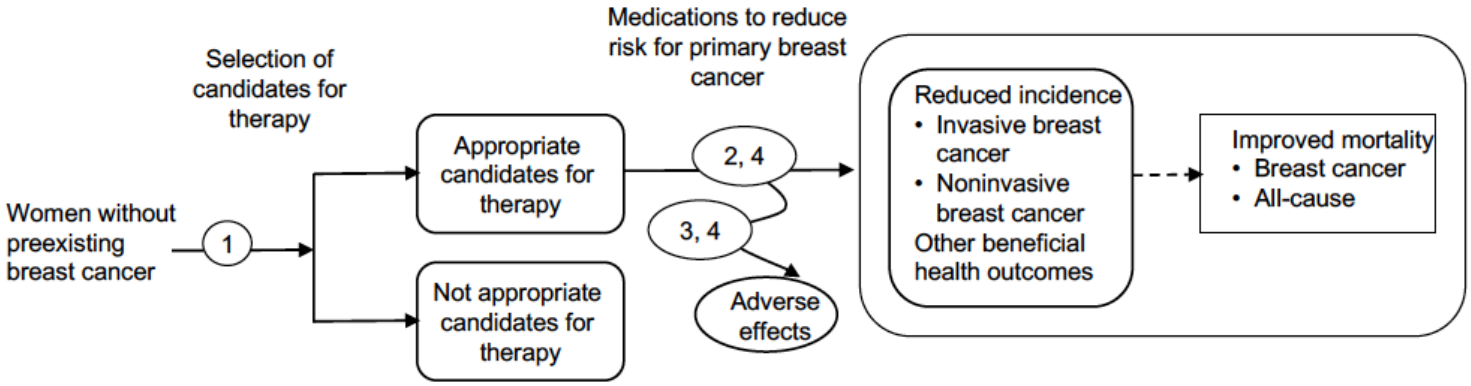
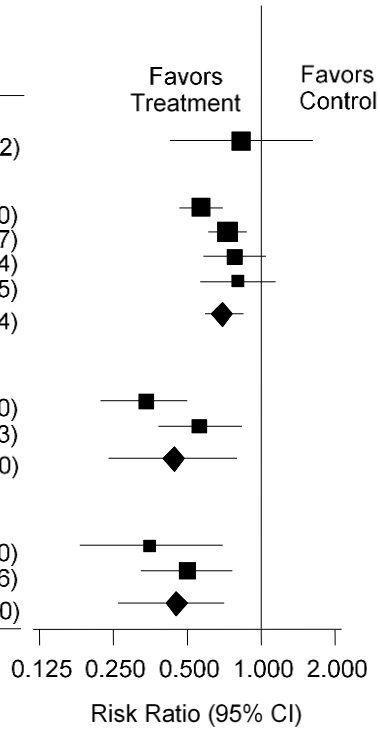


Figure 2. Meta-Analysis of Trials: Invasive Breast Cancer

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	Invasive Breast Cancer Treatment N	Invasive Breast Cancer Treatment Rate*	Invasive Breast Cancer Placebo N	Invasive Breast Cancer Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	18	3.13	22	3.78	0.83 (0.42 to 1.62)
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	145	3.59	250	6.29	0.57 (0.46 to 0.70)
IBIS-I[59]	3579	3575	5	16.0	214	3.86	289	5.29	0.73 (0.61 to 0.87)
Marsden[64]	1238	1233	5	13.2	82	4.80	104	6.10	0.78 (0.58 to 1.04)
Italian[66]	2700	2708	4†	11.2	53	1.77	66	2.21	0.80 (0.56 to 1.15)
Combined (Test of heterogeneity: Q=4.9, I^2=38.7%; df=3, p=0.180)									0.69 (0.59 to 0.84)
Raloxifene									
MORE/CORE[93]	5129	2576	4 or 8‡	5.4‡	40	1.40	58	4.20	0.34 (0.22 to 0.50)
RUTH[86]	5044	5057	5.1†	5.6	40	1.43	70	2.49	0.56 (0.38 to 0.83)
Combined (Test of heterogeneity: Q=3.0, I^2=66.4%; df=1, p=0.084)									0.44 (0.24 to 0.80)
Aromatase Inhibitor									
MAP.3[90]	2285	2275	5§	2.9	11	1.66	32	4.85	0.35 (0.18 to 0.70)
IBIS-II[17]	1920	1944	5	5	32	3.29	64	6.62	0.50 (0.32 to 0.76)
Combined (Test of heterogeneity: Q=0.8, I^2=0.0%; df=1, p=0.385)									0.45 (0.26 to 0.70)

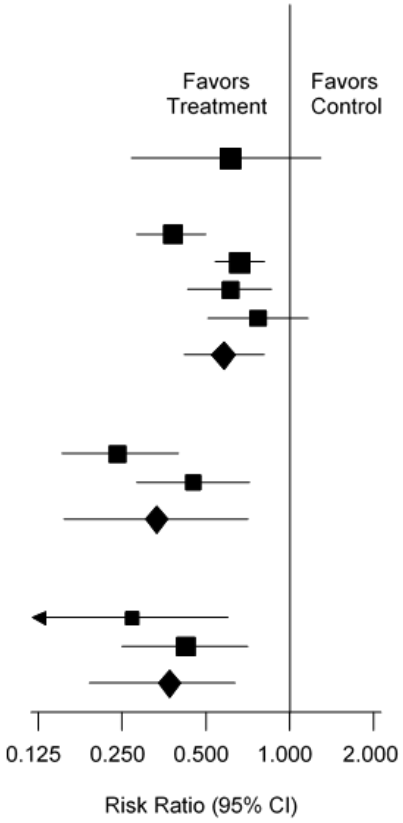


*Per 1,000 women-years.
†Veronesi, 2007 and Barrett-Connor, 2006 reported mean or median duration of the actual treatment period.
‡The analysis included data from both MORE and CORE. Participants from MORE had 4-year treatment and those who continued in CORE had 4 additional years of treatment. The total followup time is averaged over both MORE and CORE for 7705 participants.
§The intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular or toxicity event.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

Figure 3. Meta-Analysis of Trials: Estrogen Receptor Positive Breast Cancer

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	ER+ Breast Cancer Treatment N	ER+ Breast Cancer Treatment Rate*	ER+ Breast Cancer Placebo N	ER+ Breast Cancer Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	12	2.09	20	3.44	0.61 (0.27 to 1.30)
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	70	1.74	182	4.58	0.38 (0.28 to 0.50)
IBIS-I[59]	3579	3575	5	16.0	160	2.89	238	4.36	0.66 (0.54 to 0.81)
Marsden[64]	1238	1233	5	13.2	53	3.10	86	5.10	0.61 (0.43 to 0.86)
Italian[66]	2700	2708	4†	11.2	40	1.34	52	1.74	0.77 (0.51 to 1.16)
Combined (Test of heterogeneity: Q=11.6, I^2=74.2%; df=3, p=0.009)									0.58 (0.42 to 0.81)
Raloxifene									
MORE/CORE[93]	5129	2576	4 or 8‡	5.4‡	22	0.80	44	3.20	0.24 (0.15 to 0.40)
RUTH[86]	5044	5057	5.1†	5.6	25	0.89	55	1.96	0.45 (0.28 to 0.72)
Combined (Test of heterogeneity: Q=3.3, I^2=69.5%; df=1, p=0.070)									0.33 (0.15 to 0.70)
Aromatase Inhibitor									
MAP.3[90]	2285	2275	5§	2.9	7	1.06	27	4.09	0.27 (0.12 to 0.60)
IBIS-II[17]	1920	1944	5	5	20	2.06	47	4.86	0.42 (0.25 to 0.71)
Combined (Test of heterogeneity: Q=0.8, I^2=0.0%; df=1, p=0.367)									0.37 (0.19 to 0.63)

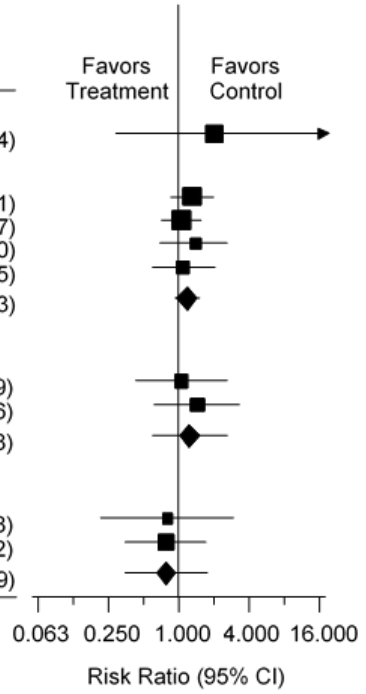


*Per 1,000 women-years.
†Veronesi, 2007 and Barrett-Connor, 2006 reported mean or median duration of the actual treatment period.
‡The analysis included data from both MORE and CORE. Participants from MORE had 4-year treatment and those who continued in CORE had 4 additional years of treatment. The total followup time is averaged over both MORE and CORE for 7705 participants.
§The intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular or toxicity event.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; ER+=estrogen receptor positive; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

Figure 4. Meta-Analysis of Trials: Estrogen Receptor Negative Breast Cancer

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	ER- Breast Cancer Treatment N	ER- Breast Cancer Treatment Rate*	ER- Breast Cancer Placebo N	ER- Breast Cancer Placebo Rate*	Risk Ratio
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	4	0.70	2	0.34	2.02 (0.29 to 22.4)
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	56	1.39	42	1.06	1.31 (0.86 to 2.01)
IBIS-I[59]	3579	3575	5	16.0	50	0.90	47	0.86	1.05 (0.71 to 1.57)
Marsden[64]	1238	1233	5	13.2	24	1.40	17	1.00	1.40 (0.70 to 2.60)
Italian[66]	2700	2708	4†	11.2	21	0.70	19	0.64	1.10 (0.59 to 2.05)
Combined (Test of heterogeneity: Q=0.9, I^2 = 0.0%; df=3, p=0.832)									1.18 (0.93 to 1.53)
Raloxifene									
MORE/CORE[93]	5129	2576	4 or 8‡	5.4‡	15	0.53	7	0.51	1.06 (0.43 to 2.59)
RUTH[86]	5044	5057	5.1†	5.6	13	0.46	9	0.32	1.44 (0.61 to 3.36)
Combined (Test of heterogeneity: Q=0.2, I^2=0.0%; df=1, p=0.628)									1.25 (0.60 to 2.58)
Aromatase Inhibitor									
MAP.3[90]	2285	2275	5§	2.9	4	0.60	5	0.76	0.80 (0.21 to 2.98)
IBIS-II[17]	1920	1944	5	5	11	1.13	14	1.45	0.78 (0.35 to 1.72)
Combined (Test of heterogeneity: Q=0.0, I^2=0.0%; df=1, p=0.974)									0.79 (0.35 to 1.79)

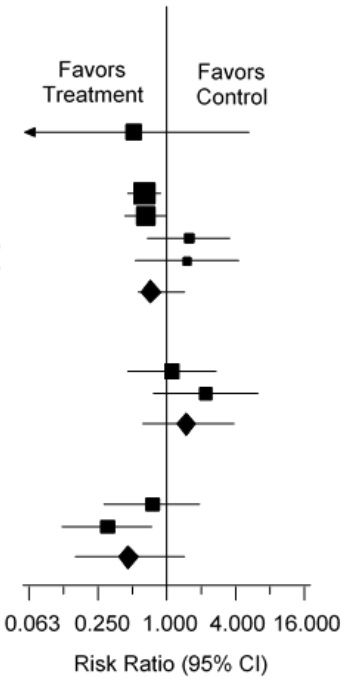


*Per 1,000 women-years.
†Veronesi, 2007 and Barrett-Connor, 2006 reported mean or median duration of the actual treatment period.
‡The analysis included data from both MORE and CORE. Participants from MORE had 4-year treatment and those who continued in CORE had 4 additional years of treatment. The total followup time is averaged over both MORE and CORE for 7705 participants.
§The intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular or toxicity event.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; ER-=estrogen receptor negative; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

Figure 5. Meta-Analysis of Trials: Noninvasive Breast Cancer

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	Non-invasive Breast Cancer Treatment N	Non-invasive Breast Cancer Treatment Rate*	Non-invasive Breast Cancer Placebo N	Non-invasive Breast Cancer Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	1	0.17	2	0.34	0.51 (0.05 to 5.33)
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	60	1.47	93	2.29	0.63 (0.45 to 0.89)
IBIS-I[59]	3579	3575	5	16.0	35	0.63	53	0.97	0.65 (0.43 to 1.00)
Marsden[64]	1238	1233	5	13.2	14	0.80	9	0.50	1.55 (0.67 to 3.57)
Italian[66]	2700	2708	4†	11.2	9	0.30	6	0.20	1.50 (0.53 to 4.20)
Combined (Test of heterogeneity: Q=6.0, I^2=49.8%; df=3, p=0.113)									0.72 (0.56 to 1.41)
Raloxifene									
MORE/CORE[93]	5129	2576	4 or 8‡	5.4‡	16	0.56	7	0.51	1.12 (0.46 to 2.73)
RUTH[86]	5044	5057	5.1	5.6	11	0.39	5	0.18	2.17 (0.75 to 6.24)
Combined (Test of heterogeneity: Q=0.9, I^2=0.0%; df=1, p=0.349)									1.47 (0.61 to 3.85)
Aromatase Inhibitor									
MAP.3[90]	2285	2275	5§	2.9	9	1.36	12‖	1.82	0.75 (0.28 to 1.93)
IBIS-II[17]	1920	1944	5	5	6	0.62	20	2.07	0.30 (0.12 to 0.74)
Combined (Test of heterogeneity: Q=1.8, I^2=44.7%; d =1, p=0.179)									0.46 (0.16 to 1.42)

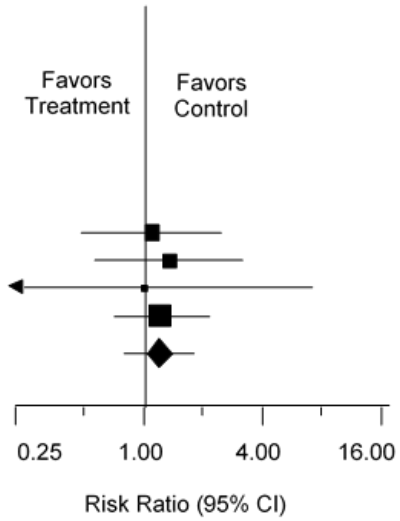


*Per 1,000 women-years.
†Veronesi, 2007 and Barrett-Connor, 2006 reported mean or median duration of the actual treatment period.
‡The analysis included data from both MORE and CORE. Participants from MORE had 4-year treatment and those who continued in CORE had 4 additional years of treatment.
‖The total followup time is averaged over both MORE and CORE for 7705 participants.
§The intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular or toxicity event.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

Figure 6. Meta-Analysis of Trials: Breast Cancer Mortality

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	Breast Cancer Mortality Treatment N	Treatment Rate*	Placebo N	Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	1	0.17	0	0.00	---
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	12	0.29	11	0.27	1.09 (0.48 to 2.46)
Marsden[64]	1238	1233	5	13.2	12	0.70	9	0.53	1.33 (0.56 to 3.16)
Italian[66]	2700	2708	4†	11.2	2	0.07	2	0.07	1.00 (0.14 to 7.10)
IBIS-I[59]	3579	3575	5	16.0	31	0.56	26	0.47	1.21 (0.70 to 2.12)
Combined	(Test of heterogeneity: Q= 0.1, I^2= 0.0%; df =3, p=0.987)								1.20 (0.79 to 1.79)

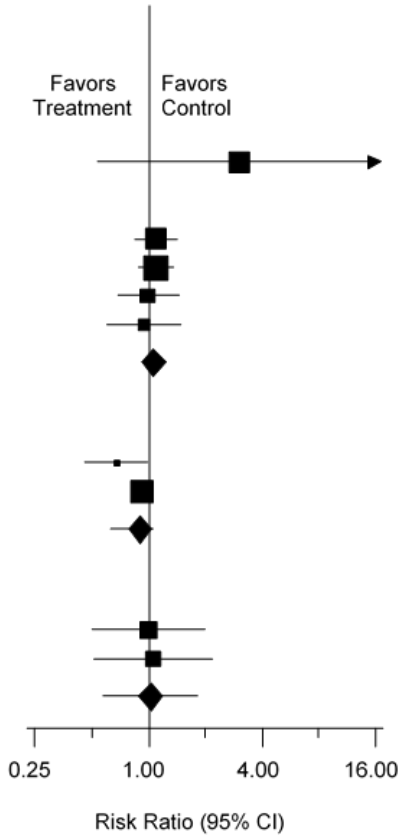


*Per 1,000 women-years.
†Veronesi, 2007 reported mean or median duration of the actual treatment period.

Abbreviations: CI=confidence interval; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study.

Figure 7. Meta-Analysis of Trials: All-cause Mortality

Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	All-Cause Mortality Treatment N	All-Cause Mortality Treatment Rate*	All-Cause Mortality Placebo N	All-Cause Mortality Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	6	1.04	2	0.34	3.03 (0.54 to 30.7)
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	126	3.08	114	2.80	1.10 (0.85 to 1.43)
IBIS-I[59]	3579	3575	5	16.0	182	3.28	166	3.04	1.10 (0.88 to 1.37)
Marsden[64]	1238	1233	5	13.2	54	3.15	54	3.15	0.99 (0.68 to 1.44)
Italian[66]	2700	2708	4†	11.2	36	1.46	38	1.54	0.95 (0.60 to 1.49)
Combined	(Test of heterogeneity: Q= 0.5, I^2=0.0%; df=3, p=0.912)								1.07 (0.91 to 1.23)
Raloxifene									
MORE/CORE[79,87]	2557	2576	4 or 8‡	5.4‡	45	NR	65	NR	0.68 (0.46 to 0.99)
RUTH[86]	5044	5057	5.1†	5.6	554	2.07	595	2.25	0.92 (0.82 to 1.03)
Combined	(Test of heterogeneity: Q=2.2, I^2=54.5%; df=1, p=0.138)								0.90 (0.63 to 1.05)
Aromatase Inhibitor									
MAP.3[90]	2285	2275	5§	2.9	19	2.87	19	0.88	1.00 (0.50 to 1.99)
IBIS-II[17]	1920	1944	5	5	18	1.85	17	0.76	1.05 (0.51 to 2.17)
Combined	(Test of heterogeneity: Q=0.0, I^2=0.0%; df=1, p=0.924)								1.02 (0.58 to 1.82)

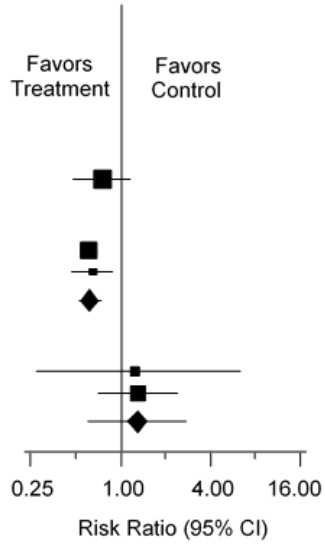


*Per 1,000 women-years.
†Veronesi, 2007 and Barrett-Connor, 2006 reported mean or median duration of the actual treatment period.
‡The analysis included a subset of data from both MORE and CORE. Participants from MORE had 4-year treatment and those who continued in CORE had 4 additional years of treatment. The total followup time is averaged over both MORE and CORE for 7705 participants.
§The intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular or toxicity event.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

Figure 8. Meta-Analysis of Trials: Vertebral Fractures

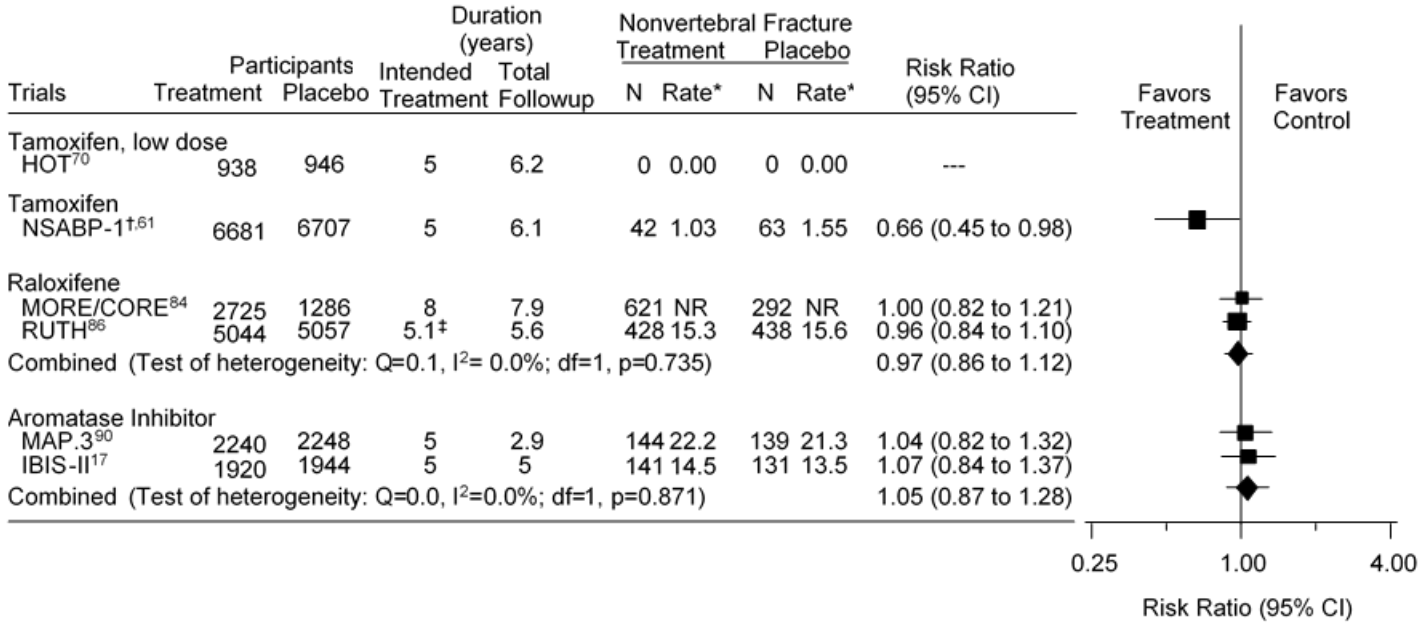
Trials	Participants Treatment	Participants Placebo	Duration (years) Intended Treatment	Duration (years) Total Followup	Vertebral Fracture Treatment N	Vertebral Fracture Treatment Rate*	Vertebral Fracture Placebo N	Vertebral Fracture Placebo Rate*	Risk Ratio (95% CI)
Tamoxifen, low dose									
HOT[70]	938	946	5	6.2	0	0.00	0	0.00	---
Tamoxifen									
NSABP-1[61]	6681	6707	5	6.1	40	0.98	53	1.31	0.75 (0.48 to 1.15)
Raloxifene									
MORE/CORE[76]	4536	2292	4.0	NR	NR	NR	NR	NR	0.60 (0.53 to 0.69)
RUTH[86]	5044	5057	5.1†	5.6	64	2.28	97	3.45	0.65 (0.47 to 0.89)
Combined (Test of heterogeneity: Q=0.2, I^2=0.0%; df=1, p=0.676)									0.61 (0.53 to 0.73)
Aromatase Inhibitor									
MAP.3[90]	2240	2248	5	2.9	5	0.77	4	0.61	1.25 (0.25 to 6.32)
IBIS-II‡[17]	1920	1944	5	5	23	2.36	18	1.86	1.29 (0.70 to 2.39)
Combined (Test of heterogeneity: Q=0.0, I^2=0.0%; df=1, p=0.971)									1.28 (0.59 to 2.75)



*Per 1,000 women-years.
†Barrett-Connor, 2006 reported median duration of the actual treatment period.
‡Included fractures from rib, spine, or collarbone.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

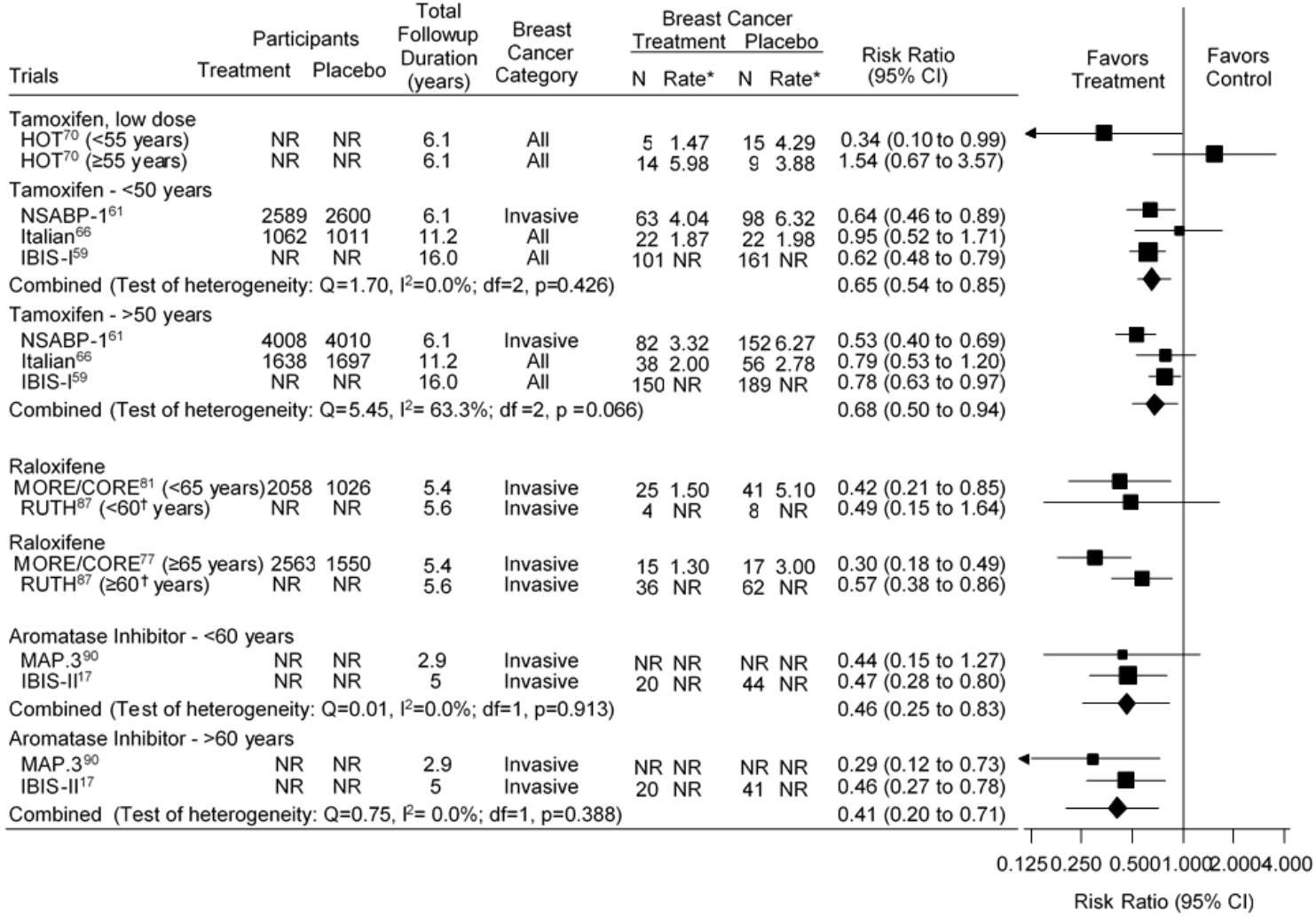
Figure 9. Meta-Analysis of Trials: Nonvertebral Fractures



*Per 1,000 women-years.
†Only hip and radius fractures were included.
‡Barrett-Connor, 2006 reported median duration of the actual treatment period.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

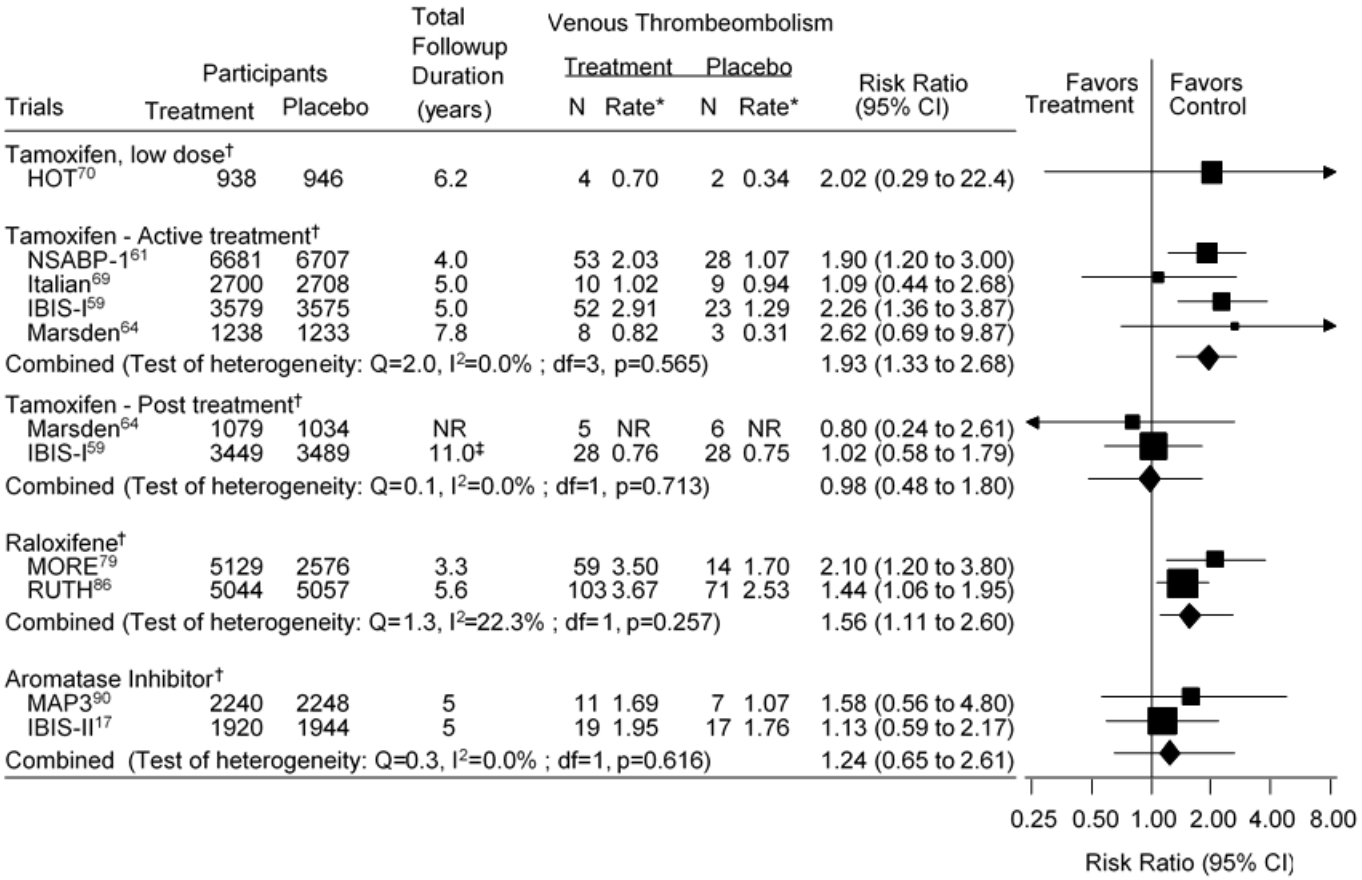
Figure 10. Meta-Analysis of Trials: Timing of Initiation



*Per 1,000 women-years.
†For Grady 2008, total n=1670 for age < 60 years and 8431 for age ≥60 years.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

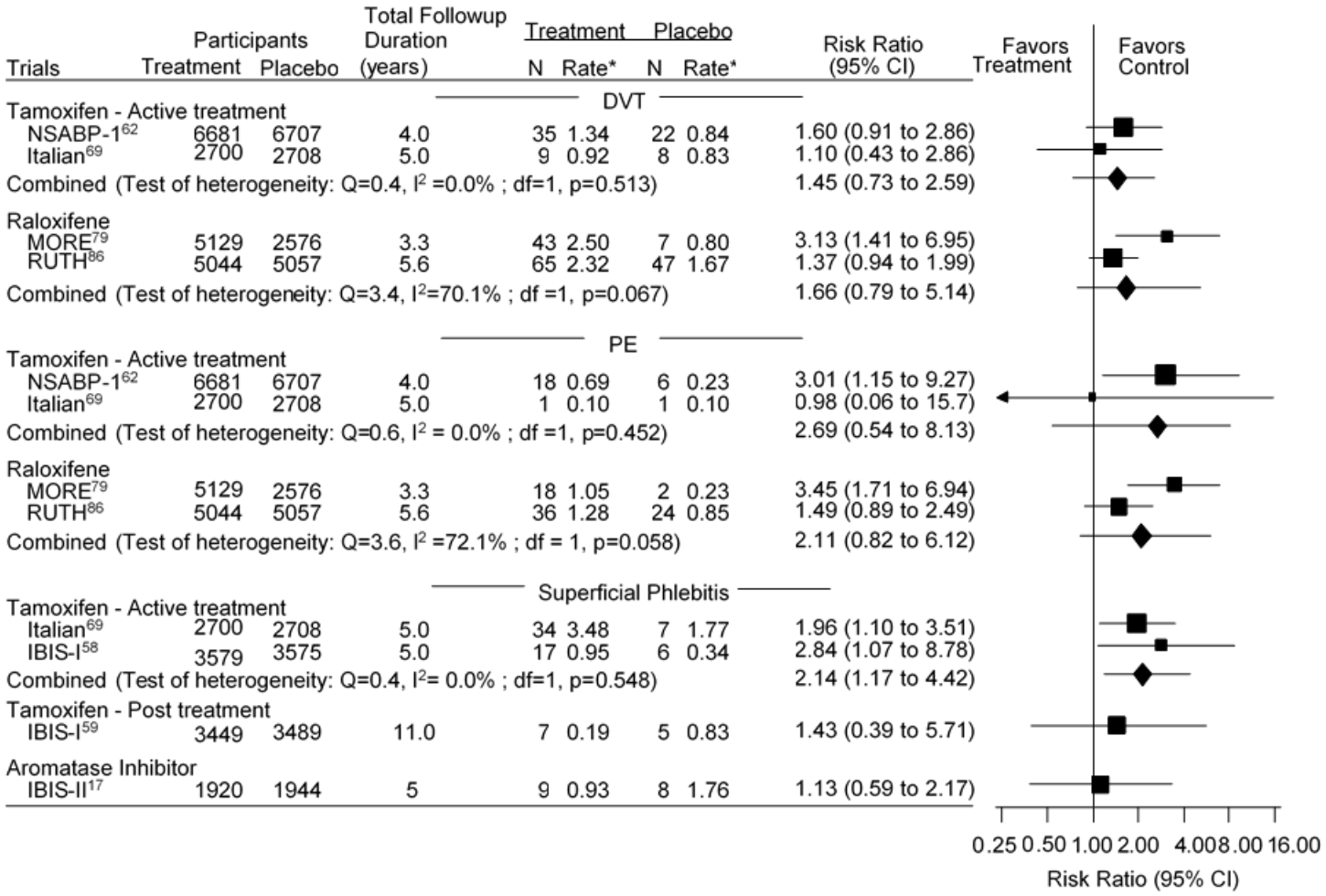
Figure 11. Meta-Analysis of Trials: Venous Thromboembolism



*Per 1,000 women-years.
†For tamoxifen and IBIS-II trials, venous thromboembolic events include deep-vein thrombosis (DVT) and pulmonary embolism (PE) only. For other trials, other events such as retinal vein thrombosis may be included, depending on the reported overall category.
‡Events were reported from at least 3 months after treatment was stopped until the end of followup.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; PE=pulmonary embolism; RUTH=Raloxifene Use for the Heart.

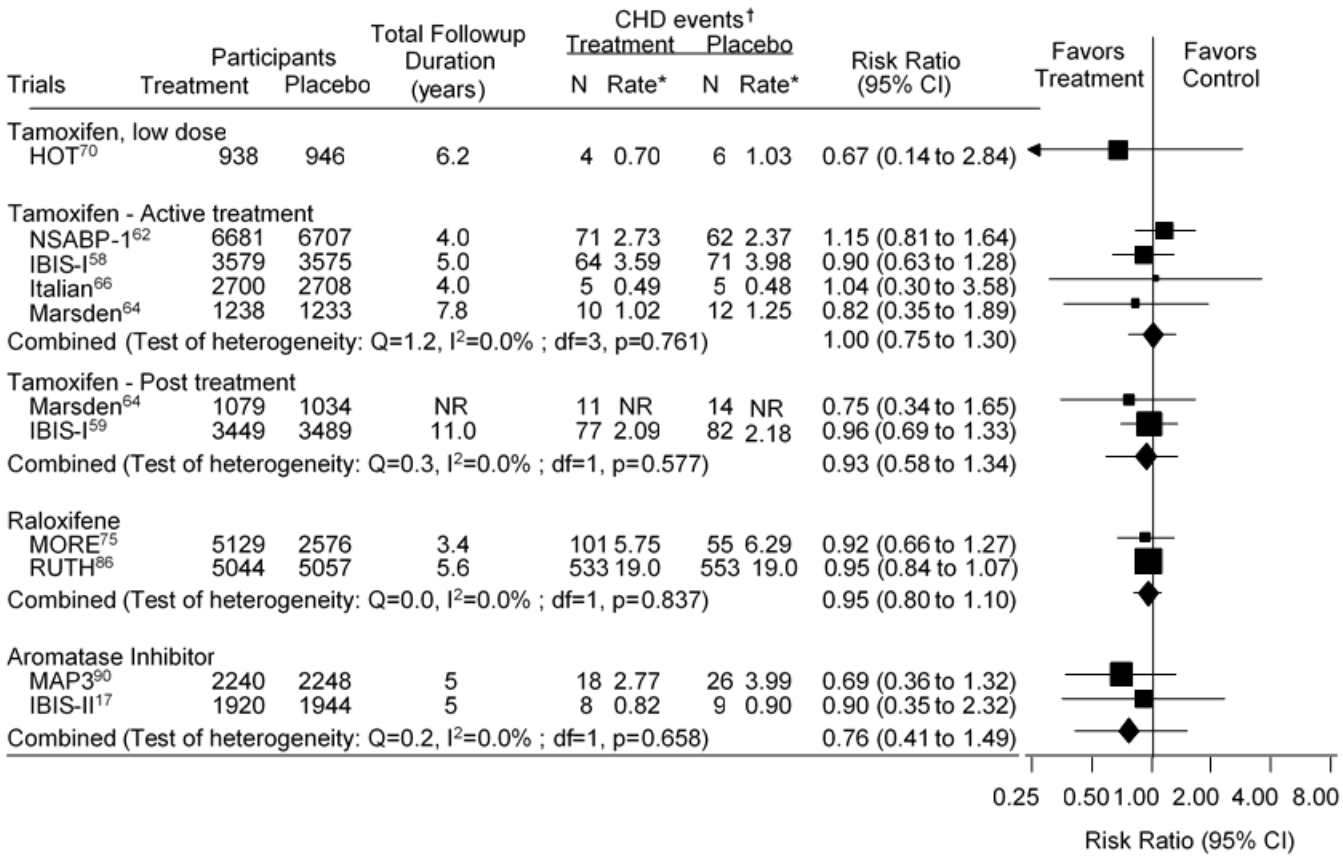
Figure 12. Meta-Analysis of Trials: Deep Vein Thrombosis, Pulmonary Embolism, and Superficial Phlebitis



*Per 1,000 women-years.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; PE=pulmonary embolism; RUTH=Raloxifene Use for the Heart.

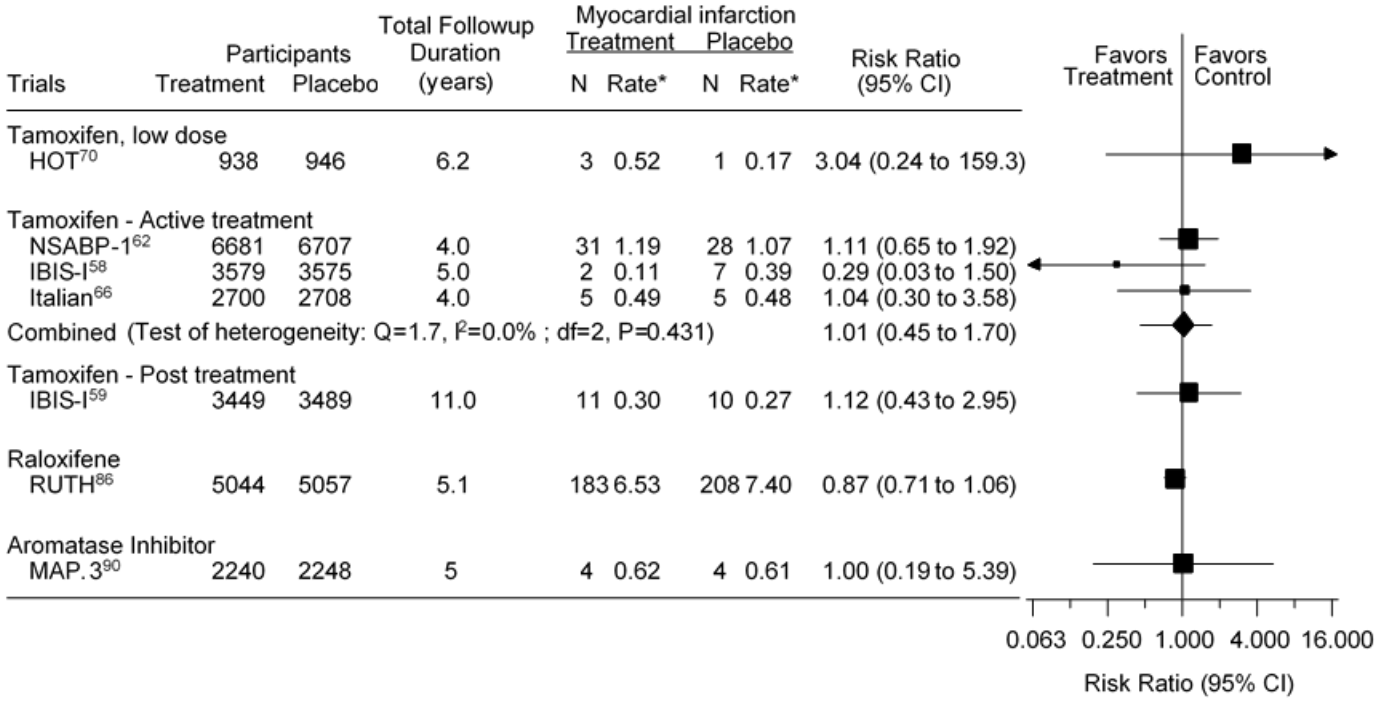
Figure 13. Meta-Analysis of Trials: Coronary Heart Disease



*Per 1,000 women-years.
†CHD events includes any reported coronary heart disease, such as myocardial infarction, angina, acute ischemic syndrome and other CHD events.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

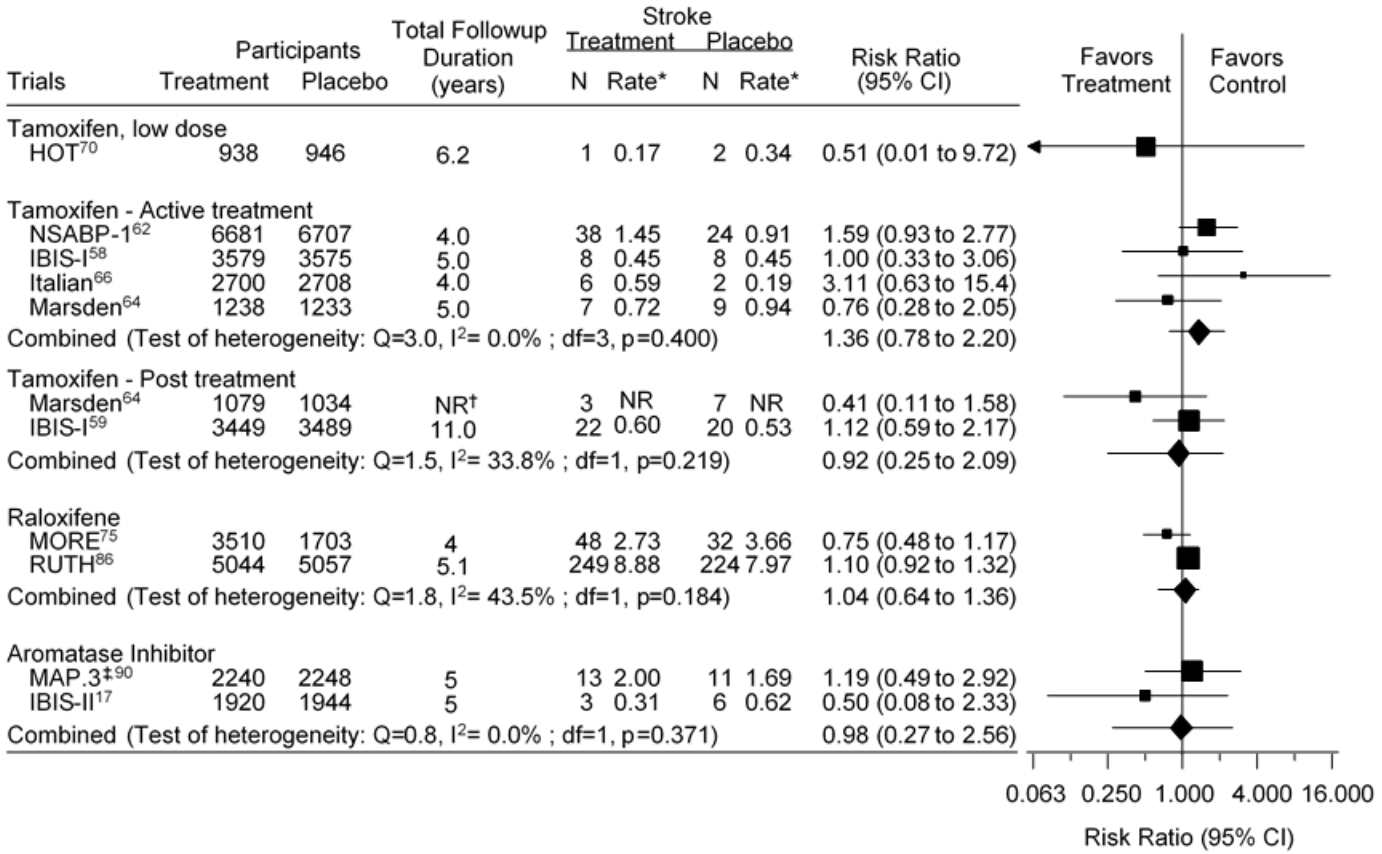
Figure 14. Meta-Analysis of Trials: Myocardial Infarction



*Per 1,000 women-years.

Abbreviations: CI=confidence interval; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; MAP.3=Mammary Prevention.3 trial; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

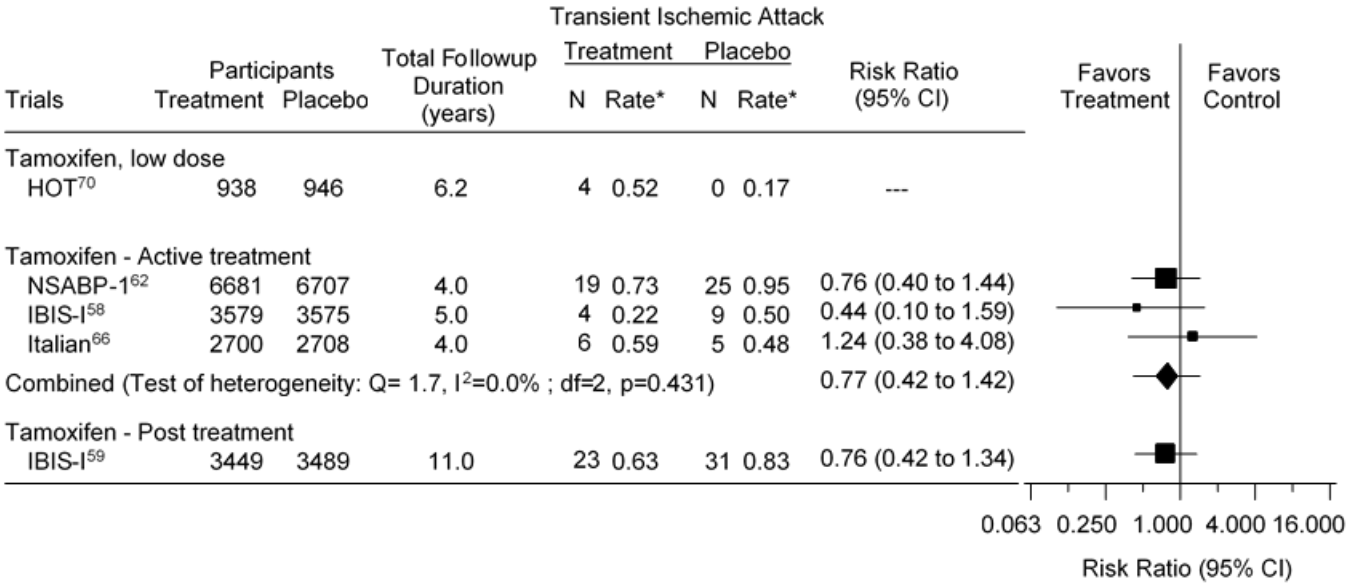
Figure 15. Meta-Analysis of Trials: Stroke



*Per 1,000 women-years.
†Events were reported from at least 3 months after treatment was stopped until the end of followup.
‡MAP3. trial reported cerebrovascular events including both stroke and transient ischemic attack.

Abbreviations: CI=confidence interval; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

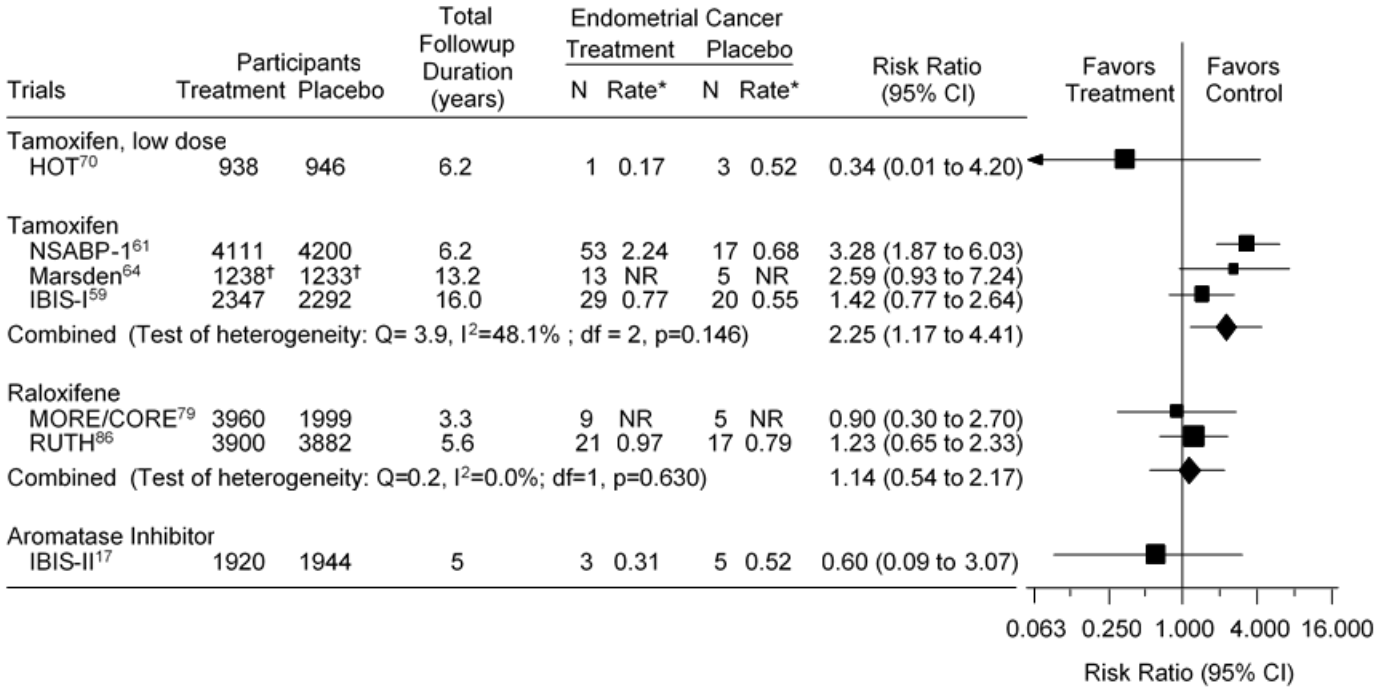
Figure 16. Meta-Analysis of Trials: Transient Ischemic Attack



*Per 1,000 women-years.

Abbreviations: CI=confidence interval; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; N=number; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study.

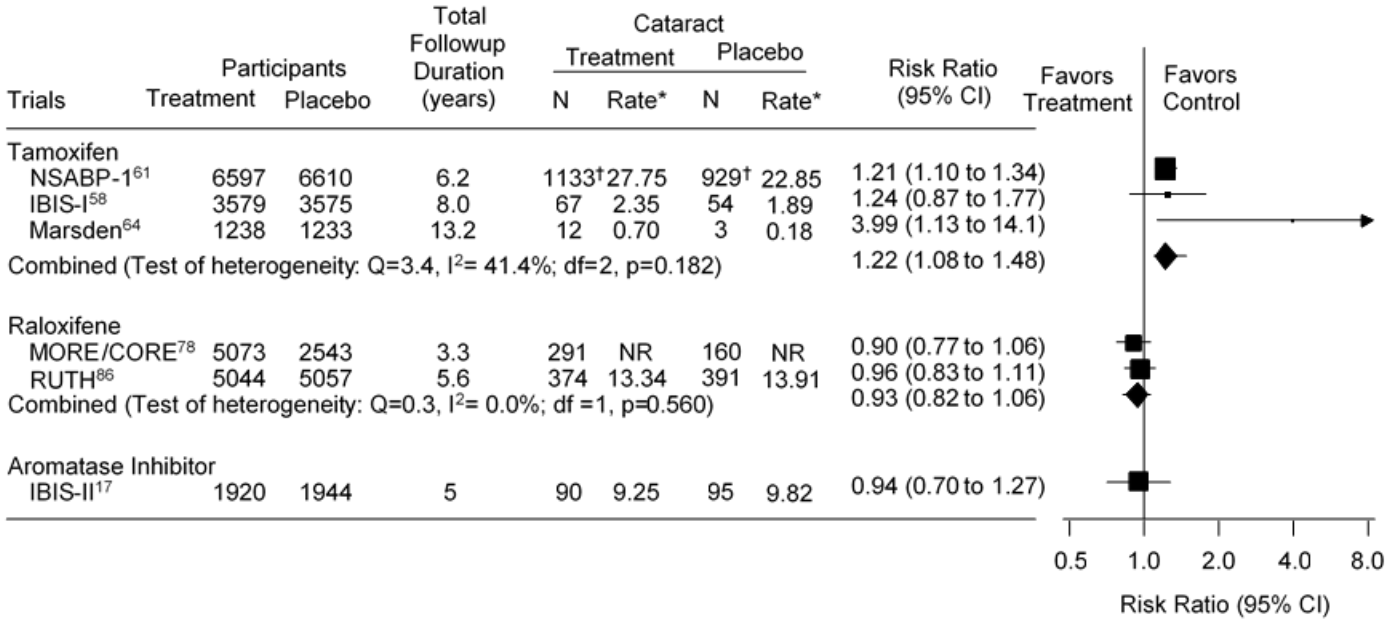
Figure 17. Meta-Analysis of Trials: Endometrial Cancer



*Per 1,000 women-years, based on number of women with an intact uterus.
†The number of women at risk (non-hysterectomized) was not reported and risk ratio is calculated based on the number of randomized subjects at baseline.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

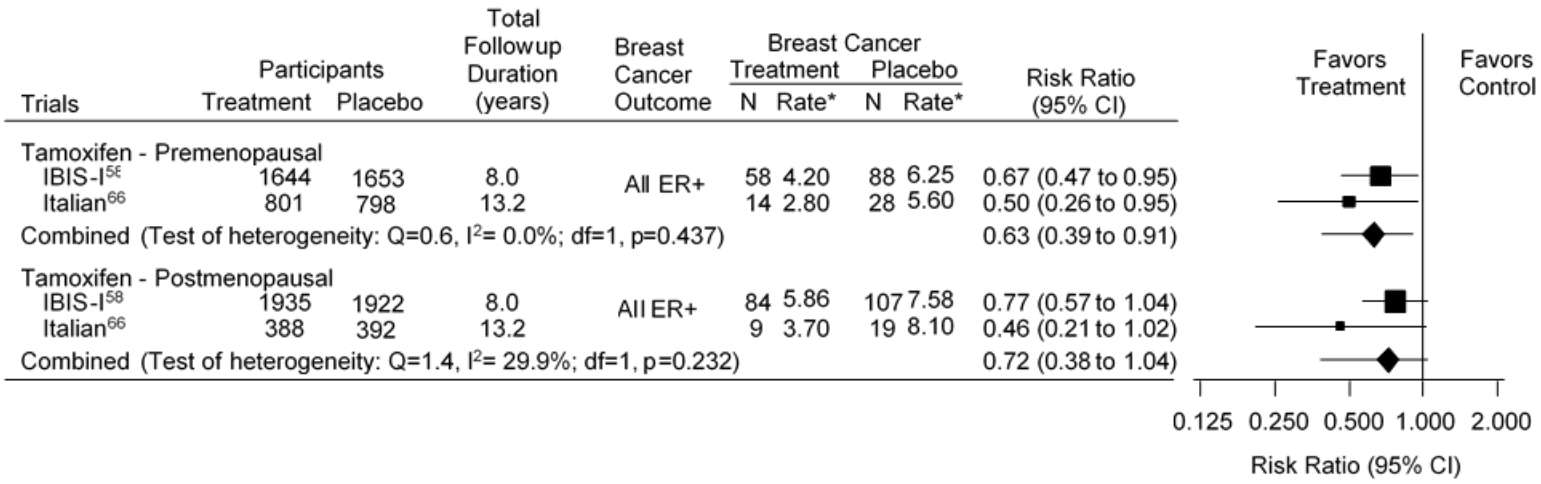
Figure 18. Meta-Analysis of Trials: Cataracts



*Per 1,000 women-years, based on number of women with an intact uterus.
†The numbers of cataract events are calculated based on the report follow-up women years and the rates of cataract.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Breast and Bowel Project P-1 study; RUTH=Raloxifene Use for the Heart.

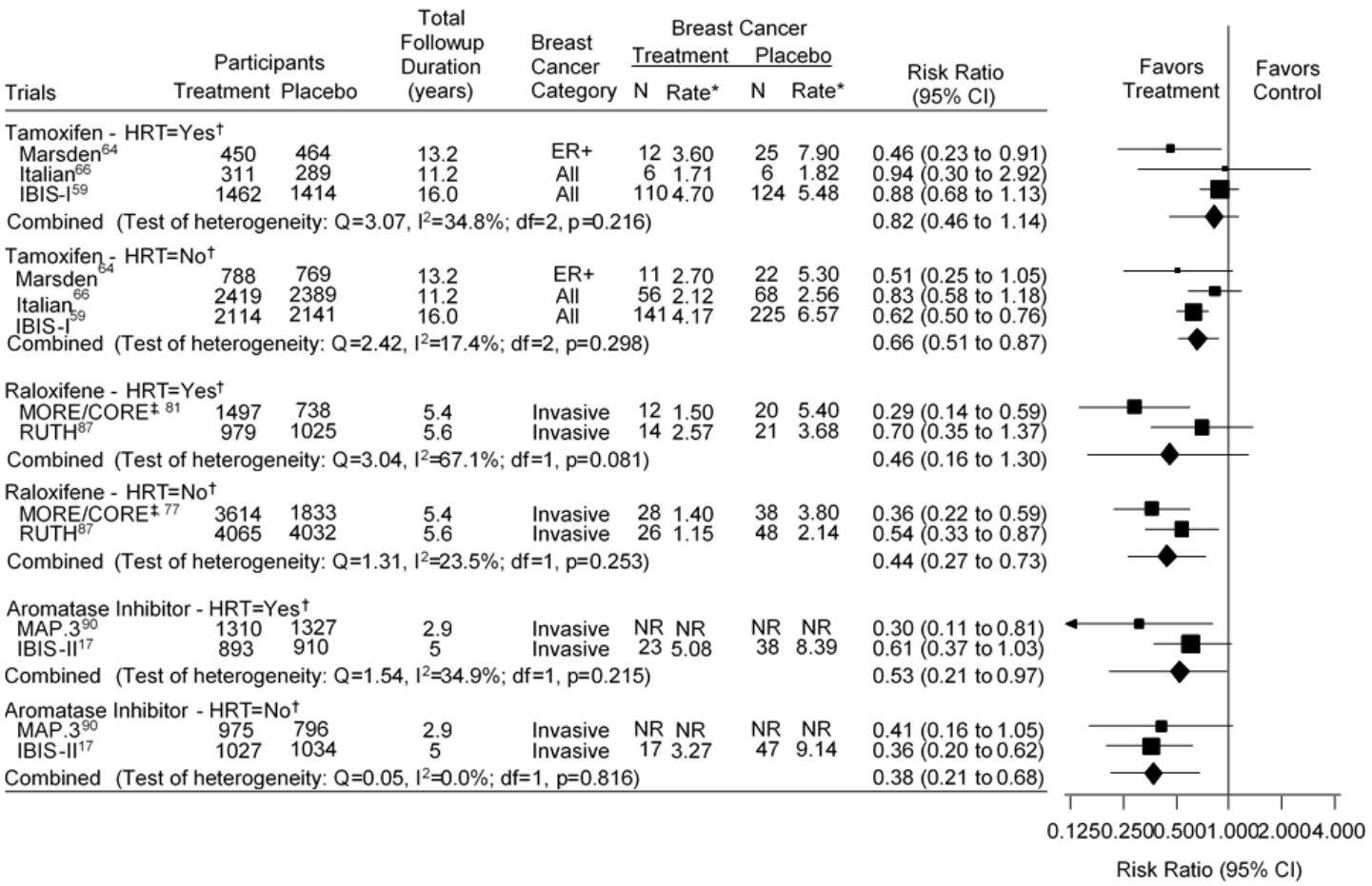
Figure 19. Meta-Analysis of Trials: Menopausal Status



*Per 1,000 women-years.

Abbreviations: CI=confidence interval; ER+=estrogen receptor positive; IBIS-I=International Breast Cancer Intervention Study; N=number.

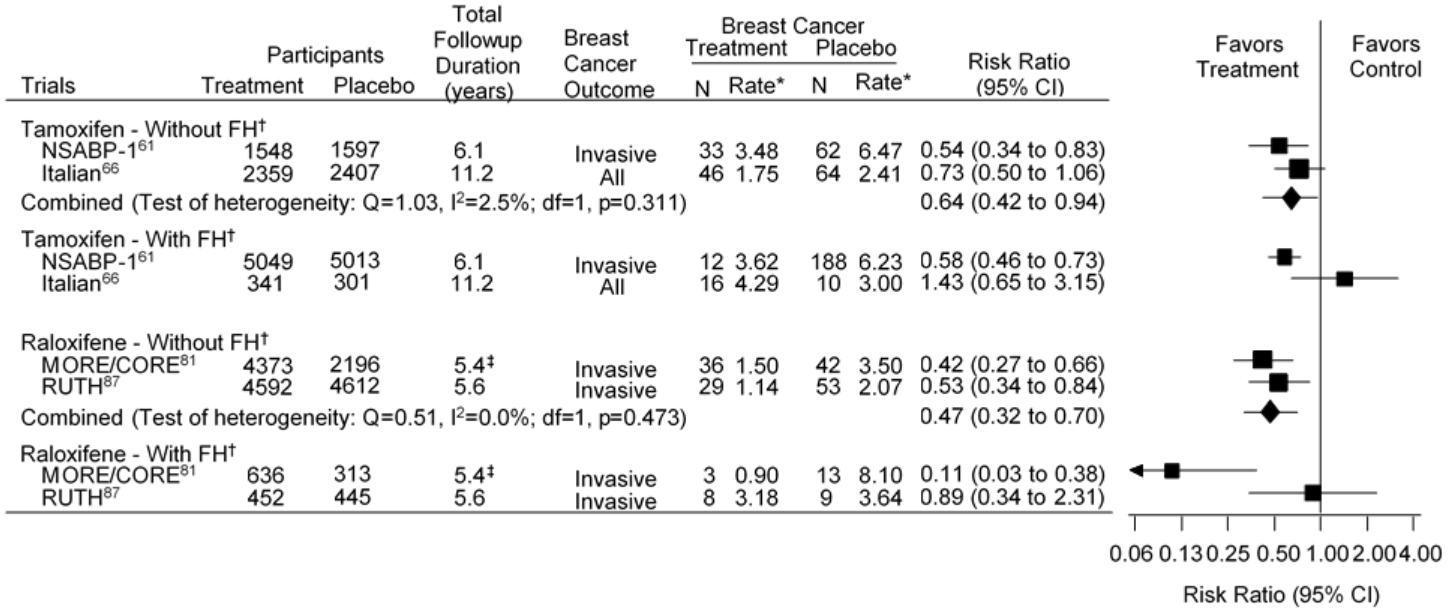
Figure 20. Meta-Analysis of Trials: Estrogen Use



*Per 1,000 women-years.
†For tamoxifen trials, hormone replacement therapy (HRT) use refers to HRT use during the trial period only.
For raloxifene and aromatase inhibitor trials, HRT use refers to prior HRT use.
‡The total followup time is averaged over both MORE and CORE for the 7705 participants.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; ER+=estrogen receptor positive; HOT=Hormone replaced therapy Opposed by low-dose Tamoxifen study; HRT=hormone replacement therapy; IBIS-I=International Breast Cancer Intervention Study; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; RUTH=Raloxifene Use for the Heart.

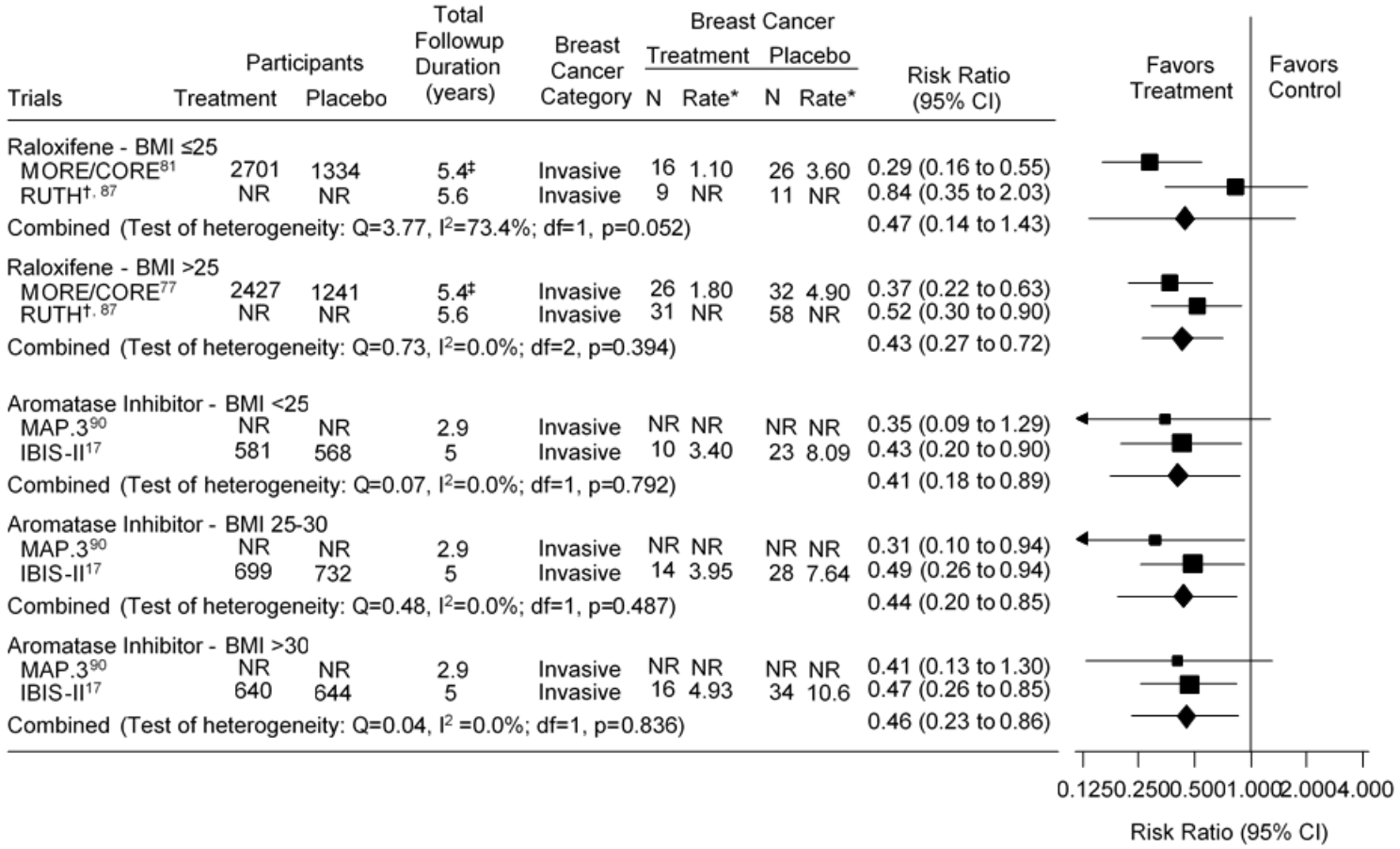
Figure 21. Meta-Analysis of Trials: Family History



*Per 1,000 women-years.
†With family history (FH) is defined as having at least one first-degree relative with breast cancer, and otherwise it is without FH.
‡The total followup time is averaged over both MORE and CORE for the 7705 participants.

Abbreviations: CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; FH=family history; MORE=Multiple Outcomes of Raloxifene; N=number; RUTH=Raloxifene Use for the Heart.

Figure 22. Meta-Analysis of Trials: Body Mass Index



*Per 1,000 women-years.
† For Grady 2008, total n=2416 for BMI ≤25, and 7655 for BMI > 25.
‡The total followup time is averaged over both MORE and CORE for the 7705 participants.

Abbreviations: BMI=body mass index; CI=confidence interval; CORE=Continuing Outcomes Relevant to Evista; IBIS-II=International Breast Cancer Intervention Study II; MAP.3=Mammary Prevention.3 trial; MORE=Multiple Outcomes of Raloxifene; N=number; NR=not reported; RUTH=Raloxifene Use for the Heart.

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Adams-Campbell et al., 2007[28]	Gail African American (invasive breast cancer)	BWHS; black women; age ≥ 35 years from 1995 to 2003	725 cases; 725 age-matched controls	Validation; nested case-control; 8 year followup	SEER	Incident invasive breast cancer; must have complete data available	Good
Amir et al., 2003[29]	Tyrer-Cuzick (10-year risk of invasive breast cancer)	Family history clinic at University Hospital of South Manchester, high-risk population; total population age 21 to 73 years (median 44); screened population age 25 to 73 years (median 46); from 1987 to 2001	64 cases among 3150 women; subanalysis on screening population; 52 cases among 1933 woman cohort	Women whose risk estimate could be derived by all the models were compared and only incident cases included	U.K. Northwest cancer registry	Complete risk data for all models being compared (Gail, Claus, Ford, Tyrer-Cuzick); excluded incomplete data	Fair
Barlow et al., 2006[30]	BCSC Barlow (1-year risk of DCIS or invasive breast cancer)	BCSC; women without breast cancer age 35 to 84 years; from 1996 to 2001	11,638 cases from 2,392,998 woman cohort	Cases within cohort of women being screened with mammography; 1 year followup	BSCS (compared with SEER)	DCIS or invasive breast cancer in women age 35 to 84 years who had previous mammography within the last 5 years; no previous breast cancer, no breast augmentation, no previous mammography but detected breast cancer within one year of first mammography; if no data on menopause, excluded from subgroup analysis	Fair
Boughey et al., 2010[31]	Tyrer-Cuzick (10-year risk of invasive breast cancer)	Mayo benign breast disease cohort including women with benign breast biopsy results; 1967 to 1991; mean age 58.1 years; 1967 to 2009; median followup, 14.6 years (86.7% >5 years)	311 cases with atypical hyperplasia in 9376 woman cohort with benign breast disease	Validation; nested case-control	Not reported	Women aged 18 to 85 years with diagnosis of atypical hyperplasia at time of biopsy	Good

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Boyle et al., 2004[32]	Italian 1-Gail Model (all breast cancer)	Derivation: Italian multicenter case-control study of diet and breast cancer,1991 to 1994; age of cases 23 to 74 years (mean age 55); controls 20 to 74 years (mean age 56). Validation: Italian Tamoxifen Prevention Study, 1992 to 1997; age of cases 35 to 70 years (median age 51)	Derivation: 2569 cases with 2588 controls; Validation: 2700 tamoxifen, 2708 placebo	Derivation: case control; Validation: cases in cohort	Regional Cancer Registry Data	Women admitted with breast cancer diagnosed within 1 year of the study interview with no prior history of cancer; no admissions for gynecological, neoplastic, hormonal diseases or those related to increased risk for breast cancer in controls	Fair
Brentnall et al., 2015[33]	Tyrer-Cuzick plus breast density vs. Gail plus breast density (invasive breast cancer)	Screening areas in Greater Manchester, U.K.; data collected 2009 to 2014	697 cases among 50,628 woman cohort	Cases within cohort of women screened	Not compared	Women invited for routine mammographic screening 2009 to 2013	Fair
Chen et al., 2006[34]	Gail plus breast density (invasive breast cancer)	BCDDP; primarily white women age > 40 years; invasive or noninvasive cancer versus control; data collected 1973 to 1979	2852 cases (1235 with mammography density); 3146 age-matched controls (1656 with breast density)	Case-control; followup through 1998	SEER	Cases with missing data excluded	Good
Chlebowski et al., 2007[35]	Expanded and simplified models versus Gail 2; (ER+ versus ER- invasive breast cancer)	WHI; age 50 to 79 years (mean age 63)	3236 cases, 363 excluded due to missing data; 2873 for subgroup analysis; 2412 ER+ cases; 461 ER- cases; 144,680 controls	Derivation and validation; case-control; 5 years followup	SEER	Unlikely to move or die within 3 years; no history of breast cancer or mastectomy	Good

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Colditz and Rosner, 2000[36]	Colditz-Rosner, Model 2 (invasive breast cancer)	NHS; age 35 to 70 years; 1980 to1994	1761 cases among 58,520 women	Derivation; cases within cohort of NHS; derivation; 14 years followup	Not compared	Incident invasive breast cancer; exclusions include pregnancy/offspring history discrepancies; inaccurate age of menarche; unknown age of menopause or death; missing height, weight, or hormone use data; hysterectomy with 1 or no ovaries removed; or missing menopause data	Good
Colditz et al., 2004[37]	Rosner-Colditz, Model 2 (invasive breast cancer)	NHS; age 35 to 79 years; 1980 to 2000	2096 cases (1281 ER+/PR+, 417 ER-/PR-, 318 ER+/PR-, 80 ER-/PR+) among 66,145 women	Validation; cases within cohort of NHS	Not reported	Invasive breast cancer with reported estrogen receptor status	Good
Costantino et al., 1999[38]	Gail (invasive breast cancer)	BCPT; white women between 1992 to 1998	5969 women in placebo group of BCPT; 204 incident cases	Validation study of Gail-1 and 2 comparing BCDDP, CASH, NHS, BCPT cohorts; followup 1 to 70 months (mean 48.4)	BCDDP rates for invasive or noninvasive cancer (Gail-1); SEER data for invasive cancer (Gail-2)	10-year life expectancy, no history of breast cancer, negative mammogram within 180 days, negative clinical breast exam, no history of DCIS, LCIS	Good
DeCarli et al., 2006[39]	Italian Gail Model; Italian 1-Gail Model* (all breast cancer)	Derivation: Italian multicenter case-control study of diet and breast cancer; Florence European Prospective Investigation into Cancer and Nutrition; 1991 to 1994; age of cases 23 to 74 years (mean age 55); age of controls 20 to 74 years (mean age 56); Validation: age 35 to 64	Derivation: 2569 cases with 2588 controls; Validation: 194 cases in 10,031 woman cohort	Derivation - case control; Validation - cases in cohort	Florence Cancer Registry	Women admitted with breast cancer diagnosed within 1 year of the study interview with no previous history of cancer. No admissions for gynecologic, neoplastic, hormonal diseases or those related to increased risk of breast cancer in controls	Good

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Gail et al., 1989[41]	Gail (invasive breast cancer and LCIS)	BCDDP; white women age 35 to 79 years with invasive or noninvasive cancer and women without cancer between 1973 to 1979	2582 cases, 3146 controls	Derivation; case-control; abstracted risk factor information from 80% of eligible cases and 83% of eligible controls; followup through 1998	243,221 white women in BCDDP registry	10-year life expectancy, no history of breast cancer, negative mammography within 180 days, negative clinical breast exam, no history of DCIS	Fair
Gail et al., 2007[40]	Gail African American (invasive breast cancer)	CARE; black women; age 35 to 64 years; 1994 to 1998 and 1993 to 1998	1607 cases; 1647 controls; women matched for 5-year age group, location, and race; 14,059 from WHI	Derivation: CARE Validation: WHI case-control; WHI Followup 7.57 years	SEER	First primary incident invasive breast cancer in black women age 35 to 64 years; must have complete data available	Fair
Matsuno et al., 2011[42]	NCI Breast Cancer Risk Assessment Tool and Gail (invasive breast cancer)	Asian American Breast Cancer Study Derivation: age 20 to 55 years; 1983 to 1987; Validation: age 50 to 79 years; 1993 to 1998	589 cases; 952 controls; same ethnicity, age, and residence	Derivation: case-control Validation: cohort	SEER	Histologically confirmed, first primary incident breast cancer diagnosed between the ages of 20 to 55 years in Asian Americans	Fair
Petracci et al., 2011[43]	Italian-2* (invasive breast cancer)	Florence registry of the EPIC study Derivation: age 23 to 74 years; 1991 to 1994 Validation: age 35 to 64 years; 1998 to 2004	Derivation: 2569 cases and 2588 controls Validation: 10,083 participants	Derivation: case-control Validation: cohort	Florence EPIC cohort	Women age 23 to 74 years with invasive breast cancer served as cases; women aged 20 to 74 years without breast cancer and admitted for acute conditions to hospitals in the same catchment areas as cases served as controls	Good
Rockhill et al., 2001[45]	Gail 5-year risk (invasive breast cancer)	NHS; white women age 45 to 71 years in 1992; study duration from 1992 to 1997	1354 cases in 82,109 woman cohort	Validation; prospective cohort; followup 60 months	SEER	White women with complete risk factor data	Good
Rockhill et al., 2003[44]	Rosner-Colditz, Model (invasive breast cancer)	NHS; age 45 to 73 years; 1992 to 1997	757 cases among 45,210 women	Validation; cases within cohort of NHS	Not reported	Invasive breast cancer; no previous cancer, natural menopause or hysterectomy without oophorectomy, complete data	Good

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Tamimi et al., 2010[46]	Rosner-Colditz, adapted to include category of benign breast disease (invasive breast cancer)	NHS; age 35 to 79 years; 1980 to 2000	240 cases; 1036 controls	Derivation; nested case-control within cohort of cohort of NHS	Not reported	Women with biopsy-proven benign breast disease; incident invasive breast cancer within this cohort with age and year of biopsy-matched control.	Good
Tice et al., 2008[47]	BCSC-Tice (invasive breast cancer)	BCSC; women without breast cancer age 35 to 84 years; 71% white	1,095,484 in cohort; 14,766 cases of invasive breast cancer; 629,229 for clinical risk factor analysis	Cases within cohort of women screened with mammography; median followup 5.3 years	SEER (BCSC versus SEER, state tumor registries, and path databases)	Women age 35 years or older with 1 previous mammography with BI-RAD measurement in BCSC; excluded women with diagnosis of breast cancer, women diagnosed within 6 months of index mammography, and women with breast implants	Good
Tice et al., 2015[48]	BCSC-Tice + benign breast disease (invasive breast cancer)	BCSC; women without breast cancer age 35 to 74 years; 75% white	1,135,977 in cohort; 17,908 cases of invasive breast cancer	Cases within cohort of women screened with mammography; mean followup 6.9 years	SEER (BCSC versus SEER, state tumor registries, and path databases)	Women age 35 to 74 years with ≥1 mammography with BI-RAD measurement in BCSC between 1994 and 2010; excluded women with diagnosis of breast cancer before first eligible mammography, women diagnosed in the first 3 months of followup, women with breast implants or mastectomy	Fair
Tyrer et al., 2004[49]	Tyrer-Cuzick (invasive breast cancer)	UK national statistics of breast cancer incidence rates in general population; BRCA risk tables from U.K.	Not reported	Derivation; data from other sources	UK rates of breast cancer and positive BRCA	Not reported	Fair

Table 1. Studies of Risk Stratification Models

Author, year	Model	Population	Participants	Study type	Comparison group	Inclusion criteria	Quality rating
Vacek et al., 2011[50]	Gail versus Tice versus Barlow versus Vermont (invasive and noninvasive breast cancer)	VBCSS; women age 70 years or older, 97.7% white	821 cases (668 invasive) among 19,779 woman cohort	Cases within cohort of women screened	SEER	Women age ≥70 years with mammography in the VBCSS between 1996 and 2001; not previously diagnosed with breast cancer; and did not decline the use of their data for research. Excluded those diagnosed with cancer or lost to followup within a year of their entry mammography	Fair
Warwick et al., 2014[51]	Tyrer-Cuzick plus breast density (invasive breast cancer)	IBIS-I; age 35 to 70 years (mean age 49)	72 cases in 558 woman cohort	Cases within cohort; median followup to diagnosis 5.1 years for cases, 11.6 years followup for controls	Not reported	Women from the placebo arm of the IBIS-I trial; breast cancer free but with a risk at least twice the population average	Poor

*Italian-Gail Model: 1) calibration varies from Gail by only 1 ordinal value for 1 variable; 2) varies by using categorical rather than ordinal.

Abbreviations: BCDDP=Breast Cancer Detection and Demonstration Project; BCPT=Breast Cancer Prevention Trial; BCSC=Breast Cancer Surveillance Consortium; BRCA=breast cancer susceptibility genes ; CARE=Women's Contraceptive and Reproductive Experiences; DCIS=ductal carcinoma in situ; EPIC=European Prospective Investigation into Cancer and Nutrition; ER+=estrogen receptor positive; ER-=estrogen receptor negative; FHESP=Family History and Evaluation Screening Program- University Hospital of South Manchester; IBIS= International Breast Cancer Intervention Study; IMCCSDBC=Italian Multicenter Case-control Study of Diet and Breast Cancer; LCIS=lobular carcinoma in situ**;** NHS=Nurses' Health Study; SEER=Surveillance, Epidemiology, and End Results Program; VBCSS=Vermont Breast Cancer Surveillance System; WHI=Women's Health Initiative.

Table 2. Risk Stratification Models Variables and Accuracy

Model	Age (years)	Menarche Age (years)	Age at birth of first child (years)	First degree relatives with breast cancer, *n*	Previous breast biopsy, *n*	Other factors	Discriminatory accuracy c-statistic (95% CIs)*
Gail-2 (5-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	0; 1; ≥2; AH: 0; ≥1	Not included	0.55 (0.51 to 0.60);[28] 0.60;[38] 0.58 (0.56 to 0.60);[45] 0.58;[32] 0.59 (0.54 to 0.63);[39] 0.60;[34] 0.61 (0.60 to 0.62)[47]
Gail-2 (10-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	0; 1; ≥2; AH: 0; ≥1	Not included	0.74 (0.67 to 0.80);[29] 0.54 (0.52 to 0.56)[33]
African American Gail (5-year risk)	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	0; 1; ≥2	African American race	0.56 (0.54 to 0.58);[40] 0.56 (0.51 to 0.60) [28]
Asian American Gail (5-year risk)	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	0; 1; ≥2	Asian American race	0.61 (0.59 to 0.64)[46]
Gail + density (10-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	Yes; no	Breast density (%); BMI	0.59 (0.57 to 0.61)[33]
Gail + density (5-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	0; 1; ≥2	Breast density (%); BMI	0.64[34]
BCSC† (premenopausal; 1-year risk)	45-84 by 5-year groups	Not included	Not included	0; 1; ≥2; unknown	Yes; no; unknown	Breast density (BIRADS)§	0.63 (0.60 to 0.66)[30]
BCSC† (postmenopausal; 1-year risk)	45-84 by 5-year groups	Not included	<30; ≥30; none; unknown	0; 1; ≥2; unknown	0; ≥1; unknown	Breast density (BIRADS), prior false-positive mammogram, BMI, menopause type, HT, race or ethnicity	0.62 (0.62 to 0.63)[30]
BCSC (5-year risk)	45-84 by 5-year groups	Not included	Not included	Yes; no	Yes; no	Breast density (BIRADS), race or ethnicity	0.66 (0.65 to 0.66);[47] 0.664[48]
BCSC + BBD† (5-year risk)	45-84 by 5-year groups	Not included	Not included	Yes; no	Yes; no	Breast density (BIRADS), race or ethnicity, benign breast disease	0.665[48]
Rosner-Colditz‡	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	Yes; no	Not included	BMI, benign breast disease, menopause type, menopause age, HT use and duration, height, alcohol use, parity	0.57 (0.55 to 0.59);[44] 0.64 (0.63 to 0.66) (ER+/PR+);[37] 0.61 (0.58 to 0.64) (ER-/PR-)[37]
Rosner-Colditz-2‡	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	Yes; no	AH: 0; ≥1	Benign breast disease presence or type	0.63 (0.61 to 0.65);[44] 0.64 (type)[44]

Table 2. Risk Stratification Models Variables and Accuracy

Model	Age (years)	Menarche Age (years)	Age at birth of first child (years)	First degree relatives with breast cancer, *n*	Previous breast biopsy, *n*	Other factors	Discriminatory accuracy c-statistic (95% CIs)*
Tyrer-Cuzick (10-year risk)	<50; ≥50	≤12; >12	≤30; >30; none	1; 2; ≥3	0; 1; ≥2; LCIS: 0; ≥1	BMI, height, menopause age, family history of ovarian or other cancer, age of cancer onset, bilateral or male breast cancer	0.76 (0.70 to 0.82);[29] 0.54 (0.42 to 0.65);[31] 0.57 (0.55 to 0.59)[33]
Tyrer-Cuzick + density (10-year risk)	<50; ≥50	≤12; >12	≤30; >30; none	1; 2; ≥3	Yes; no	BMI, height, menopause age, family history of ovarian or other cancer, age of cancer onset, bilateral or male breast cancer; breast density (%)	0.61 (0.58 to 0.63)[33]
Italian-1 (5-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	Not included	Age of relative at diagnosis, diet score, alcohol use, BMI, HT, physical activity	0.59 (vitamin);[32] 0.60 (diet)[32]
Italian-2[ll] (20-year risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; or none	0; 1; ≥2	0; 1; ≥2	Occupational and leisure physical activity, education, alcohol use, BMI	0.62 (0.56 to 0.69) (age <50 years);[43] 0.57 (0.52 to 0.61) (age ≥50 years)[43]
Chlebowski (5-year risk)	50-59; 60-69; 70-79	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30 or none	0; ≥1	0; 1; ≥2	BMI, menopause age, HT use and duration, race, alcohol use, parity, breast-feeding, smoking status, physical activity	0.61 (0.59 to 0.63);[35] 0.62 (0.60 to 0.64) (ER+);[35] 0.53 (0.47 to 0.58) (ER-)[35]
Chlebowski-simplified (5-year risk)	<50; ≥50	Not included	Not included	0; ≥1	0; 1; ≥2	Not included	0.58 (0.56 to 0.60) (ER+)[35]

*For invasive breast cancer, other outcomes are specifically indicated.
[†]Includes nonproliferative, proliferative without atypia, proliferative with atypia, and lobular carcinoma in situ.
[‡]Invasive and noninvasive breast cancer.
[§]BI-RADS categories include 0=unknown; 1=entirely fat; 2=scattered fibroglandular densities; 3=heterogeneously dense; 4=extremely dense.
[ll]Includes an Italian population and used incidence rates from the Italian Multicenter case-control study of Diet and Breast Cancer and from Italian cancer registries.

Abbreviations: AH=atypical hyperplasia; BBD=benign breast disease; BCSC=Breast Cancer Surveillance Consortium; BI-RADS=Breast Imaging Reporting and Data System; BMI=body mass index (mg/kg^2); DCIS=ductal carcinoma in situ; ER-=estrogen receptor negative; ER+=estrogen receptor positive; HT=hormone therapy; LCIS=lobular carcinoma in situ.

Table 3. Randomized Controlled Trials of Medications to Reduce Risk for Breast Cancer

Trial	Treatment (n); comparison (n)	Breast cancer risk criteria	Participants, setting	Age, median (years)	White (%)	Post hysterectomy (%)	Used estrogen during trial (%)	Primary outcomes	Followup, median (years)	Exposure, median (years)	Quality rating
STAR[54-56]	Tamoxifen 20 mg/day (9872); raloxifene 60 mg/day (9875)	5-year predicted breast cancer risk ≥1.66% based on the modified Gail model*	Postmenopausal, age ≥35 years, U.S.-based with sites in North America	58.5*	18204 (93.5)	10,027 (51.5)	0 (0)	Invasive breast cancer	3.9† initial; 6.8† long-term	3.6-3.9†	Good
IBIS-I[57-59]	Tamoxifen 20 mg/day (3573); placebo (3566)	2-fold relative risk for breast cancer for ages 45-70 y, 4-fold for ages 40-44 y, 10-fold for ages 35-39 y based on family history criteria.‡	35-70 years, U.K., Australia, New Zealand, Europe	50.8*	NR	2515 (35)	2844 (40)	Invasive and noninvasive breast cancer	4.2 initial; 8.0 long-term; 16 longer term	5	Good
NSABP-P1[60-62]	Tamoxifen 20 mg/day (6576); placebo (6599)	Age ≥60 y or 35-59 y with a 5-year predicted breast cancer risk ≥1.66% based on the modified Gail model,* or history of LCIS	≥35 years, U.S.-based with sites in North America	Median NR; 5177 (39.3%) <50	12706 (96.4)	4884 (37)	0 (0)	Invasive and noninvasive breast cancer	4.6 initial; 7.0 long-term	4.0 when unblinded	Good
Royal Marsden Hospital Trial[63,64]	Tamoxifen 20 mg/day (1238); placebo (1233)	Family history of breast cancer§	30-70 y, UK	47	NR	NR	389 (15.6)	Invasive breast cancer	5.8 initial; 13.2 long-term	NR	Good
Italian Tamoxifen Prevention Study[65-66, 68-69]	Tamoxifen 20 mg/day (2700); placebo (2708)	None	35-70 y, Italy-based with in Europe and South America	51	NR	100 (100)	751 (14)	Breast cancer incidence and mortality	3.8 initial; 11.2 long-term	4	Fair; dropout rate 26.3%
HOT[70]	Tamoxifen 5 mg/day (938); placebo (946)	None	Postmenopausal, Italy-based	53*	NR	NR	100 (100)	Invasive breast cancer	6.2*	5[b]	Good

Table 3. Randomized Controlled Trials of Medications to Reduce Risk for Breast Cancer

Trial	Treatment (n); comparison (n)	Breast cancer risk criteria	Participants, setting	Age, median (years)	White (%)	Post hysterectomy (%)	Used estrogen during trial (%)	Primary outcomes	Followup, median (years)	Exposure, median (years)	Quality rating
MORE and CORE[71-81, 83-85,93]	MORE: raloxifene 60 or 120 mg/day (5129); placebo (2576); CORE: raloxifene 60 mg/day (2725); placebo (1286)	None	Postmenopausal, age 31-80 y, with osteoporosis, ‖ US-based with sites in 25 countries; CORE includes a subset of MORE participants	66.9	NR (96)	NR (23)	0 (0)	MORE: Incident radiographic vertebral fractures and clinical nonvertebral fractures CORE: Breast cancer	MORE: 3, 4; CORE: 4, 8 (combines data)	NR	Good
RUTH[86-87, 96]	Raloxifene 60 mg/day (5044); placebo (5057)	None	Postmenopausal, age ≥55 y, CHD or risk factors,¶ US-based with sites in 26 countries	67.5	8481 (84)	2319 (23)	0 (0)	Coronary events, invasive breast cancer	5.6	5.1	Good
IBIS-II[17,88-89]	Anastrozole 1 mg/day (1920); placebo (1944)	Increased risk for breast cancer: age 45-60 y ≥2 times higher than the general population; age 60-70 y 1.5 times higher; age 40-44 y 4 times higher	Postmenopausal, age 40-70 y, UK-based with sites in 18 countries	59.5	NR	1287 (33.3)	0 (0)	Invasive and noninvasive breast cancer	5	5	Good
MAP.3[90-91]	Exemestane 25 mg/day (2285); placebo (2275)	Risk factors for breast cancer: age ≥60 y; Gail risk score >1.66%; prior ADH, ALH, LCIS or DCIS	Postmenopausal, ≥35 years, US-based with sites in 4 countries	62.5	4261 (93.4)	NR	0 (0)	Invasive breast cancer	2.9	3	Good

*STAR & NSABP-1: The Gail model includes age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of benign breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. The original model was further modified to predict expected rates of invasive breast cancer only (not invasive and noninvasive as originally designed) and to allow for race-specific determinations of risk.

† Values are means.

‡IBIS: All criteria permit entry to trial at age 45 years: first-degree relative with breast cancer age ≤50 y; first-degree relative with bilateral breast cancer (permits entry from age 40 y; if relative age ≤40 y, permits entry at age 35 y); ≥2 first-degree or second-degree relatives with breast cancer (permits entry from age 40 y if both developed breast cancer before age 50 y; permits entry at age 35 y if both relatives are first-degree and both developed breast cancer before age 50 y); benign breast biopsy and first-degree relative with breast

cancer; lobular carcinoma in situ (permits entry from age 35); atypical hyperplasia (permits entry from age 40); nulliparous and a first-degree relative who developed breast cancer; risk equivalent (strong family history, not fitting specific categories, but judged to be at higher risk than eligibility category by the study chairman).
[§]Family history criteria for Royal Marsden Hospital Trial: one first-degree relative age <50 y with breast cancer, or one first-degree relative with bilateral breast cancer, or one affected first-degree of any age plus another affected first-degree or second-degree relative; benign breast biopsy and a first-degree relative with breast cancer.
[||]MORE: Study Group 1, femoral neck or lumbar spine bone mineral density (BMD) T-score < -2.5; Study Group 2, low BMD and one or more moderate or severe vertebral fractures or ≥2 milder vertebral fractures (20-25% reduction in height); or ≥2 moderate fractures (25-40% reduction from expected vertebral height), regardless of BMD.
[¶]Cardiovascular risk score ≥4: established coronary heart disease (4 points), arterial disease of the leg (4 points), age ≥70 y (2 points), diabetes mellitus (3 points), cigarette smoking (1 point), hypertension (1 point), and hyperlipidemia (1 point).

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CHD, coronary heart disease; CORE, Continuing Outcomes Relevant to Evista; DCIS, ductal carcinoma in situ; HOT, Hormone replacement therapy Opposed by low-dose Tamoxifen; IBIS-I, International Breast Cancer Intervention Study; IBIS-II, International Breast cancer Intervention Study II; LCIS, lobular carcinoma in situ; MAP.3, Mammary Prevention.3 trial; mg, milligram; MORE, Multiple Outcomes of Raloxifene Evaluation; NSABP-P1, National Surgical Adjuvant Breast and Bowel Project P-1 Study; RUTH, Raloxifene Use for the Heart; STAR, Study of Tamoxifen and Raloxifene; UK, United Kingdom; US, United States.

Table 4. Outcomes Reported in Trials

Outcomes	Placebo-controlled Trials Reporting Outcomes	Included in Meta-analysis	Reported in STAR Trial
Benefits			
All breast cancer	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, HOT, IBIS-II	X	NR
Invasive breast cancer	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, IBIS-II	X	X
ER+ breast cancer	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, IBIS-II	X	NR
ER- breast cancer	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, IBIS-II	X	NR
Noninvasive breast cancer	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, IBIS-II	X	X
DCIS	Marsden, IBIS-I, MORE, MAP.3, IBIS-II		X
Breast cancer mortality	NSABP-1, Marsden, IBIS-I, Italian, MORE, MAP.3, IBIS-II	X	NR
All-cause mortality	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, IBIS-II	X	X
All fractures	Marsden, IBIS-I, MAP.3, HOT, IBIS-II	X	NR
Hip, wrist, spine fractures	NSABP-1, IBIS-I, MAP.3	X	X
Vertebral fractures	NSABP-1, MORE, RUTH, MAP.3, IBIS-II	X	X
Nonvertebral fractures	NSABP-1, MORE, RUTH, MAP.3, IBIS-II	X	NR
Hip fractures	NSABP-1, MORE, MAP.3		X
Wrist fractures	NSABP-1, MORE, MAP.3		X
Harms			
Thromboembolic events	NSABP-1, Marsden, IBIS, Italian, MORE, RUTH, MAP.3, HOT, IBIS-II	X	X
Deep vein thrombosis	NSABP-1, Italian, MORE, RUTH	X	X
Pulmonary embolus	NSABP-1, Italian, MORE, RUTH	X	X
Superficial phlebitis	Italian, IBIS-I, IBIS-II	X	NR
Coronary heart events	NSABP-1, Marsden, IBIS-I, Italian, MORE, RUTH, MAP.3, HOT, IBIS-II	X	X
Myocardial infarction	NSABP-1, IBIS-I, Italian, MAP.3, IBIS-II	X	X
Stroke	NSABP-1, Marsden, IBIS-I, Italian, RUTH, MORE, MAP.3, HOT, IBIS-II	X	X
Transient ischemic attack	NSABP-1, IBIS, Italian, MAP.3	X	X
Endometrial cancer	NSABP-1, Marsden, IBIS-I, MORE, RUTH, MAP.3, HOT, IBIS-II	X	X
Cataracts	NSABP-1, Marsden, IBIS-I, MORE, RUTH, IBIS-II	X	X
Quality of life			
Depression	NSABP-1, IBIS-II, MAP.3		X
Anxiety	IBIS-II		NR
Sleep disturbances	Marsden, MAP.3		NR
Sexual functioning	NSABP-1, Marsden, MAP.3		X
Vasomotor symptoms	IBIS, Marsden, IBIS-II, MAP.3		X
Vaginal dryness	Italian, IBIS, IBIS-II, MAP.3, HOT		X
Vaginal discharge	NSABP-1, IBIS, Marsden, Italian, HOT		X
Hot flashes or flushes	NSABP-1, Italian, Marsden, MORE, RUTH, IBIS-II, MAP.3, HOT		X
Night sweats	NSABP-1, MAP.3, HOT		NR
Gynecological conditions	IBIS-II		X
Leiomyomas	NSABP-1		X
Ovarian cysts	NSABP-1, IBIS		X
Uterine fibroids	IBIS		NR
Endometrial polyps	IBIS, HOT		NR
Cervical polyps	IBIS		NR

Table 4. Outcomes Reported in Trials

Outcomes	Placebo-controlled Trials Reporting Outcomes	Included in Meta-analysis	Reported in STAR Trial
Uterine polyps	MORE		NR
Polyps, unspecified	NSABP-1		X
Endometriosis	NSABP-1, IBIS		X
Endometritis	NSABP-1		NR
Gynecological procedures			
Currettage	NSABP-1		X
Hysterectomy	NSABP-1, Marsden, IBIS		X
Oophorectomy	NSABP-1, IBIS		X
Laparoscopy	NSABP-1		X
Hysteroscopy	NSABP-1, IBIS		X

Abbreviations: DCIS=ductal carcinoma *in situ*; ER+=estrogen receptor positive; ER-=estrogen receptor negative; HOT=Hormone replacement therapy Opposed by low dose Tamoxifen; IBIS=International Breast Cancer Intervention Study; MAP.3=Mammary Prevention.3 Trial; MORE=Multiple Outcomes of Raloxifene Evaluation; NR=not reported; NSABP-1=National Surgical Adjuvant Brest and Bowel Project P-1 Study; RUTH=Raloxifene Use for the Heart; STAR=Study of Tamoxifen and Raloxifene.

Table 5. Results of the STAR Trial

Outcome	RR (95% CI)	Events Reduced or Increased (95% CI), *n**
Benefits		
Invasive breast cancer	1.24 (1.05 to 1.47)†	5 (1 to 9) fewer with tamoxifen
ER+ breast cancer	0.93 (0.72 to 1.24)‡	–
ER− breast cancer	1.15 (0.75 to 1.77)‡	–
Noninvasive breast cancer	1.22 (0.95 to 1.59)†	–
Breast cancer mortality	0.36 (0.08 to 1.21)†	–
All-cause mortality	0.84 (0.70 to 1.02)†	–
Vertebral fracture	0.98 (0.65 to 1.46)‡	–
Nonvertebral fracture	Not reported	–
Harms		
Thromboembolic events§	0.75 (0.60 to 0.93)†	4 (1 to 7) more with tamoxifen
DVT	0.72 (0.54 to 0.95)†	3 (1 to 5) more with tamoxifen
PE	0.80 (0.57 to 1.11)†	–
CHD events	1.10 (0.85 to 1.43)‡	–
Stroke	0.96 (0.64 to 1.43)‡	–
Endometrial cancer	0.55 (0.36 to 0.83)†	5 (2 to 9) more with tamoxifen
Cataracts	0.80 (0.72 to 0.95)†	15 (8 to 22) more with tamoxifen

* Numbers of events reduced for benefits or increased for harms compared with raloxifene per 1000 women, assuming 5 years of use.
†Updated results from STAR, 2010.[52]
‡Initial results from STAR, 2006.[50]
§Includes DVT and PE.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; DVT=deep vein thrombosis; ER−=estrogen receptor negative; ER+=estrogen receptor positive; n=number; PE=pulmonary embolism; RR=risk ratio; STAR=Study of Tamoxifen and Raloxifene.

Table 6. Meta-Analysis of Results of Placebo-Controlled Trials—Benefits

Outcome	RR for Tamoxifen vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with Tamoxifen (95% CI), *n*‡	RR for Raloxifene vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with Raloxifene (95% CI), *n*‡	RR for AIs vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with AIs (95% CI), *n*‡
Breast cancer												
Invasive	0.69 (0.59 to 0.84)	4	4.58 ± 0.96	7 (4 to 12) fewer	0.44 (0.24 to 0.80)	2	3.19 ± 0.59	9 (3 to 15) fewer	0.45 (0.26 to 0.70)	2	5.90 ± 0.64	16 (8 to 24) fewer
ER+	0.58 (0.42 to 0.81)	4	3.62 ± 0.76	8 (4 to 13) fewer	0.33 (0.15 to 0.70)	2	2.45 ± 0.42	8 (4 to 13) fewer	0.37 (0.19 to 0.63)	2	4.55 ± 0.53	15 (8 to 20) fewer
ER−	1.18 (0.93 to 1.53)	4	–	–	1.25 (0.60 to 2.58)	2	–	–	0.79 (0.35 to 1.79)	2	–	–
Noninvasive	0.72 (0.56 to 1.41)§	4	–	–	1.47 (0.61 to 3.85)	2	–	–	0.46 (0.16 to 1.42)	2	–	–
Mortality												
Breast cancer	1.20 (0.79 to 1.79)	4	–	–	NR‖	–	–	–	NR	–	–	–
All-cause	1.07 (0.91 to 1.23)	4	–	–	0.90 (0.63 to 1.05)	2	–	–	1.02 (0.58 to 1.82)	2	–	–
Fracture												
Vertebral	0.75 (0.48 to 1.15)¶	1	–	–	0.61 (0.53 to 0.73)	2	3.45 ± 0.35**	7 (5 to 9) fewer	1.28 (0.59 to 2.75)	2	–	–
Nonvertebral	0.66 (0.45 to 0.98)¶	1	1.55 ± 0.20	3 (0.2 to 5) fewer	0.97 (0.86 to 1.12)	2	–	–	1.05 (0.87 to 1.28)	2	–	–

* Number of trials included in meta-analysis.
†Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.
‡Numbers of events reduced for benefits or increased for harms compared with placebo per 1000 women assuming 5 y of use.
§The RR was significantly reduced in NSABP P-1, 2005 (60 vs. 93 events; RR, 0.63 [CI, 0.45–0.89]).[57]
‖2 breast cancer deaths in 7601 women for raloxifene vs. 0 in 7633 women for placebo.[75, 83]
¶NSABP P-1, 2007.[57]
** Estimated from the placebo group of the RUTH trial, 2006.[82]

Abbreviations: AIs=aromatase inhibitors; CI=confidence interval; ER−=estrogen receptor–negative; ER+=estrogen receptor–positive; n=number; NR=not reported; NSABP=National Surgical Adjuvant Breast and Bowel Project; PE=pulmonary embolism; RR=risk ratio; RUTH=Raloxifene Use for the Heart; SE=standard error.

Table 7. Methods of Followup for Adverse Events in Trials

Trial	References	Methods
Tamoxifen (20 mg/day) vs. Raloxifene (60 mg/day)		
Study of Tamoxifen and Raloxifene (STAR)	Vogel, 2006; Land, 2006; Vogel, 2010	Participants were followed every 6 months for 5 years and annually thereafter. Gynecologic examinations, complete blood counts, and routine serum chemistry tests were obtained annually. Information about the occurrence of all protocol-defined endpoints (endometrial cancer, cardiovascular disease, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attack, osteoporotic fracture, cataracts, death, quality of life, other cancers) was ascertained at each follow-up visit and verified by reviewing medical records. Self-reported symptoms were also collected at each visit.
Tamoxifen (20 mg/day) vs. Placebo		
International Breast Cancer Intervention Study (IBIS-I)	IBIS, 2002; Cuzick, 2007; 2015	Adverse effects were assessed using a checklist of predefined outcomes with a free text field. These included myocardial infarction, cardiovascular disease events, thromboembolic events, osteoporotic fractures, any non-breast cancer, nausea, vomiting, hot flushes, headaches, vaginal discharge, vaginal dryness, and vaginal bleeding. During the active treatment phase, these questions were asked directly to participants, while during the followup phase, a less detailed version of the checklist was mailed to participants. For postal replies, adverse outcomes were confirmed by medical record review. Approximately 85% of women returned at least one questionnaire during followup.
National Surgical Adjuvant Breast and Bowel Project P-1 Study (NSABP-1)	Fisher, 1998; 2005; Day, 2001; Brisson, 2000; Chalas, 2005; Reis, 2001	Adverse effects were documented by using a global index modeled after the Women's Health Initiative. Followup visits occurred at 3 and 6 months, and then every 6 months thereafter. Endometrial cancer and thromboembolic events were considered secondary end points. Gynecologic symptoms of hot flashes, vaginal discharge, vaginal dryness, and abnormal vaginal bleeding were monitored, and clinical sites reported additional uterine and ovarian disorders and gynecologic procedures. Medical records for participants with suspected cardiovascular disease events were collected by the clinical sites and adjudicated by investigators blinded to treatment assignment.
Royal Marsden Hospital Trial	Powles, 1998; 2007	Followup visits occurred every 6 months during the course of the trial and acute toxicity and other conditions were assessed at each visit. Further details of the followup procedures for adverse effects were not reported.
Italian Tamoxifen Prevention Study	Veronesi, 1998; 2003; 2007; Decensi, 2005; Bruno, 2005	Adverse effects were evaluated at visits and physical examinations every 6 months. After completion of treatment, or in the case of dropouts, women were followed on an annual basis, although only adverse events that occurred during study treatment were reported. Information about major endpoints, such as death, serious adverse events, or cancer, was collected and submitted to the data center. Secondary endpoints included cardiovascular disease, psychological measures, and cognitive function. Surveillance for onset of acute or chronic liver injury based on blood levels of transaminases was also included.
Tamoxifen (5 mg/day) vs. Placebo		
Hormone replacement therapy Opposed by low-dose Tamoxifen (HOT) study	DeCensi, 2013	Clinical examinations were repeated every 6 months during treatment. Transvaginal ultrasounds were obtained at baseline and repeated if atypical bleeding was reported, followed by hysteroscopy if clinically indicated. Clinical visits were repeated annually up to 10 years during the follow-up period, although he details of the visits were not specified.

Table 7. Methods of Followup for Adverse Events in Trials

Trial	References	Methods
Raloxifene (60 or 120 mg/day) vs. Placebo		
Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista (CORE)	Ettinger, 1999; Cummings, 1999; Cauley, 2001; Barrett-Connor, 2002; Delmas, 2002; 2003; Grady, 2004; Barrett-Connor, 2004; Silverman, 2004; Johnell, 2004; Martino, 2005; Duvernoy, 2005; Keech, 2005; Siris, 2005; Lippman, 2006	Participants were followed every 6 months in the MORE trial and were queried about potential adverse effects at every visit. Fasting plasma glucose levels were evaluated annually. Endometrial changes were monitored with transvaginal ultrasound, however some of the 17 centers only performed transvaginal ultrasound on a subset of women. Three physicians who were blinded to treatment assignment (the outcome adjudication panel) reviewed medical records of any patient with a reported case of endometrial cancer to confirm the diagnosis.
Raloxifene Use for the Heart (RUTH)	Barrett-Connor, 2006; Grady, 2008; Ensrud, 2008	Participants reported adverse events every 6 months at either a visit or by a telephone call. Electrocardiograms were performed at baseline, years 2 and 4, and the final visit. Serum lipids were measured at baseline, years 1 and 5, and the final visit. Committees of experts blinded to treatment assignment adjudicated coronary events, breast cancer, stroke, thromboembolism, and death outcomes.
Anastrozole (1 mg/day) vs. Placebo		
International Breast cancer Intervention Study II (IBIS-II)	Cuzick, 2014; Sestak, 2014; Spagnolo, 2016	Secondary end points included other cancer, cardiovascular disease, fractures, adverse events, and deaths. Participants had clinical visits at baseline, 6 months, 12 months, and annually until the 5-year visit. Followup after 5 years varied and included clinic visits, annual questionnaires, and record linkage systems in the United Kingdom.
Exemestane (25 mg/day) vs. Placebo		
Mammary Prevention.3 trial (MAP.3)	Goss, 2011; Maunsell, 2014	Secondary end points included adverse cardiovascular events, incidence of other cancer, side effect profile and safety, and health-related and menopause-specific qualities of life. Clinical assessments occurred at 6 and 12 months after randomization and then yearly during the trial. These included physical examinations, symptoms, adverse events, and quality of life assessments. Safety data across study sites were reviewed every 6 months by an independent data and safety monitoring committee.

Table 8. Meta-Analysis of Results of Placebo-Controlled Trials—Harms

	RR for Tamoxifen vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with Tamoxifen (95% CI), *n*‡	RR for Raloxifene vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with Raloxifene (95% CI), *n*‡	RR for AIs vs. Placebo (95% CI)	Trials, *n**	Placebo Rate (±SE)†	Events Reduced or Increased with AIs (95% CI), *n*‡
Vascular												
VTE‖	1.93 (1.33 to 2.68)	4	0.91 ± 0.19	5 (2 to 9) more	1.56 (1.11 to 2.60)	2	2.34 ± 0.25	7 (0.3 to 17) more	1.24 (0.65 to 2.16)	2	–	–
DVT	1.45 (0.73 to 2.59)	2	–	–	1.66 (0.79 to 5.14)	2	–	–	NR	–	–	–
PE	2.69 (0.54 to 8.13)	2	–	–	2.11 (0.82 to 6.12)	2	–	–	NR	–	–	–
CHD events	1.00 (0.75 to 1.30)	4	–	–	0.95 (0.80 to 1.10)	2	–	–	0.76 (0.41 to 1.49)	2	–	–
Stroke	1.36 (0.78 to 2.20)	4	–	–	1.04 (0.64 to 1.36)	2	–	–	0.98 (0.27 to 2.56)	2	–	–
Other												
Endometrial cancer	2.25 (1.17 to 4.41)	3	0.62 ± 0.10	4 (1 to 8) more	1.14 (0.54 to 2.17)	2	–	–	0.60 (0.09 to 3.07)	1	–	–
Cataracts	1.22 (1.08 to 1.48)	3	22.85 ± 0.75¶	26 (5 to 50) more	0.93 (0.82 to 1.06)	2	–	–	0.94 (0.70 to 1.27)	1	–	–

* Number of trials included in meta-analysis.
†Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.
‡Number of events reduced for benefits or increased for harms compared with placebo per 1000 women assuming 5 years of use.
‖Includes DVT and PE.
¶The placebo rate was from NSABP P-1, 2005.[57]

Abbreviations: AI=aromatase inhibitors; CHD=coronary heart disease; CI=confidence interval; DVT=deep vein thrombosis; n=number; NR=not reported; NSABP=National Surgical Adjuvant Breast and Bowel Project; PE=pulmonary embolism; RR=risk ratio; SE=standard error; VTE=venous thromboembolism.

Table 9. Facilitators and Barriers to Uptake of Risk-Reducing Medications for Breast Cancer

Facilitators	Barriers
Patients	
Higher objective or perceived risk of breast cancer	Concern for side effects of medication
Healthcare provider recommendation	Concern for contraindications with estrogen
Knowing others with a good experience with medications	Knowing others with a poor experience with medications
Positive attitude and perception of medication effectiveness	Perception that medication is for treatment and not risk reduction
Higher level of anxiety or worry	Perception that medication is a daily reminder of illness
Abnormal breast biopsy*	Preference for other preventive management such as mastectomy
Enrollment in a trial of risk-reducing medications	Being better informed about benefits and harms of medications
Physicians	
More breast cancer diagnoses in clinical practice	Lack of training, experience, or comfort with medications
Perception that benefits of medications outweigh harms	Negative perception of benefit of medications in relation to harms
Patients asking about medications	Perception that patients lack interest in medications
Personal experience with breast cancer in self or a relative	Perception that prescribing medications should be initiated by specialists
Perception that eligibility for medications is easy to determine	Lack of comfort or certainty with identifying women eligible for medications
	Time constraints at visits for discussion of medications

*Including atypical hyperplasia and lobular carcinoma in situ.

Table 10. Summary of Evidence Table

Key Question	Interventions	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 1. Diagnostic accuracy of risk assessment methods	Breast cancer risk assessment	24 discriminatory accuracy studies of 17 risk stratification models (n>5,000,000)	Most models have low discriminatory accuracy in predicting the probability of breast cancer in individuals (c-statistics 0.55 to 0.65)	Consistent; precise	While some studies used inappropriate reference groups, enrolled small numbers, or inadequately described methods, most studies met criteria for good quality	High	High
KQ 1a. Optimal age at which to begin risk assessment	Breast cancer risk assessment	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 1b. Optimal frequency of risk assessment	Breast cancer risk assessment	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 2. Benefits of risk reducing medications	Tamoxifen vs. raloxifene	1 RCT (n=19,747)	Tamoxifen reduced invasive breast cancer compared with raloxifene (RR 1.24; 95% CI 1.05 to 1.47; 5 fewer cases [95% CI 1 to 9]*). No differences for ER+, ER-, or noninvasive breast cancer; all-cause or breast cancer-specific mortality; or fractures	Not applicable	None	High; one large definitive trial	High
KQ 2. Benefits of risk reducing medications, continued	Tamoxifen vs. placebo	4 RCTs (n=28,193)	Tamoxifen reduced invasive breast cancer (RR 0.69; 95% CI 0.59 to 0.84; 7 fewer cases [95% CI 4 to 12]*); ER+ breast cancer (RR 0.58; 95% CI 0.42 to 0.81; 8 fewer cases [95% CI 4 to 13]*); and nonvertebral fractures (RR 0.66; 95% CI 0.45 to 0.98; 3 fewer cases [95% CI 0.2 to 5]*) compared with placebo. No differences for ER- or noninvasive breast cancer; all-cause or breast cancer-specific mortality; or vertebral fractures	Consistent; precise	Clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	High for all outcomes except fractures (based on one trial)	High

Table 10. Summary of Evidence Table

Key Question	Interventions	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 2. Benefits of risk reducing medications, continued	Raloxifene vs. placebo	2 RCTs (n=17,806)	Raloxifene reduced invasive breast cancer (RR 0.44; 95% CI 0.24 to 0.80; 9 fewer cases [95% CI 3 to 15]*); ER+ breast cancer (RR 0.33; 95% CI 0.15 to 0.70; 8 fewer cases [95% CI 4 to 13]*); and vertebral fractures (RR 0.61; 95% CI 0.53 to 0.73; 7 fewer cases [95% CI 5 to 9]*) compared with placebo. No differences for ER- or noninvasive breast cancer; all-cause or breast cancer-specific mortality; or nonvertebral fractures	Consistent; precise	Trials were primarily designed for osteoporosis and cardiovascular outcomes; participants were not selected based on breast cancer risk	High for all outcomes	High
KQ 2. Benefits of risk reducing medications, continued	Aromatase inhibitors (anastrozole; exemestane) vs. placebo	2 RCTs (n=8,424)	Aromatase inhibitors reduced invasive breast cancer (RR 0.45; 95% CI 0.26 to 0.70; 16 fewer cases [95% CI 8 to 24]*); and ER+ breast cancer (RR 0.37; 95% CI 0.19 to 0.63; 15 fewer cases [95% CI 8 to 20]*) compared with placebo. No differences for ER- or noninvasive breast cancer; all-cause or breast cancer-specific mortality; or fractures	Consistent; precise	Trials use different medications and exposure durations	High for all outcomes	High
KQ 2a. Benefits of risk reducing medications —timing and duration	Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	9 RCTs (n=74,170)	No significant differences in breast cancer outcomes by age. Despite variations in exposure time from 3 to 5 years, comparisons across similar medications indicated consistency in risk reduction for invasive breast cancer	Consistent; precise	No trials compared timing and duration directly. Age categories and durations varied across trials.	Moderate for tamoxifen; insufficient for other medications	High
KQ 2a. Benefits of risk reducing medications —persistence of effects	Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen (n=9,610); no trials of other medications	Tamoxifen reduced invasive and ER+ breast cancer 8 years after discontinuation	Consistent; precise	Long term followup data are lacking from most trials	Moderate for tamoxifen; insufficient for other medications	High

Table 10. Summary of Evidence Table

Key Question	Interventions	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3. Harms of risk reducing medications	Tamoxifen vs. raloxifene	1 RCT (n=19,747)	Tamoxifen increased thromboembolic events (RR 0.75; 95% CI 0.60 to 0.93; 4 more cases [95% CI 1 to 7]*); DVT (RR 0.72; 95% CI 0.54 to 0.95; 3 more cases [95% CI 1 to 5]*); endometrial cancer (RR 0.55; 95% CI 0.36 to 0.83; 5 more cases [95% CI 2 to 9]*); and cataracts (RR 0.80; 95% CI 0.72 to 0.95; 15 more cases [95% CI 8 to 22]*) compared with raloxifene. No differences for PE; CHD events; or stroke	Not applicable	None	High; one large definitive trial	High
KQ 3. Harms of risk reducing medications, continued	Tamoxifen vs. placebo	4 RCTs (n=28,193)	Tamoxifen increased thromboembolic events (RR 1.93; 95% CI 1.33 to 2.68; 5 more cases [95% CI 2 to 9]*); endometrial cancer (RR 2.25; 95% CI 1.17 to 4.41; 4 more cases [95% CI 1 to 8]*); and cataracts (RR 1.22; 95% CI 1.08 to 1.48; 26 more cases [95% CI 5 to 50]*) compared with placebo. No differences for DVT; PE; CHD events; or stroke	Consistent; precise	Clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	High for all outcomes except DVT, PE (based on 2 trials)	High
KQ 3. Harms of risk reducing medications, continued	Raloxifene vs. placebo	2 RCTs (n=17,806)	Raloxifene increased thromboembolic events (RR 1.56; 95% CI 1.11 to 2.60; 7 more cases [95% CI 0.3 to 17]*); endometrial cancer (RR 2.25; 95% CI 1.17 to 4.41; 4 more cases [95% CI 1 to 8]*); and cataracts (RR 1.22; 95% CI 1.08 to 1.48; 26 more cases [95% CI 5 to 50]*) compared with placebo. No differences for DVT; PE; CHD events; stroke; endometrial cancer; or cataracts	Consistent; precise	Trials were primarily designed for osteoporosis and cardiovascular outcomes; participants were not selected based on breast cancer risk	High for all outcomes	High
KQ 3. Harms of risk reducing medications, continued	Aromatase inhibitors (anastrozole; exemestane) vs. placebo	2 RCTs (n=8,424)	No differences between aromatase inhibitors and placebo for thromboembolic events; DVT; PE; CHD events; stroke; endometrial cancer; or cataracts	Consistent; precise	Trials use different medications and exposure durations	Low to moderate; followup inadequate for several outcomes	High

Table 10. Summary of Evidence Table

Key Question	Interventions	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3a. Harms of risk reducing medication—timing and duration	Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen for thrombo-embolic events (n=18,583); 1 RCT of tamoxifen (n=13,175) for endometrial cancer; no trials of other medications	Risks for thromboembolic events and endometrial cancer with tamoxifen were higher for older compared with younger women	Consistent; precise	No trials compared timing and duration directly. Age categories and durations varied across trials.	Moderate for tamoxifen; insufficient for other medications	High
KQ 3a. Harms of risk reducing medication — persistence of effects	Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen for thrombo-embolic events (n=9,610); 1 RCT of tamoxifen (n=7,139) for endometrial cancer; no trials of other medications	Risks for thromboembolic events and endometrial cancer with tamoxifen declined to normal after discontinuation	Consistent; precise	Long term followup data are lacking from most trials	Moderate for tamoxifen; insufficient for other medications	High

Table 10. Summary of Evidence Table

Key Question	Interventions	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 4. Variability by sub-populations	Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs for menopausal status (n=12,547); 5 RCTs for family history (n=56,136); 4 RCTs for BMI (n=26,230); 4 RCTs for breast lesions (n=41,346); 4 RCTs for risk categories (n=13,965); 1 RCT for reproductive factors (n=10,101)	Reduced risk for invasive cancer: • Tamoxifen in both pre and postmenopausal women. • Tamoxifen and raloxifene in women with or without family history of breast cancer, but inconsistent results, with sometimes more reduction in women without family histories. • Raloxifene, anastrozole, and exemestane in all BMI categories. • Tamoxifen and anastrozole had more effect when previous breast lesions (LCIS, ADH, ALH). • Tamoxifen, raloxifene, and anastrozole in all modified Gail model risk categories. • Raloxifene regardless of age at menarche, parity, or age at first live birth.	Inconsistent; imprecise	Trials were not designed for subgroup comparisons and analysis of differences between groups may be underpowered	Low and insufficient	High

* Per 1000 women over 5 years of use.

Abbreviations: ADH=atypical ductal hyperplasia; ALH=atypical lobular hyperplasia; CHD=coronary heart disease; CI=confidence interval; DVT=deep vein thrombosis; ER+=estrogen receptor positive; ER-=estrogen receptor negative; KQ=key question; LCIS=lobular carcinoma in situ; PE=pulmonary embolism; RCT=randomized control trial; RR=risk ratio.

Appendix A1. Search Strategies

Database: Database: Ovid MEDLINE®
Search Strategy:
---
1 exp Breast Neoplasms/pc [Prevention & Control]
2 exp aromatase inhibitors/ad, ae, tu, to
3 1 and 2
4 exp breast neoplasms/
5 Chemoprevention/
6 4 and 5
7 2 and 6
8 ((prevent* or chemoprev* or prophyla* or risk*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (exemestane or Aromasin or anastrozole or Arimidex or letrozole or Femara or (aromatas* adj3 (block* or interfer* or inhibit* or antagoni*))))).mp.
9 (chemoprev* adj7 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10 (risk* adj5 (reduc* or lower* or adjust* or assess* or compar* or alter* or chang* or calculat*) adj7 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11 9 or 10
12 2 and 11
13 3 or 7 or 8
14 3 or 7 or 8 or 12
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16

Database: Database: Ovid MEDLINE® without Revisions
Search Strategy:
---
1 exp Breast Neoplasms/pc [Prevention & Control]
2 exp Tamoxifen/ad, ae, tu, to
3 1 and 2
4 exp breast neoplasms/
5 Chemoprevention/
6 4 and 5
7 2 and 6
8 ((prevent* or chemoprev* or prophyla*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (tamoxif* or raloxif* or serm* or (selectiv* adj3 estrogen* adj3 receptor* adj3 modulat*)))).mp.
9 (chemoprev* adj7 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*))).mp. [mp=title, abstract, original title, name of substance

word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10 (risk* adj5 (reduc* or lower* or adjust* or assess* or compar* or alter* or chang* or calculat*) adj7 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*))).mp.
11 9 or 10
12 2 and 4 and 11
13 3 or 7 or 8 or 12
14 limit 13 to humans
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((prevent* or chemoprev* or prophyla*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (exemestane or Aromasin or anastrozole or Arimidex or letrozole or Femara or (aromatas* adj3 (block* or interfer* or inhibit* or antagoni*))))).mp.
2 ((prevent* or chemoprev* or prophyla*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (tamoxif* or raloxif* or serm* or (selectiv* adj3 estrogen* adj3 receptor* adj3 modulat*)))).mp.
3 limit 2 to yr="2013 -Current"
4 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj10 ((drug* or pharmac* or prescri* or dose* or dosag*) adj7 (risk* adj5 (reduc* or lower* or adjust* or assess* or compar* or alter* or chang* or calculat*)))).mp. [mp=title, abstract, full text, keywords, caption text]
5 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj10 chemoprev*).mp. [mp=title, abstract, full text, keywords, caption text]
6 1 or 3 or 4 or 5
7 1 or 3 or 4 or 5

Appendix A1. Search Strategies

Database: Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((prevent* or chemoprev* or prophyla*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (exemestane or Aromasin or anastrozole or Arimidex or letrozole or Femara or (aromatas* adj3 (block* or interfer* or inhibit* or antagoni*))))).mp.
2 ((prevent* or chemoprev* or prophyla*) adj10 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj7 (tamoxif* or raloxif* or serm* or (selectiv* adj3 estrogen* adj3 receptor* adj3 modulat*)))).mp.
3 limit 2 to yr="2013 -Current"
4 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj10 ((drug* or pharmac* or prescri* or dose* or dosag*) adj7 (risk* adj5 (reduc* or lower* or adjust* or assess* or compar* or alter* or chang* or calculat*)))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 ((breast* or mammar*) adj5 (cancer* or neoplas* or tumor* or tumour* or carcino* or adenocarcin* or malig*) adj10 chemoprev*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 1 or 3 or 4 or 5

Database: Elsevier Embase®
Search Strategy:

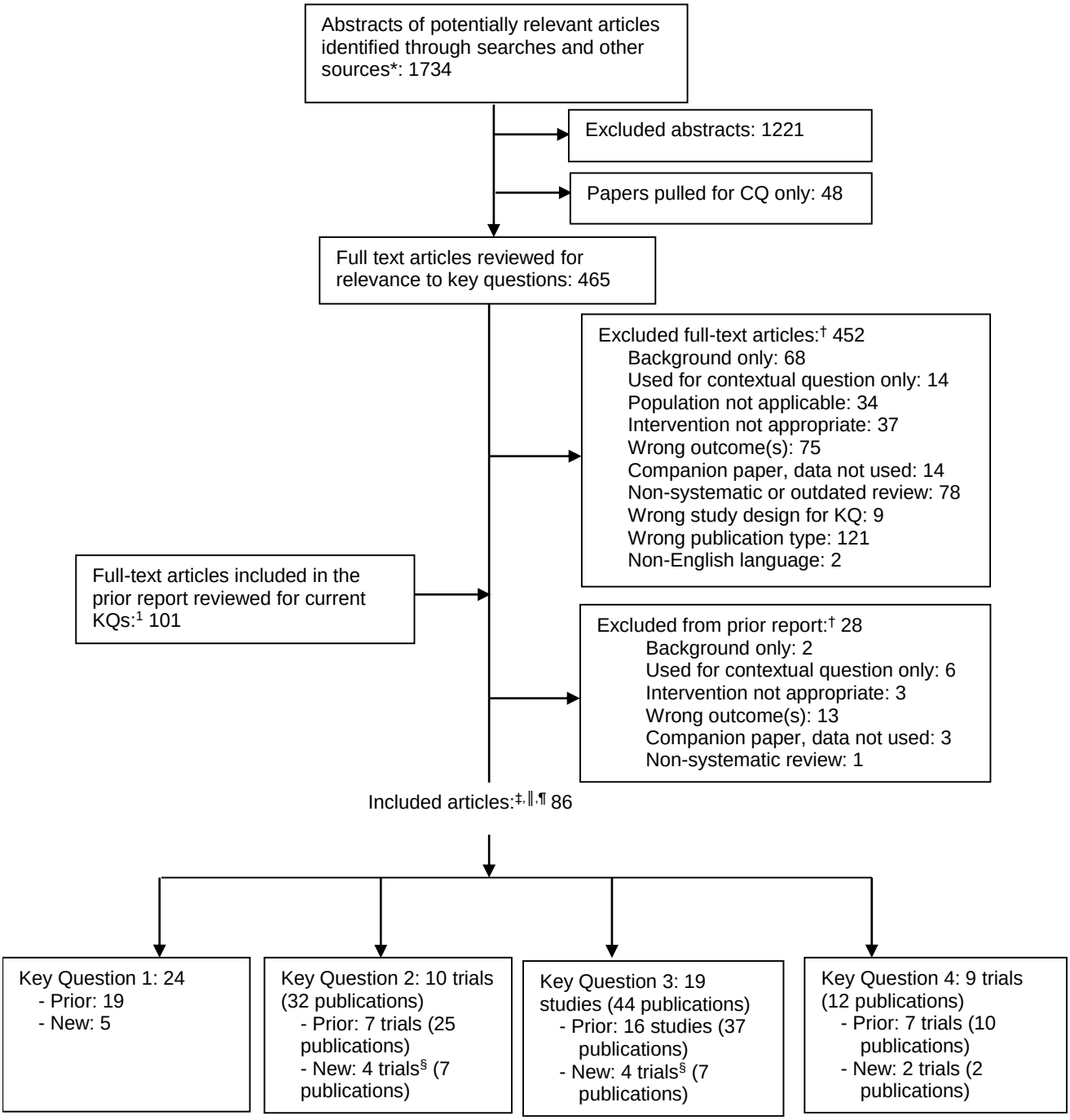
((((('tamoxifen'/exp OR 'tamoxifen'/exp OR tamoxifen OR 'raloxifene'/exp OR 'raloxifene'/exp OR raloxifene) AND 'breast cancer'/exp AND 'risk reduction'/exp OR 'breast cancer'/exp) AND 'chemoprophylaxis'/exp AND [embase]/lim NOT [medline]/lim OR 'aromatase inhibitor'/exp OR 'aromatase inhibitor' OR 'aminoglutethimide'/exp OR 'aminoglutethimide'/exp OR aminoglutethimide OR 'testolactone'/exp OR 'testolactone'/exp OR testolactone OR 'anastrozole'/exp OR 'anastrozole'/exp OR anastrozole OR 'letrozole'/exp OR 'letrozole'/exp OR letrozole OR 'exemestane'/exp OR 'exemestane'/exp OR exemestane OR 'vorozole'/exp OR 'vorozole'/exp OR vorozole OR 'formestane'/exp OR 'formestane'/exp OR formestane OR 'fadrozole'/exp OR 'fadrozole'/exp OR fadrozole) AND 'breast cancer'/exp AND 'risk reduction'/exp OR 'breast cancer'/exp) AND 'chemoprophylaxis'/exp AND [embase]/lim NOT [medline]/lim AND [english]/lim AND [humans]/lim

Appendix A2. Inclusion Criteria

	Included	Excluded
Populations	Women without preexisting breast cancer, including women who are known carriers of BRCA genetic mutations and women with previous nonmalignant breast biopsies (e.g., atypical hyperplasia)	Women with preexisting breast cancer (invasive or ductal carcinoma in situ); men; populations dissimilar to those in the United States
Interventions	**KQ 1:** Risk assessment **KQs 2–4:** Tamoxifen, raloxifene, and aromatase inhibitors	**KQ 1:** Risk assessment done by a specialist or not able to be completed in primary care setting **KQs 2–4:** Medications not used or available in the United States; other medications not listed as included
Comparisons	**KQ 1:** Risk assessment methods vs. usual care or an alternative risk assessment method **KQs 2–4**: Medication vs. placebo; tamoxifen vs. raloxifene, tamoxifen vs. aromatase inhibitors, and raloxifene vs. aromatase inhibitors	Comparisons with other types of medications
Outcomes	**KQ 1:** Measures of risk assessment test performance (sensitivity, specificity; positive and negative likelihood ratio; c-statistic) **KQs 2, 4:** Invasive and noninvasive breast cancer incidence; breast cancer and all-cause mortality; other beneficial outcomes (e.g., reduced fractures caused by certain medications) **KQs 3, 4:** Adverse effects (including but not limited to: thromboembolic events, cardiovascular events, metabolic disorders, musculoskeletal symptoms, mental health, genitourinary outcomes, adverse breast outcomes, other malignancies, ophthalmologic disorders, gastrointestinal/hepatobiliary disorders, other adverse events affecting quality of life)	Other outcomes
Setting	Primary care settings; settings comparable to U.S. practice	Practice settings dissimilar to those in the United States
Study Design	**KQ 1:** Discriminatory accuracy studies **KQs 1a, 1b, 2–4:** Randomized, controlled trials; observational studies, with or without comparison groups, except for efficacy (**KQ 2**)	Other study designs
Study Quality	Good- and fair-quality studies for meta-analyses	Poor-quality studies

Abbreviations: BRCA=breast cancer susceptibility gene; KQ=key questions; U.S.=United States.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews

†See Appendix A4 for the list of excluded studies and Appendix A2 for the list of exclusion criteria.

‡Studies that provided data and contributed to the body of evidence were considered 'included.'

‖Studies may have been used to answer more than one question.

¶This includes 43 studies in 86 publications.

§This includes 1 new publication of long-term results for the International Breast Cancer Intervention Study (IBIS-I), which was included in the prior report and 3 new trials (2 of aromatase inhibitors and 1 of low dose tamoxifen)

1. Nelson HD, Smith ME, 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):604-614.

Exclusions from Key Questions code: 2: background information only; 3: contextual information only; 4: ineligible population; 5: ineligible intervention; 6: ineligible outcome; 7; ineligible publication type; 9: ineligible study design; 10: non-English paper; 11: nonsystematic review or companion paper not used for evidence.

Excludes from Prior Report

1. Archer DF, Pinkerton JV, Utian WH, et al. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. Menopause. 2009;16(6):1109-115. doi: 10.1097/gme.0b013e3181a818db PMID: 19543129 Exclusion: 5
2. Armstrong K, Quistberg DA, Micco E, et al. Prescription of tamoxifen for breast cancer prevention by primary care physicians. Arch Intern Med. 2006 Nov 13;166(20):2260-5. doi: 10.1001/archinte.166.20.2260. PMID: 17101945. Exclusion: 3
3. Bastian LA, Lipkus IM, Kuchibhatla MN, et al. Women's interest in chemoprevention for breast cancer. Arch Intern Med. 2001 Jul 9;161(13):1639-44. PMID: 11434796. Exclusion: 6
4. Bober SL, Hoke LA, Duda RB, et al. Decision-making about tamoxifen in women at high risk for breast cancer: Clinical and psychological factors. J Clin Oncol. 2004;22(24):4951-7. doi: 10.1200/JCO.2004.05.192. PMID: 15598980. Exclusion: 3
5. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. doi: 10.1056/NEJMoa062790. PMID: 17229950. Exclusion: 6
6. Coopey SB, Mazzola E, Buckley JM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012 Dec;136(3):627-33. doi: 10.1007/s10549-012-2318-8. PMID: 23117858. Exclusion: 2
7. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008 Jan-Feb;11(1):44-7. doi: 10.1111/j.1524-4733.2007.00213.x. PMID: 18237359. Exclusion: 6
8. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. N Engl J Med. 2008;359(7):697-708. doi: 10.1056/NEJMoa0800743. PMID: 18703472. Exclusion: 5
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RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups
- For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
- For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Single arm cohort studies were rated based on initial assembly of group, consideration of potential confounders, important outcomes considered, measurements: equal, reliable, and valid (includes masking of outcome assessment), and reporting of attrition if applicable.

Definition of ratings based on above criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients

Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

*Reference: U.S. Preventive Services Task Force Procedure Manual. December 2015. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A6. Expert Reviewers of the Draft Report

- Therese Bartholomew Bevers, MD, FAAFP, Medical Director, Cancer Prevention Center, Professor of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center; Houston, TX.
- Jack Cuzick, PhD, FRS, CBE, Director and Head of Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine; London, UK.
- Leslie Ford, MD, Associate Director for Clinical Research, Division of Cancer Prevention, National Cancer Institute; Washington DC.
- Brandy Heckman-Stoddard, PhD, MPH, Chief, Division of Cancer Prevention, National Cancer Institute; Washington DC.
- Barry Kramer, MD, MPH, Director, Division of Cancer Prevention, National Cancer Institute; Washington DC.
- Sam G. Smith, MSc, PhD, Cancer Research UK Postdoctoral Fellow, University Academic Fellow, Leeds Institute of Health Sciences; London, UK.
- Diana Petitti, MD, MPH, Department of Biomedical Informatics, University of Arizona; Tucson, AZ.
- Brandy Peaker, MD, MPH, Centers for Disease Control and Prevention; Atlanta, GA.

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the final report findings.

Appendix B1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?
Prior review						
Adams-Campbell, 2007	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Amir, 2003	Yes	Yes	Yes	NR	No	Yes
Barlow, 2006	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Yes
Boughey, 2010	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Yes
Boyle, 2004	Unclear	No	Yes	NR	NA, evaluated cutoff values	Yes
Chen, 2006	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Chlebowski, 2007	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Unclear
Colditz, 2000	Yes	No	Yes	NR	NA, evaluated cutoff values	Unclear
Colditz, 2004	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Unclear
Costantino, 1999	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Yes
DeCarli, 2006	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Gail, 1989	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Gail, 2007	Unclear	No	Unclear	NR	Unclear	Unclear
Petracci, 2011	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Rockhill, 2001	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Unclear

Appendix B1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality rating
Prior review						
Adams-Campbell, 2007	Yes	Yes	Yes	Unclear	Yes	Good
Amir, 2003	Unclear	Yes	Yes	Unclear	Yes	Fair
Barlow, 2006	Yes	Yes	Unclear	Unclear	Yes	Fair
Boughey, 2010	NR	Yes	Yes	Yes	Yes	Good
Boyle, 2004	NR	Unclear	Yes	Yes	Yes	Fair
Chen, 2006	NR	Yes	Yes	Yes	Yes	Good
Chlebowski, 2007	NR	Yes	Yes	Yes	Yes	Good
Colditz, 2000	NR	Yes	Yes	Yes	Yes	Good
Colditz, 2004	NR	Yes	Yes	Yes	Yes	Good
Costantino, 1999	NR	Yes	Yes	Yes	Yes	Good
DeCarli, 2006	NR	Yes	Yes	Yes	Yes	Good
Gail, 1989	NR	Yes	Yes	Yes	Yes	Good
Gail, 2007	NR	Unclear	Unclear	Unclear	NR	Fair
Petracci, 2011	NR	Yes	Yes	Yes	Yes	Good
Rockhill, 2001	NR	Yes	Yes	Yes	Yes	Good

Appendix B1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?
Rockhill, 2003	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Unclear
Tamimi, 2010	Yes	No	Yes	NR	NA, evaluated cutoff values	Yes
Tice, 2008	Yes	Yes	Yes	NR	NA, evaluated cutoff values	Yes
Tyrer, 2004	Yes	Unclear	Unclear	NR	NA, evaluated cutoff values	Yes
Current review						
Brentnall, 2015	Yes	Yes	Yes	Yes	Unclear	Yes
Matsuno, 2011	Yes	No	Yes	Unclear	Yes	Unclear
Tice, 2015	Unclear	Yes	Yes	Unclear	Unclear	Yes
Vacek, 2011	Yes	Yes	Yes	Unclear	Unclear	Yes
Warwick, 2014	No	No	Unclear	Unclear	Unclear	Unclear

Appendix B1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality rating
Rockhill, 2003	NR	Yes	Yes	Yes	Yes	Good
Tamimi, 2010	NR	Yes	Yes	Yes	Yes	Good
Tice, 2008	NR	Yes	Yes	Yes	Yes	Good
Tyrer, 2004	NR	NR	Yes	Yes	Yes	Fair
Current review						
Brentnall, 2015	Unclear	Yes	No, only those suspected of cancer	Yes	Yes	Fair
Matsuno, 2011	Unclear	Unclear	Unclear	Unclear	Yes	Fair
Tice, 2015	Unclear	Yes	Yes	Yes	Yes	Fair
Vacek, 2011	Unclear	Unclear	Yes	Yes	Yes	Fair
Warwick, 2014	Unclear	Unclear	Unclear	Unclear	Yes	Poor

Appendix B2. Quality Assessment of Randomized Controlled Trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?
Primary prevention trials								
STAR Vogel, 2006	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
IBIS-I Cuzick, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
NSABP-1 Fisher, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Royal Marsden Powles, 1998	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Italian Veronesi, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RUTH Barrett-Connor, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MORE Cummings, 1999	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CORE Martino, 2004	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MAP.3 Goss, 2011	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
HOT DeCensi, 2013	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
IBIS-II Cuzick, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raloxifene trials								
Cohen, 2000*	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Delmas, 1997*	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Goldstein, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Johnston, 2000*	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Jolly, 2003*	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Lufkin, 1998	Yes	Unclear	Mostly, differences in age and alcohol use	Yes	Yes	Yes	Yes	No
McClung, 2006	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes
Meunier, 1999	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes

Appendix B2. Quality Assessment of Randomized Controlled Trials

Author, year	Loss to followup: differential (>10%)/ high (>20%)?	Analyze patients in the groups in which they were randomized?	Quality rating
Primary prevention trials			
STAR Vogel, 2006	No/No	Yes	Good
IBIS-I Cuzick, 2002	Unclear	Yes	Good
NSABP-1 Fisher, 1998	No/No	Yes	Good
Royal Marsden Powles, 1998	No/No	Yes	Good
Italian Veronesi, 1998	No/No	Yes	Good
RUTH Barrett-Connor, 2006	No/No	Yes	Good
MORE Cummings, 1999	No/Yes (23% overall)	Yes	Good
CORE Martino, 2004	No/No	Yes	Good
MAP.3 Goss, 2011	No/No	Yes	Good
HOT DeCensi, 2013	No/No	Yes	Good
IBIS-II Cuzick, 2014	No/No	Yes	Good
Raloxifene trials			
Cohen, 2000*	Unclear	Yes	Fair
Delmas, 1997*	Not reported/Yes (25% overall)	Yes	Fair
Goldstein, 2005	No/No	Yes	Good
Johnston, 2000*	Not reported/Yes (37% overall)	Yes	Fair
Jolly, 2003*	Unclear	Yes	Fair
Lufkin, 1998	Unclear	Yes	Fair
McClung, 2006	33% discontinued overall, no other information	Yes	Fair
Meunier, 1999	No/No	Yes	Fair

Appendix B2. Quality Assessment of Randomized Controlled Trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?
Raloxifene trials								
Morii, 2003	Yes	Yes	Mostly, differences in lumbar spine bone mineral density, and serum parathyroid hormone	Yes	Unclear	Yes	Yes	Yes
Palacios, 2004	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes

Author, year	Loss to followup: differential (>10%)/ high (>20%)?	Analyze patients in the groups in which they were randomized?	Quality rating
Raloxifene trials			
Morii, 2003	No/No	Yes	Fair
Palacios, 2004	No/No	Yes	Good

*Same study participants (Cohen, 2000; Delmas, 1997; Johnston, 2000; and Jolly, 2003)

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Age (years)	Interventions	Exposure time (years)	Followup time (years)	Cut-off date	N for outcome (A vs. B)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	Mean: 58.5	A) Tamoxifen 20 mg/day B) Raloxifene 60 mg/day	Mean: 3.1 vs. 3.2 Mean: 3.6 vs. 3.9 NR	Mean: 3.9 Median: 6.8 Median: 6.8	12/31/2005 3/31/2009 3/31/2009	9726 vs. 9745 9736 vs. 9754 4739 vs. 4717
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	Mean: 50.8	A) Tamoxifen 20 mg/day B) Placebo	Unclear 5 5	Median: 4.2 Median: 8.0 Median: 16.0	1/1/2002 4/1/2006 5/1/2014	3573 vs. 3566 3573 vs. 3566 3579 vs. 3575
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	All ≥35; 2.8% 35-39; 36.5% 40-49; 30.6% 50-59; 24.1% 60-69; 6.0% ≥70	A) Tamoxifen 20 mg/day B) Placebo	Median: 4.0	Median: 4.6 Median: 7.0 Mean: 4.2	3/31/1998 3/31/2005 3/31/1998	6576 vs. 6599 6597 vs. 6610 4110 vs. 4199
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	Median: 47	A) Tamoxifen 20 mg/day B) Placebo	Unclear 5 Unclear	Median: 5.8 Median: 13.2 Median: 2.9 years	Unclear 9/1/2006 Unclear	1238 vs. 1233
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	Median: 51	A) Tamoxifen 20 mg/day B) Placebo	Median: 2.5 Unclear Mean: 4 Unclear	Median: 3.8 Median: 6.8 Mean 11.2 Median: 6.8	Unclear 2/1/2001 12/31/2005 Unclear	2700 vs. 2708

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Woman-years of followup (A v.s B)	BC deaths (A vs. B)	RR of BC deaths (95% CI)	All-cause mortality (A vs. B)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR	4 vs. 2 11 vs. 4 NR	NR	101 vs. 92 236 vs. 202 NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	14,998 vs. 14,969 28,555 vs. 28,573 55,419 vs. 54,624	2 vs. 2 11 vs. 13 31 vs. 26	NR 0.85 (0.34 to 2.05) 1.19 (0.68 to 2.10)*	25 vs. 11 65 vs. 55 182 vs. 166
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	26,154 vs. 26,247 40,844 vs. 40,648 NR	3 vs. 6 12 vs. 11 NR	0.81 (0.56 to 1.16) 1.10 (0.85 to 1.43) NR	57 vs. 71 126 vs. 114 NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	4 vs. 1 12 vs. 9 NR	NR	9 vs. 6 54 vs. 54 NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	0 vs. 0 0 vs. 0 2 vs. 2 NR	NA NA NR NR	NR 10 vs. 20 36 vs. 38 NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of all-cause mortality (95% CI)	All BC occurrence (A vs. B)	RR of all BC occurrence (95% CI)	Invasive BC (A vs. B)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	0.94 (0.71 to 1.26) 0.84 (0.70 to 1.02) NR	NR	NR	163 vs. 168 -ER+: 115 vs. 109 -ER-: 44 vs. 51 247 vs. 310 NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	NR 1.18 (0.81 to 1.73) 1.10 (0.88 to 1.37)*	69 vs. 101 142 vs. 195 251 vs. 350	0.68 (0.50 to 0.92)* 0.73 (0.58 to 0.91) 0.71 (0.60 to 0.83)†	64 vs. 85 -ER+: 16 vs. 23 -ER-: 19 vs. 19 124 vs. 168 -ER+: 87 vs. 132 -ER-: 35 vs. 35 214 vs. 289 -ER+: 160 vs. 238 -ER-: 50 vs. 47
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	0.81 (0.56 to 1.16) 1.10 (0.85 to 1.43) NR	124 vs. 244 205 vs. 343 NR	NR	89 vs. 175 -ER+: 41 vs. 130 -ER-: 38 vs. 31 145 vs. 250 -ER+: 70 vs. 182 -ER-: 56 vs. 42 NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR 0.99 (0.68 to 1.44)† NR	34 vs. 36 96 vs. 113 NR	1.06 (0.7 to 1.7) 0.84 (0.64 to 1.10)† NR	NR 82 vs. 104 -ER+: 53 vs. 86 -ER-: 24 vs. 17 NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR NR 0.95 (0.60 to 1.49) NR	19 vs. 22 34 vs. 45 62 vs. 74 NR	NR NR 0.84 (0.60 to 1.17) NR	NR NR 9 vs. 6 NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of invasive BC (95% CI)	Noninvasive BC (A vs. B)	RR of noninvasive BC (95% CI)	Invasive EC (A vs. B)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	1.02 (0.82 to 1.28) -ER+: 0.93 (0.72 to 1.24) -ER-: 1.15 (0.75 to 1.77) 1.24 (1.05 to 1.47) NR	57 vs. 80 -DCIS: 30 vs. 44 -LCIS: 21 vs. 29 -Mixed: 6 vs. 7 101 vs. 137 -DCIS: 70 vs. 86 -LCIS: 33 vs. 34 -Mixed: 8 vs. 17 NR	1.46 (0.90 to 2.41) -DCIS: 1.37 (0.76 to 2.54) -LCIS: 1.16 (0.33 to 4.18) -Mixed: 1.40 (0.98 to 2.00) 1.22 (0.95 to 1.59) -DCIS: 1.22 (0.88 to 1.69) -LCIS: 1.02 (0.61 to 1.70) -Mixed: 2.11 (0.86 to 5.64) NR	36 vs. 23 65 vs. 37 NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	0.75 (0.54 to 1.04)* -ER+: 0.69 (0.37 to 1.02* -ER-: 1.00 (0.53 to 1.87)* 0.74 (0.58 to 0.94) -ER+: 0.66 (0.50 to 0.87) -ER-: 1.00 (0.61 to 1.65) 0.73 (0.61 to 0.87)† -ER+: 0.66 (0.54 to 0.81)† -ER-: 1.05 (0.71 to 1.57)†	5 vs. 16 17 vs. 27 35 vs. 53 Defined as DCIS	0.31 (0.12 to 0.82)* 0.63 (0.32 to 1.20) 0.65 (0.43 to 1.00)†	11 vs. 5 17 vs. 11 29 vs. 20 -Note: these were not specifically invasive
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	0.51 (0.39 to 0.66) -ER+: 0.31 (0.22 to 0.45) -ER-: 1.22 (0.74 to 2.03) 0.57 (0.46 to 0.70) -ER+: 0.38 (0.28 to 0.50) -ER-: 1.31 (0.86 to 2.01) NR	35 vs. 69 60 vs. 93 NR Definition not specified	0.50 (0.33 to 0.77) 0.63 (0.45 to 0.89) NR	36 vs. 15 53 vs. 17 NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR 0.78 (0.58 to 1.04)† -ER+: 0.61 (0.43 to 0.86)† -ER-: 1.4 (0.7 to 2.6)† NR	4 vs. 4 14 vs. 9 NR Defined as DCIS	NR	4 vs. 1 13 vs. 5 NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR NR 9 vs. 6 NR Definition not specified	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of invasive EC (95% CI)	DVT (A vs. B)	RR of DVT (95% CI)	PE (A vs. B)	RR of PE (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	0.62 (0.35 to 1.08) 0.55 (0.36 to 0.83) NR	87 vs. 65 118 vs. 86 NR	0.74 (0.53 to 1.03) 0.72 (0.54 to 0.95) NR	54 vs. 35 84 vs. 68 NR	0.64 (0.41 to 1.00) 0.80 (0.57 to 1.11) NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	2.20 (0.80 to 6.06)* 1.55 (0.68 to 3.65) 1.45 (0.79 to 2.71)*	24 vs. 5 68 vs. 37 -Note: DVT/PE combined 50 vs. 29	NR 1.84 (1.21 to 2.82) 1.73 (1.07 to 2.85)*	13 vs. 10 See DVT column 30 vs. 22	NR See DVT column 1.37 (0.76 to 2.49)*
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	2.53 (1.35 to 4.97) 3.28 (1.87 to 6.03) NR	35 vs. 22 49 vs. 34 NR	1.60 (0.91 to 2.86) 1.44 (0.91 to 2.30) NR	18 vs. 6 28 vs. 13 NR	3.01 (1.15 to 9.27) 2.15 (1.08 to 4.51) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	4 vs. 2 NR NR	NR	3 vs. 2 NR NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	6 vs. 3 7 vs. 6 NR NR	NR	1 vs. 1 2 vs. 1 NR NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Overall thrombo event (A vs. B)	RR of overall thromob events (95% CI)	Stroke (A vs. B)	RR of stroke (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	141 vs. 100 202 vs. 154 NR	0.70 (0.54 to 0.91) 0.75 (0.60 to 0.93) NR	53 vs. 51 NR NR	0.96 (0.64 to 1.43) NR NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	43 vs. 17 117 vs. 68 104 vs. 62	NR 1.72 (1.27 to 2.36) 1.70 (1.22 to 2.37)*	13 vs. 11 15 vs. 12 -Note: Stroke/CVA combined 30 vs. 28 -Note: stroke/CVA combined	NR 1.25 (0.55 to 2.93) 1.07 (0.62 to 1.86)
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR	38 vs. 24 71 vs. 50 NR	1.59 (0.93 to 2.77) 1.42 (0.97 to 2.08) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR 7 vs. 9 NR	NR	NR 7 vs. 9 NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	38 vs. 18 NR 44 vs. 28 NR	NR NR 1.63 (1.02 to 2.62) NR	5 vs. 0 NR NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	TIA (A vs. B)	RR of TIA (95% CI)	Overall cerebrovascular events (A vs. B)	RR of overall cerebrovascular events (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	41 vs. 50 NR NR	1.21 (0.79 to 1.88) NR NR	NR	NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	3 vs. 6 17 vs. 22 27 vs. 40	NR 0.77 (0.39 to 1.52) 0.67 (0.40 to 1.12)	16 vs. 17 32 vs. 34 62 vs. 74	NR 0.94 (0.56 to 1.57) 0.83 (0.58 to 1.19)*
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	19 vs. 25 31 vs. 34 NR	0.76 (0.40 to 1.44) 0.91 (0.54 to 1.52) NR	NR	NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	9 vs. 5 15 vs. 9 12 vs. 7 NR	NR NR 1.78 (0.70 to 4.52) NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	MI (A vs. B)	RR of MI (95% CI)	Angina (A vs. B)	RR of angina (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	48 vs. 37 NR NR	0.77 (0.48 to 1.20) NR NR	51 vs. 63 NR NR	1.23 (0.84 to 1.81) NR NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	5 vs. 5 9 vs. 15 13 vs. 17	NR 0.60 (0.23 to 1.46) 0.76 (0.34 to 1.67)*	39 vs. 34 60 vs. 51 60 vs. 51	NR 1.18 (0.80 to 1.74) 1.18 (0.80 to 1.75)
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	31 vs. 28 43 vs. 44 NR	1.11 (0.65 to 1.92) 0.97 (0.62 to 1.52) NR	13 vs. 14 34 vs. 33 NR	0.93 (0.40 to 2.14) 1.03 (0.62 to 1.71) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR 5 vs. 5 NR NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Acute ischemic syndrome (A vs. B)	RR of acute ischemic syndrome (95% CI)	Overall cardiovascular events (A vs. B)	RR of overall cardiovascular event (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	15 vs. 26 NR NR	1.72 (0.88 to 3.50) NR NR	114 vs. 126 NR NR	1.10 (0.85 to 1.43) NR NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	NR	NR	73 vs. 63 122 vs. 123 141 vs. 153	NR 0.99 (0.77 to 1.29) 0.92 (0.72 to 1.17)
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	27 vs. 20 36 vs. 32 NR	1.36 (0.73 to 2.55) 1.12 (0.68 to 1.86) NR	71 vs. 62 113 vs. 109 NR	1.15 (0.81 to 1.64) 1.03 (0.79 to 1.36) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR 10 vs. 12 NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Any fractures (A vs. B)	RR of any fractures (95% CI)	Hip fractures (A vs. B)	RR of hip factures (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	104 vs. 96 NR NR	0.92 (0.69 to 1.22) NR NR	26 vs. 23 NR NR	0.88 (0.48 to 1.60) NR NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	116 vs. 127 240 vs. 235 NR	NR 1.02 (0.86 to 1.21) NR	45 vs. 40 -Note: hip, spine, wrist, or forearm combined 91 vs. 76 -Note: hip, spine, wrist, or forearm combined NR	NR 1.19 (0.89 to 1.62) NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	111 vs. 137 -Note: this includes other lower radius fractures, which are not included below 80 vs. 116 NR	0.81 (0.63 to 1.05) 0.68 (0.51 to 0.92) NR	12 vs. 22 24 vs. 35 NR	0.55 (0.25 to 1.15) 0.68 (0.39 to 1.18) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR 19 vs. 22 NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Spine (vertebral) fractures (A vs. B)	RR of spine (vertebral) fractures (95% CI)	Radius (wrist) fractures (A vs. B)	RR of radius fractures (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	53 vs. 52 NR NR	0.98 (0.65 to 1.46) NR NR	27 vs. 23 NR NR	0.85 (0.46 to 1.53) NR NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	NR See hip fracture column NR	NR See hip fracture column NR	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	23 vs. 31 40 vs. 53 NR	0.74 (0.41 to 1.32) 0.75 (0.48 to 1.15) NR	14 vs. 23 20 vs. 29 NR	0.61 (0.29 to 1.23) 0.69 (0.37 to 1.25) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Hysterectomy (A vs. B)	RR of hysterectomy (95% CI)	Cataracts (A vs. B)	RR cataracts (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	244 vs. 111 349 vs. 162 349 vs. 162	0.44 (0.35 to 0.56) 0.45 (0.37 to 0.54) 0.45 (0.37 to 0.54)	394 vs. 313 739 . 603 NR	0.79 (0.68 to 0.92) 0.80 (0.72 to 0.89) NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	-Pre: 76 vs. 53 -Post: 27 vs. 14 NR NR	NR	38 vs. 37 67 vs. 54 NR	NR 1.24 (0.87 to 1.77) NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR NR 1.7 (1.46 to 2.02) -Pre: 1.6 (1.29 to 1.88) -Post: 2.2 (1.60 to 3.13)	574 vs. 507 NR NR	1.14 (1.01 to 1.29) 1.21 (1.10 to 1.34) NR
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR 177 vs. 96 29 vs. 16	NR	NR 12 vs. 3 NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Endometrial cancer (A vs. B)	RR of endometrial cancer (95% CI)	Hyperplasia (A vs. B)	RR of hyperplasia (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	36 vs. 23 65 vs. 37 65 vs. 37	0.62 (0.35 to 1.08) 0.550.36 to 0.83) 0.55 (0.36 to 0.83)	84 vs. 14 126 vs. 25 126 vs. 25	0.16 (0.09 to 0.29) 0.190.12 to 0.29) 0.19 (0.12 to 0.29)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	11 vs. 5 17 vs. 11 29 vs. 20 -Note: these were not specifically invasive	2.20 (0.80 to 6.06)* 1.550.68 to 3.65) 1.45 (0.79 to 2.71)*	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR 53 vs. 17 NR	NR 3.281.87 to 6.03) NR	NR NR 310 vs. 183	NR NR -Pre: 1.65 (1.34 to 2.04) -Post: 2.38 (1.56 to 3.71)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR NR NR 2.4 (1.5 to 4.0)*	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Hyperplasia without atypia (A vs. B)	RR of hyperplasia without atypia (95% CI)	Hyperplasia with atypia (A vs. B)	RR of hyperplasia with atypia (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	72 vs. 13 104 vs. 21 104 vs. 21	0.18 (0.09 to 0.32) 0.190.11 to 0.31) 0.19 (0.11 to 0.31)	12 vs. 1 22 vs. 4 22 vs. 4	0.08 to (0 to 0.55) 0.170.04 to 0.51) 0.17 (0.04 to 0.51)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	NR	NR	-Pre: 118 vs. 53 -Post: 27 vs. 14 NR NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR NR - Simple: 224 vs. 115 -Complex: 59 vs. 47	NR NR -Simple: 2.06 (1.64 to 2.60) -Complex: 1.33 (0.89 to 1.99)	NR NR -Simple: 10 vs. 4 -Complex: 17 vs. 17	NR NR -Simple: 2.64 (0.76 to 11.54) -Complex: 1.06 (0.51 to 2.20)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Oophorectomy (A vs. B)	RR of oophorectomy (95% CI)	Currettage (A vs. B)	RR of currettage (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR NR 271 vs. 192 Bilateral	NR NR 0.50 (0.42 to 0.60)	NR NR 673 vs. 218	NR NR 0.30 (0.26 to 0.35)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	-Pre: 106 vs. 76 - Post: 72 vs. 18 NR NR	NR	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR NR 1.6 (1.34 to 1.98) -Pre: 1.5 (1.19 to 1.87) -Post: 2.1 (1.39 to 3.27) Bilateral	NR	NR NR 2.0 (1.74 to 2.35) -Pre: 1.5 (1.23 to 1.77) -Post: 3.8 (2.86 to 5.09)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR NR 15 vs. 19	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Laparoscopy (A vs. B)	RR of laparoscopy (95% CI)	Hysteroscopy (A vs. B)	RR of hysteroscopy (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR NR 14 vs. 4	NR NR 0.28 (0.07 to 0.90)	NR NR 493 vs. 151	NR NR 0.29 (0.24 to 0.35)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	- Pre: 136 vs. 107 -Post: 92 vs. 31 NR NR	NR	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR NR 1.5 (1.17 to 1.85) -Pre: 1.3 (0.96 to 1.65) -Post: 2.2 (1.40 to 3.51)	NR	NR NR 1.9 (1.33 to 2.62) -Pre: 1.4 (0.91 to 2.09) -Post: 3.5 (1.82 to 6.99)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR NR 4 vs. 5	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Leiomyomas (A vs. B)	RR of leiomyomas (95% CI)	Ovarian cysts (A vs. B)	RR of ovarian cysts (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR NR 757 vs. 443	NR NR 0.55 (0.49 to 0.62)	NR NR 236 vs. 147	NR NR 0.60 (0.049 to 0.74)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	-Pre: 86 vs. 33 -Post: 15 vs. 9 NR NR	NR	-Pre: 69 vs. 43 -Post: 61 vs. 22 NR NR Defined as endometrial polyps	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR NR 1.3 (1.17 to 1.54) -Pre: 1.3 (1.14 to 1.55) -Post: 1.4 (1.04 to 1.80)	NR	NR NR 1.4 (1.18 to 1.70) - Pre: 1.5 (1.20 to 1.78) -Post: 1.2 (0.76 to 1.92)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR NR -Pre: 44 vs. 40 -Post 13 vs. 4	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Polyps (A vs. B)	RR of polyps (95% CI)	Endometriosis (A vs. B)	RR of endometriosis (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR NR 575 vs. 185 Definition not specified	NR NR 0.30 (0.25 to 0.35)	NR NR 190 vs. 64	NR NR 0.32 (0.24 to 0.43)
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	Pre: 14 vs. 16 Post: 6 vs. 5 NR NR	NR	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR Definition not specified	NR NR 2.1 (1.74 to 2.45) -Pre: 1.9 (1.55 to 2.41) -Post: 2.4 (1.76 to 3.24)	NR	NR NR 2.0 (1.50 to 2.78) -Pre: 1.9 (1.35 to 2.70) -Post: 2.6 (1.29 to 5.58)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Endometritis (A vs. B)	RR of endometritis (95% CI)
STAR	Vogel, 2006 Vogel, 2010 Runowicz, 2011	NR	NR
IBIS-I	Cuzick, 2002 Cuzick, 2007 Cuzick, 2015	NR	NR
NSABP-1	Fisher, 1998 Fisher, 2005 Chalas, 2005	NR	NR NR 0.8 (0.44 to 1.62) -Pre: 0.8 (0.41 to 1.64) -Post: 1.0 (0.07 to 14.26)
Marsden	Powles, 1998 Powles, 2007 Powles, 1994	NR	NR
Italian	Veronesi, 1998 Veronesi, 2002 Veronesi, 2007 Veronesi, 2003	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Age (years)	Interventions	Exposure time (years)	Followup time (years)	Cut-off date	N for outcome (A vs. B)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	Median: 66.5	A) Raloxifene 60 or 120 mg/day B) Placebo	3 3 3 4 4 4 4	Median: 3.3 Median: 4 Median: 8 Mean: 7.8 Median: 4 Median: 8 Median: 8	Unclear	2557 vs. 2572 vs. 2576 2557 vs. 2572 vs. 2576 3510 vs. 1703 2725 vs. 1286 2557 vs. 2572 vs. 2576 2725 vs. 1286 2725 vs. 1286
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	Median: 67.5	A) Raloxifene 60 mg/day B) Placebo	Median: 5.1	Median: 5.6	2/2/2006	5044 vs. 5057
HOT	DeCensi, 2013	Mean: 53	A) Tamoxifen 5 mg/day B) Placebo	Mean: 3.5 vs. 3.6	Mean: 6.1 vs. 6.2	Unclear	938 vs. 946
MAP.3	Goss, 2011 Maunsell, 2014	Median: 62.5	A) Exemestane 25 mg/day B) Placebo	3	Median: 2.9	11/5/2010	2285 vs. 2275
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	Median: 59.5	A) Anastrozole 1 mg/day B) Placebo	5	Median: 5	5/15/2013	1920 vs. 1944

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Woman-years of followup (A v.s B)	BC deaths (A vs. B)	RR of BC deaths (95% CI)	All-cause mortality (A vs. B)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	1 vs. 0 1 vs. 0 1 vs. 0 NR NR NR NR	NR	NR 2 vs. 1 CORE: 47 vs. 29 47 vs. 29 NR NR NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	2 vs. 0 NR NR	NR	NR
HOT	DeCensi, 2013	69,044 vs. 69,839	1 vs. 0	NR	6 vs. 2
MAP.3	Goss, 2011 Maunsell, 2014	NR	1 vs. 0	NR	19 vs. 19
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	9727 vs. 9672	2 vs. 0	NR	18 vs. 17

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of all-cause mortality (95% CI)	All BC occurrence (A vs. B)	RR of all BC occurrence (95% CI)	Invasive BC (A vs. B)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	22 vs. 32 33 vs. 44 CORE: 31 vs. 30 -MORE+CORE: 56 vs. 65 NR NR NR NR	0.35 (0.21 to 0.58) 0.38 (0.24 to 058) CORE: 0.50 (0.30 to 0.82)† -MORE+CORE: 0.42 (0.29 to 0.60)† NR NR NR NR	13 vs. 27 -ER+: 4 vs. 20 -ER-: 7 vs. 4 22 vs. 39 -ER+: 10 vs. 31 -ER-: 9 vs. 4 CORE: 24 vs. 28 -ER+: 15 sv. 21 -ER-: 7 vs. 3 MORE+CORE: 40 vs. 58 -ER+: 22 vs. 44 -ER-: 15 vs. 7 NR NR NR NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	52 vs. 76 52 vs. 76 NR	0.67 (0.47 to 0.96)† 0.67 (0.47 to 0.96)† NR	40 vs. 70 -ER+: 25 vs. 55 -ER-: 13 vs. 9 40 vs. 70 -ER+: 25 vs. 55 -ER-: 13 vs. 9NR
HOT	DeCensi, 2013	NR	19 vs. 24	0.80 (0.44 to 1.46)	18 vs. 22 -ER+: 12 vs. 20 -ER-: 8 vs. 3
MAP.3	Goss, 2011 Maunsell, 2014	NR	20 vs. 44	0.47 (0.27 to 0.79)†	11 vs. 32 -ER+: 7 vs. 27 -ER-: 4 vs. 5
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	40 vs. 85	0.47 (0.32 to 0.68)†	32 vs. 64 -ER+: 20 vs. 47 -ER-: 11 vs. 14

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of invasive BC (95% CI)	Noninvasive BC (A vs. B)	RR of noninvasive BC (95% CI)	Invasive EC (A vs. B)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	0.24 (0.13 to 0.44) -ER+: 0.10 (0.04 to 0.24) -ER-: 0.88 (0.26 to 3.00) 0.28 (0.17 to 0.46) -ER+: 0.16 (0.09 to 0.30) -ER-: 1.13 (0.35 to 3.66) CORE: 041 (0.24 to 0.71)† -ER+: 0.34 (0.18 to 0.66)† -ER-: 1.13 (0.29 to 4.35)† MORE+CORE: 0.34 (0.22 to 0.50)† -ER+: 0.24 (0.15 to 0.40)† -ER-: 1.06 (0.43 to 2.59)† NR NR NR NR	7 vs. 5 9 vs. 5 CORE: 7 vs. 2 -MORE+CORE: 16 vs. 7 NR NR NR NR All were DCIS in MORE Unspecified in CORE	NR 0.90 (0.30 to 2.69) CORE: 1.78 (0.37 to 8.61)† -MORE+CORE: 1.12 (0.46 to 2.73)† NR NR NR NR	6 vs. 4 9 vs. 5 CORE: 4 vs. 3 -MORE+CORE: 7 vs. 4 7 vs. 4 NR NR NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	0.56 (0.38 to 0.83)† -ER+: 0.45 (0.28 to 0.72)† - ER-: 1.44 (0.61 to 3.36)† 0.56 (0.38 to 0.83)† -ER+: 0.45 (0.28 to 0.72)† - ER-: 1.44 (0.61 to 3.36)† NR	11 vs. 5 11 vs. 5 NR All were DCIS	2.17 (0.75 to 6.24)† 2.17 (0.75 to 6.24)† NR	NR 21 vs. 17 NR
HOT	DeCensi, 2013	NR	NR	NR	1 vs. 3
MAP.3	Goss, 2011 Maunsell, 2014	0.35 (0.18 to 0.70)† - -ER+: 0.27 (0.12 to 0.60)† - -ER-: 0.80 (0.21 to 2.98)†	9 vs. 14 Defined as DCIS	0.65 (0.28 to 1.51)†	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	0.50 (0.32 to 0.76)† - -ER+: 0.42 (0.25 to 0.71)† - -ER-: 0.78 (0.35 to 1.72)†	6 vs. 20 Defined as DCIS	0.30 (0.12 to 0.74)†	3 vs. 5

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	RR of invasive EC (95% CI)	DVT (A vs. B)	RR of DVT (95% CI)	PE (A vs. B)	RR of PE (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	0.80 (0.20 to 2.70) NR NR NR NR NR NR	38 vs. 5 44 vs. 8 CORE: 17 vs. 5 -MORE+CORE: 31 vs. 10 31 vs. 10 NR NR NR	NR	17 vs. 3 22 vs. 4 CORE: 9 vs. 0 -MORE+CORE: 17 vs. 2 17 vs. 2 NR NR NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR 65 vs. 47 NR	NR 1.37 (0.94 to 1.99)[†] NR	NR 36 vs. 24 NR	NR 1.49 (0.89 to 2.49)[†] NR
HOT	DeCensi, 2013	0.34 (0.04 to 3.25	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	0.61 (0.15 to 2.54)	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Overall thrombo event (A vs. B)	RR of overall thrombo events (95% CI)	Stroke (A vs. B)	RR of stroke (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	49 vs. 8 59 vs. 12 CORE: 23 vs. 5 -MORE+CORE: 47 vs. 13 47 vs. 13 NR NR NR	NR	NR NR NR 78 vs. 32 NR NR NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR 103 vs. 71 NR	NR 1.44 (1.06 to 1.95)† NR	NR 249 vs. 224 -Hemorrhagic: 18 vs. 30 -Ischemic: 198 vs. 171 -Undetermined: 39 vs. 30 NR	NR 1.10 (0.92 to 1.32)† -Hemorrhagic: 0.59 (0.33 to 1.06)† -Ischemic: 1.15 (0.93 to 1.41)† -Undetermined: 1.28 (0.80 to 2.07)† NR
HOT	DeCensi, 2013	5 vs. 2	2.64 (0.51 to 13.6)	1 vs. 2	0.51 (0.01 to 9.72)
MAP.3	Goss, 2011 Maunsell, 2014	11 vs. 7	NR	13 vs. 11 -Note: stroke/TIA combined	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	19 vs. 17	1.13 (0.59 to 2.17)	3 vs. 6	0.50 (0.08 to 2.33)

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	TIA (A vs. B)	RR of TIA (95% CI)	Overall cerebrovascular events (A vs. B)	RR of overall cerebrovascular events (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	NR	NR	5 vs. 2	2.11 (0.39 to 11.5)
MAP.3	Goss, 2011 Maunsell, 2014	See stroke column	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	3 vs. 6 -Note: cerebrovascular accident	0.51 (0.13 to 2.02)

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	MI (A vs. B)	RR of MI (95% CI)	Angina (A vs. B)	RR of angina (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR NR NR 74 vs. 34 NR NR NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR 183 vs. 208 -Note: only nonfatal MI here 3) NR	NR 0.87 (0.71 to 1.06)† NR	NR	NR
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	4 vs. 4	NR	5 vs. 13 -Note: ongoing, no surgical intervention	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	8 vs. 9 -Note: includes cardiac failure	0.90 (0.35 to 2.32)	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Acute ischemic syndrome (A vs. B)	RR of acute ischemic syndrome (95% CI)	Overall cardiovascular events (A vs. B)	RR of overall cardiovascular event (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR 533 vs. 553 -Note: this seems to include everything, stroke, VTE, etc. NR	NR 0.95 (0.84 to 1.07) NR
HOT	DeCensi, 2013	NR	NR	4 vs. 6 -Note: coronary heart syndrome	0.70 (0.20 to 2.50)
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	106 vs. 111	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Any fractures (A vs. B)	RR of any fractures (95% CI)	Hip fractures (A vs. B)	RR of hip factures (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR NR NR NR NR Nonvertebral: 621 vs. 292 NR	NR NR NR NR NR Nonvertebral: 1.00 (0.82 to 1.21) NR	NR NR NR NR NR 27 vs. 10 NR	NR NR NR NR NR 1.280.47 to 3.53)† NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR NR 492 vs. 535 - Nonvertebral: 428 vs. 438	1) NR 2) NR 3) NR - Nonvertebral: 0.96 (0.84 to 1.10)†	NR	NR NR 0.85 (0.64 to 1.13)†
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	149 vs. 143	NR	7 vs. 3	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	164 vs. 149	1.11 (0.90 to 1.38)	9 vs. 10 -Note: includes pelvic	0.91 (0.37 to 2.24)

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Spine (vertebral) fractures (A vs. B)	RR of spine (vertebral) fractures (95% CI)	Radius (wrist) fractures (A vs. B)	RR of radius fractures (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR NR NR NR 0.600.53 to 0.69)† NR NR	NR NR NR NR NR 98 vs. 51 NR	NR NR NR NR NR 0.880.55 to 1.41)† NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR NR Clinical vertebral: 64 vs. 97	NR NR Clinical vertebral: 0.65 (0.47 to 0.89)†	NR	NR NR 0.95 (0.73 to 1.24)†
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	5 vs. 4	NR	26 vs. 18	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	23 vs. 18 -Note: includes rib or collarbone	1.29 (0.70 to 2.39)	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Hysterectomy (A vs. B)	RR of hysterectomy (95% CI)	Cataracts (A vs. B)	RR cataracts (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR NR NR NR NR NR 291 vs. 160	NR NR NR NR NR NR 0.9 (0.8 to 1.1)
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR 374 vs. 391 NR	NR NR NR
HOT	DeCensi, 2013	18 vs. 7 -Note: for benign disease	5.27 (1.15 to 24.1)	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	90 vs. 95	0.96 (0.72 to 1.27)

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Endometrial cancer (A vs. B)	RR of endometrial cancer (95% CI)	Hyperplasia (A vs. B)	RR of hyperplasia (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	6 vs. 4 9 vs. 5 CORE: 4 vs. 3 -MORE+CORE: 7 vs. 4 7 vs. 4 NR NR 9 vs. 5	0.80 (0.20 to 2.70) NR NR NR NR NR 0.9 (0.3 to 2.7)	NR NR CORE: 1 vs. 2 -MORE+CORE: 8 vs. 3 8 vs. 3 NR NR 8 vs. 3 -Simple: 3 vs. 2 -Complex: 2 vs. 1	NR NR NR NR NR NR 1.3 (0.4 to 5.1) -Simple: NR -Complex: NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR 21 vs. 17 NR	NR	NR	NR
HOT	DeCensi, 2013	1 vs. 3	0.34 (0.04 to 3.25)	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	3 vs. 5	0.61 (0.15 to 2.54)	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Hyperplasia without atypia (A vs. B)	RR of hyperplasia without atypia (95% CI)	Hyperplasia with atypia (A vs. B)	RR of hyperplasia with atypia (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Oophorectomy (A vs. B)	RR of oophorectomy (95% CI)	Currettage (A vs. B)	RR of currettage (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor,2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Laparoscopy (A vs. B)	RR of laparoscopy (95% CI)	Hysteroscopy (A vs. B)	RR of hysteroscopy (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Leiomyomas (A vs. B)	RR of leiomyomas (95% CI)	Ovarian cysts (A vs. B)	RR of ovarian cysts (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	NR	NR	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Polyps (A vs. B)	RR of polyps (95% CI)	Endometriosis (A vs. B)	RR of endometriosis (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR NR NR 70 vs. 19 NR NR NR Defined as uterine polyps	NR	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR	NR	NR
HOT	DeCensi, 2013	27 vs. 6 Endometrial polyps	4.74 (1.96 to 11.5)	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR	NR	NR

Appendix B3. Evidence Table of Trials of Risk-Reducing Medications for Breast Cancer

Trial	Papers used	Endometritis (A vs. B)	RR of endometritis (95% CI)
MORE/ CORE	Cummings, 1999 Cauley, 2001 Martino, 2004 Martino, 2005 Delmas, 2002 Siris, 2005 Grady, 2004	NR	NR
RUTH	Grady, 2008 Barrett-Connor, 2006 Ensrud, 2008	NR	NR
HOT	DeCensi, 2013	NR	NR
MAP.3	Goss, 2011 Maunsell, 2014	NR	NR
IBIS-II	Cuzick, 2014 Sestak, 2014 Spagnolo, 2016	NR	NR

*OR instead of RR
†HR instead of RR

Abbreviations: BC=breast cancer; CHD=coronary heart disease; CI=confidence interval; DCIS=ductal carcinoma in situ; DVT=deep vein thrombosis; EC=endometrial cancer; ER+=estrogen receptor positive; ER-=estrogen receptor negative; HOT=Hormone replacement therapy Opposed by low dose Tamoxifen; IBIS=International Breast Cancer Intervention Study; MAP.3=Mammary Prevention.3 Trial; MI=myocardial infarction; MORE=Multiple Outcomes of Raloxifene Evaluation; N=number; NR=not reported; NSABP-1=National Surgical Adjuvant Brest and Bowel Project P-1 Study; PE=pulmonary embolism; RR=risk ratio; RUTH=Raloxifene Use for the Heart; STAR=Study of Tamoxifen and Raloxifene.

Tamoxifen vs Raloxifene

Study of Tamoxifen and Raloxifene (STAR)

- At least a 5-year predicted breast cancer risk of 1.66% based on the Gail model.
- At least 35 years old and postmenopausal.
- Not taking tamoxifen, raloxifene, hormone therapy, oral contraceptives, or androgens for a least the previous 3 months.
- Not currently taking either warfarin or cholestyramine.
- No history of stroke, pulmonary embolism, or deep vein thrombosis and no history of any malignancy diagnosed less than 5 years before randomization except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix.
- No uncontrolled atrial fibrillation, uncontrolled diabetes, or uncontrolled hypertension.
- No psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day.

Tamoxifen vs Placebo

National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-1)

- 60 years of age or older or between the ages of 35 and 59 with a 5-year predicted risk for breast cancer of at least 1.66% or had a history of lobular carcinoma in situ.
- Life expectancy of at least 10 years.
- Breast exam demonstrated no clinical evidence of cancer.
- Mammogram within 180 days before randomization had no evidence of breast cancer.
- Normal white blood cell and platelet counts and normal hepatic and renal function tests.
- Not pregnant upon entry into the study or planned not to become pregnant while on protocol therapy.
- Accessible for follow up.
- Underwent endometrial sampling before randomization if they had a uterus and were randomly assigned after July 8, 1994.
- No estrogen or progesterone replacement therapy, oral contraceptives, or androgens for at least 3 months before randomization.
- No history of deep vein thrombosis or pulmonary embolism.

International Breast Cancer Intervention Study (IBIS-I)

Increased risk for breast cancer based on family history criteria:

- 35 to 39 years with 10-fold relative risk
- 40 to 44 years with 4-fold relative risk
- 45 to 70 years with 2-fold relative risk

All criteria permit entry to trial at age 45 years:

- First-degree relative who developed breast cancer at or before age 50.
- First-degree relative with bilateral breast cancer (permits entry from age 40; if relative diagnosed before age 40, permits entry at age 35).
- Two or more first-degree or second-degree relatives with breast cancer (permits entry from age 40 if both developed breast cancer before age 50, permits entry at age 35 if both relatives are first-degree and both developed breast cancer before age 50).
- Benign breast biopsy and first-degree relative with breast cancer.
- Lobular carcinoma in situ (permits entry from age 35).

- Atypical hyperplasia (permits entry from age 40).
- Nulliparous and a first-degree relative who developed breast cancer.
- Risk equivalent (strong family history, not fitting specific categories, but judged to be at higher risk than eligibility category by the study chairman).

Royal Marsden
Between the ages of 30 to 70 with no clinical or screening evidence of breast cancer and with an increased risk of breast cancer because of family history:

- At least 1 first degree relative under 50 with breast cancer, or
- One first degree relative with bilateral breast cancer, or
- One affected first degree relative of any age plus another affected first degree or second degree relative, or
- History of a benign breast biopsy and had a first-degree relative with breast cancer

Italian Trial
Healthy women aged 35 to 70 years at average risk for breast cancer who had had a total hysterectomy to avoid the risk of endometrial cancer associated with tamoxifen use.

Raloxifene vs Placebo
Multiple Outcomes of Raloxifene (MORE/CORE)

- At least 2 years postmenopausal and no older than 80 years.
- Osteoporosis defined as bone density at least 2.5 SDs below mean for normal young women at either the lumbar spine or femoral neck, or had at least 1 moderate or 2 mild vertebral fractures that were detected by lateral spine radiography.
- Women with a history of breast cancer, invasive endometrial cancer, or history of stroke or venous thromboembolism during the past 10 years were excluded.

Raloxifene Use for the Heart (RUTH)

- 1 year or more postmenopausal and age 55 years and older.
- Have established CHD or at increased risk for CHD based on a cardiovascular risk score of 4 or more according to a point system that takes into account the presence of:
  - Established CHD (4 points)
  - Arterial disease of the leg (4 points)
  - Age of at least 70 years (2 points)
  - Diabetes mellitus (3 points)
  - Cigarette smoking (1 point)
  - Hypertension (1 point)
  - Hyperlipidemia (1 point)

Exemestane vs Placebo

Mammary Prevention.3 (MAP.3)

Women who were 35 years and older, postmenopausal, and at least 1 of the following risk factors:

- 60 years or older
- Gail risk score greater than 1.66%
- Prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ on breast biopsy or prior ductal carcinoma in situ treated with mastectomy.

Prior menopausal hormone therapies, luteinizing hormone-releasing hormone analogues, prolactin inhibitors, antiandrogens, or selective estrogen receptor modulators were allowable but not within 3 months of randomization.

Anastrozole vs Placebo

International Breast Cancer Intervention Study (IBIS-II)

Postmenopausal with increased risk for breast cancer:

- 40 to 44 years with risk 4 times higher than in the general population
- 45 to 60 years with risk 2 times higher
- 60 to 70 with risk 1.5 times higher

40-44, meeting at least one of the criteria:

- Two or more first or second degree relatives who developed breast cancer or ovarian cancer at age 50 or less
- First degree relative with bilateral breast cancer who developed first breast cancer at age 50 or less
- Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer at age 40 or less
- Benign biopsy with proliferative disease and first degree relative who developed breast cancer at 40 or less

45-70 years, meeting at least one of the criteria:

- First degree relative who developed breast cancer at age 50 or less
- First degree relative who developed bilateral cancer
- Two or more first degree relatives who developed breast or ovarian cancer
- Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer
- Benign biopsy with proliferative disease and first degree relative who developed breast cancer
- Mammographic opacity covering at least 50% of the breast
- First degree relative with breast cancer at any age
- Age at menopause 55 years or more
- Nulliparous or age 30 or above at first birth

Women in all age groups

- Lobular carcinoma in situ (LCIS)
- Atypical ductal or lobular hyperplasia in a benign lesion
- DCIS (ER-positive) diagnosed within last 6 months with completed adequate local treatment
- Women with a clearly apparent family history indicating appropriate increased risk

Appendix C2 Table 1. Primary Prevention Randomized Controlled Trials

Comparators	Primary Prevention Trial	N (drug vs. comparator)	Mean age, *y*	Menopause	Increased breast cancer risk	Active Duration, *y*	Follow up Duration, *y*
Tamoxifen vs. Raloxifene	Study of Tamoxifen & Raloxifene (STAR)	9872 vs. 9875	58.5	post	X	3.6 to 3.9	6.8
Tamoxifen vs. Placebo	National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-1)	6681 vs.6707	53	pre/post	X	4	7
	International Breast Cancer Intervention Study (IBIS-I)	3579 vs. 3575	51	pre/post	X	5	16
	Royal Marsden Hospital Trial	1238 vs. 1233	47	pre/post	X	5	13
	Italian Trial	2700 vs. 2708	51	pre/post		4	11
Raloxifene vs. Placebo	Multiple Outcomes of Raloxifene (MORE/CORE)	5129 vs. 2576	67	post		4 to 8	5 to 8
	Raloxifene Use for the Heart (RUTH)	5044 vs. 5057	67.5	post		5	5.6
Exemestane vs. Placebo	Mammary Prevention.3 (MAP.3)	2285 vs. 2275	62.5	post	X	3	3
Anastrozole vs. Placebo	International Breast Cancer Intervention Study (IBIS-II)	1920 vs. 1044	59.5	post	X	5	5

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	Age	Post-menopausal	>1.66% 5-yr Gail	Family History	Breast pathology	Other BC risk factors
Tamoxifen vs. Raloxifene	Study of Tamoxifen & Raloxifene (STAR)	X	X	X			
Tamoxifen vs. Placebo	National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-1)	X		X		LCIS	
	International Breast Cancer Intervention Study (IBIS-I)	X			X	X	X
	Royal Marsden Hospital Trial	X			X	X	
	Italian Trial	X					
Raloxifene vs. Placebo	Multiple Outcomes of Raloxifene (MORE/CORE)		X	Osteoporosis			
	Raloxifene Use for the Heart (RUTH)	X	X	CHD or risk factors			
Exemestane vs. Placebo	Mammary Prevention.3 (MAP.3)	X	X	X		X	
Anastrozole vs. Placebo	International Breast Cancer Intervention Study (IBIS-II)	X	X		X	X	X

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs comparator)	Mean age (SD) or range, *y*	Age, n (%) ≤ 50 y	Age, n (%) 50-59 y	Age, n (%) 60-69 y	Age, n (%) ≥60 y	Age, n (%) ≥70 y
Tamoxifen vs. Raloxifene	STAR	9872	58.5	884 (9.1)	4850 (49.9)	3133 (32.2)		859 (8.8)
		9875		877 (9.0)	4848 (49.7)	3173 (32.6)		847 (8.7)
Tamoxifen vs. Placebo	NSABP-1	6681	53	2581 (39.2)	2031 (30.9)	1571 (23.9)		393 (6.0)
		6707		2596 (39.3)	2017 (30.6)	1590 (24.1)		396 (6.0)
	IBIS-I	3579	50.7 (7.0)					
		3575	50.8 (6.7)					
	Royal Marsden	1238	47 (30-70)	774 (61.9)				
		1233	47 (31-70)	749 (60.2)				
	Italian	2700	51	1062 (39.3)	1317 (48.8)		321 (11.9)	
		2708		1011 (37.3)	1395 (51.5)		302 (11.2)	
Raloxifene vs. Placebo	MORE/CORE	2725	65.7 (6.8)					
		1286	65.9 (6.7)					
	RUTH	5044	67.5 (6.6)					1952 (38.7)
		5057	67.5 (6.7)					1982 (39.2)
Exemestane vs. Placebo	MAP.3	2285	62.5 (38.5-88.2)				1545 (67.6)	
		2275	62.4 (37.1-89.9)				1572 (69.1)	
Anastrozole vs. Placebo	IBIS-II	1920	59.5 (55.0-63.5)*					
		1944	59.4 (55.1-63.3)*					

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs comparator)	No 1^0 Relatives with Breast Cancer, n (%)	One 1^0 Relative with Breast Cancer, n (%)	Two 1^0 Relatives with Breast Cancer, n (%)	Three 1^0 Relatives with Breast Cancer, n (%)	≥1 1^0 Relatives with Breast Cancer, n (%)	≥2 1^0 Relatives with Breast Cancer, n (%)	≥3 1^0 Relatives with Breast Cancer, n (%)
Tamoxifen vs. Raloxifene	STAR	9726	2835 (29.1)	5041 (51.8)	1532 (15.8)	318 (3.3)			
		9745	2789 (28.6)	5130 (52.6)	1559 (16.0)	267 (2.7)			
Tamoxifen vs. Placebo	NSABP-1	6576	1540 (23.4)	3754 (57.1)	1069 (16.3)				213 (3.2)
		6599	1595 (24.2)	3731 (56.5)	1092 (16.5)				181 (2.7)
	IBIS-I	3573						2204 (61.7)	
		3566						2206 (61.9)	
	Royal Marsden	1250	2359 (87.4)				341 (12.6)	225 (18)	
		1244	2407 (88.9)				301 (11.1)	205 (16.5)†	
	Italian	2700							
		2708							
Raloxifene vs. Placebo	MORE/ CORE	2725							
		1286							
	RUTH	5044							
		5057							
Exemestane vs. Placebo	MAP.3	2285							
		2275							
Anastrozole vs. Placebo	IBIS-II	1920							
		1944							

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs. comparator)	1^0 relative with breast cancer at any age	1^0 relative with breast cancer at ≤50	1^0 relative with bilateral breast cancer	≥2 1^0 or 2^0 relatives with breast or ovarian cancer	Family history of breast cancer (not defined)
Tamoxifen vs. Raloxifene	STAR	9726					
		9745					
Tamoxifen vs. Placebo	NSABP-1	6576					
		6599					
	IBIS-I	3573		1689 (47.3)	579 (16.2)	2204 (61.7)	
		3566		1744 (48.9)	601 (16.9)	2206 (61.9)	
	Royal Marsden	1250		698 (55.8)			
		1244		668 (53.7)†			
	Italian	2700					
		2708					
Raloxifene vs. Placebo	MORE/CORE	2725					636 (12.4)‡
		1286					312 (12.1)‡
	RUTH	5044					494 (9.8)
		5057					491 (9.7)
Exemestane vs. Placebo	MAP.3	2285					
		2275					
Anastrozole vs. Placebo	IBIS-II	1920	488 (25.4%)	675 (35%)	164 (9%)	956 (50%)	
		1944	499 (25.7%)	653 (34%)	141 (7%)	938 (48%)	

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs comparator)	5-year Predicted Risk Score (Gail model), mean (SD)	5-year Predicted Risk ≥1.66 (Gail model), n (%)	5-year Predicted Risk ≤ 2.00 (Gail model), n (%)	5-year Predicted Risk 2.01-3.00 (Gail model), n (%)	5-year Predicted Risk 3.01-5.00 (Gail model), n (%)	5-year Predicted Risk ≥5.01 (Gail model), n (%)	10-year risk, % (Tyrer-Cuzick model)
Tamoxifen vs. Raloxifene	STAR	9726			1055 (10.8)	2988 (30.7)	3039 (31.2)	2644 (27.2)	
		9745			1097 (11.3)	2893 (29.7)	3082 (31.6)	2673 (27.4)	
Tamoxifen vs. Placebo	NSABP-1	6576			1636 (24.9)	2057 (31.3)	1714 (26.1)	1169 (17.8)	
		6599			1660 (25.2)	2031 (30.8)	1791 (27.1)	1117 (16.9)	
	IBIS-I	3573							
		3566							
	Royal Marsden	1250							
		1244							
	Italian	2700							
		2708							
Raloxifene vs. Placebo	MORE/ CORE	2725							
		1286							
	RUTH	5044	1.73 (0.76)	2103 (41.7)					
		5057	1.73 (0.77)	2083 (41.2)					
Exemestane vs. Placebo	MAP.3	2285		929 (40.7)					
		2275		905 (39.8)					
Anastrozole vs. Placebo	IBIS-II	1920							7.6 (5.8-9.9)
		1944							7.8 (5.1-10.2)

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs comparator)	Prior ADH, ALH, LCIS on biopsy, n (%)	Prior LCIS, n (%)	Prior atypical hyperplasia, n (%)	Benign biopsy and 1^0 relative, n (%)	Prior DCIS treated with mastectomy, n (%)	DCIS (ER-positive), n (%)
Tamoxifen vs. Raloxifene	STAR	9726						
		9745						
Tamoxifen vs. Placebo	NSABP-1	6576		415 (6.3)	579 (8.8)			
		6599		411 (6.2)	614 (9.3)			
	IBIS-I	3573		44 (1.2)	97 (2.7)	123 (3.4)		
		3566		44 (1.2)	104 (2.9)	132 (3.7)		
	Royal Marsden	1250						
		1244						
	Italian	2700						
		2708						
Raloxifene vs. Placebo	MORE/CORE	2725						
		1286						
	RUTH	5044						
		5057						
Exemestane vs. Placebo	MAP.3	2285	185 (8.1)	56 (2.5)				
		2275	188 (8.3)	56 (2.5)				
Anastrozole vs. Placebo	IBIS-II	1920		50 (2.6)	55 (2.8)			160 (8.3)
		1944		55 (2.8)	135 (6.9)			166 (8.5)

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Comparators	Primary Prevention Trial	N (drug vs comparator)	Nulliparous or ≥30 at first birth and a 1^0 relative with breast cancer, n (%)	Hysterectomy, n (%)	No hysterectomy, n (%)
Tamoxifen vs. Raloxifene	STAR	9726		4994 (51.3)	4732 (48.7)
		9745		5033 (51.6)	4712 (48.4)
Tamoxifen vs. Placebo	NSABP-1	6576		2479 (37.7)	4097 (62.3)
		6599		2554 (71.6)	4194 (63.6)
	IBIS-I	3573	314 (8.8)	2453 (68.7)	1120 (31.3)§
		3566	325 (9.1)	2554 (71.6)	1012 (28.4)§
	Royal Marsden	1250			
		1244			
	Italian	2700		2700 (100)	0
		2708		2708 (100)	0
Raloxifene vs. Placebo	MORE/CORE	2725		559 (20.5)	2166 (79.5)§
		1286		260 (20.2)	1026 (79.8)§
	RUTH	5044		1178 (23.3)	3879 (76.7)§
		5057		1145 (22.7)	3899 (77.3)§
Exemestane vs. Placebo	MAP.3	2285			
		2275			
Anastrozole vs. Placebo	IBIS-II	1920	207 (10.6)	631 (33)	1289 (67)
		1944	211 (11.0)	656 (34)	1288 (66)§

*Data presented as median IQR.
† Each participant had at least one first-degree relative aged under 50 with breast cancer, or one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age plus another affected first-degree or second-degree relative but data not shown for all.
‡Data from MORE study, MORE-CORE is a subset of MORE, n=4011 of 7705.
§Calculated from available data.

Appendix C3. Summary of Treatment Trials of Aromatase Inbibitors With Fracture and Cardiovascular Disease Outcomes

Study	Comparison	N	Method	Analysis	Major Adverse Outcomes
EBCTCG, 2015	AI vs tamoxifen for early breast cancer (meta-a)	31,920	Individual-level data on postmenopausal women with ER+ early breast cancer in treatment RCTs: • AI (5 year) vs tamoxifen (5 year) • AI (5 year) vs tamoxifen (2-3 year), then AI to year 5 • Tamoxifen (2-3 year), then AI to year 5 vs tamoxifen (5 year)	Intention-to-treat; log-rank analyses, stratified by age, nodal status, and trial, yielded aromatase inhibitor versus tamoxifen first-event rate ratios (RRs).	• Fractures: 5-year risk for AI 8.2% vs. 5.5% (RR 1.42; 1.28 to1.57 years 0-4; RR 1.29; 1.09-1.53 years 5-9) • CVD: no differences for VTE, CVA, CAD deaths
Forbes, 2016	Anastrozole vs tamoxifen for DCIS (RCT)	2980	Multicenter RCT of women with locally excised ER+ DCIS given 1 mg oral anastrozole or 20 mg oral tamoxifen every day for 5 years. Median follow-up 7·2 years (IQR 5·6 to 8·9).	Modified intention-to-treat; proportional hazard models.	• Fractures: 9% AI vs. 7% tamoxifen (OR 1.36; 1.03-1.80) • CVD: increased VTE with tamoxifen; no CHD differences • TIA: AI OR 2.69 (0.90 to 9.65) • CVA: AI OR 3.36 (1.04 to 14.18)
Goldvaser, 2018	Extended AIs vs placebo or no treatment for early ER+ breast cancer (meta-a)	16,349	Seven RCTs that compared extended AIs to placebo or no treatment published between 2013 and 2016.	Odds ratios, absolute risks, and the number needed to harm were computed for pre-specified safety and tolerability outcomes.	• Fractures: 6.3% AI vs. 4.8% (OR 1.34; 1.16 to 1.55) • CVD events: 7% AI vs. 6% (OR 1.18; 1.00 to 1.40) • Treatment discontinuation for adverse events: (OR 1.45, 1.25 to 1.68)

References:

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