JAMA | US Preventive Services Task Force | **EVIDENCE REPORT**

Medication Use for the Risk Reduction of Primary Breast Cancer in Women
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Medications to reduce risk of breast cancer are effective for women at increased risk but also cause adverse effects.

OBJECTIVE To update the 2013 US Preventive Services Task Force systematic review on medications to reduce risk of primary (first diagnosis) invasive breast cancer in women.

DATA SOURCES Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, EMBASE, and MEDLINE (January 1, 2013, to February 1, 2019); manual review of reference lists.

STUDY SELECTION Discriminatory accuracy studies of breast cancer risk assessment methods; randomized clinical trials of tamoxifen, raloxifene, and aromatase inhibitors for primary breast cancer prevention; studies of medication adverse effects.

DATA EXTRACTION AND SYNTHESIS Investigators abstracted data on methods, participant characteristics, eligibility criteria, outcome ascertainment, and follow-up. Results of individual trials were combined by using a profile likelihood random-effects model.

MAIN OUTCOMES AND MEASURES Probability of breast cancer in individuals (area under the receiver operating characteristic curve [AUC]); incidence of breast cancer, fractures, thromboembolic events, coronary heart disease events, stroke, endometrial cancer, and cataracts; and mortality.

RESULTS A total of 46 studies (82 articles [>5 million participants]) were included. Eighteen risk assessment methods in 25 studies reported low accuracy in predicting the probability of breast cancer in individuals (AUC, 0.55-0.65). In placebo-controlled trials, tamoxifen (risk ratio [RR], 0.69 [95% CI, 0.59-0.84]; 4 trials [n = 28 421]), raloxifene (RR, 0.44 [95% CI, 0.24-0.80]; 2 trials [n = 17 806]), and the aromatase inhibitors exemestane and anastrozole (RR, 0.45 [95% CI, 0.26-0.70]; 2 trials [n = 8424]) were associated with a lower incidence of invasive breast cancer. Risk for invasive breast cancer was higher for raloxifene than tamoxifen in 1 trial after long-term follow-up (RR, 1.24 [95% CI, 1.05-1.47]; n = 19 747). Raloxifene was associated with lower risk for vertebral fractures (RR, 0.61 [95% CI, 0.53-0.73]; 2 trials [n = 16 929]) and tamoxifen was associated with lower risk for nonvertebral fractures (RR, 0.66 [95% CI, 0.45-0.98]; 1 trial [n = 13 388]) compared with placebo. Tamoxifen and raloxifene were associated with increased thromboembolic events compared with placebo; tamoxifen was associated with more events than raloxifene. Tamoxifen was associated with higher risk of endometrial cancer and cataracts compared with placebo. Symptomatic effects (eg, vasomotor, musculoskeletal) varied by medication.

CONCLUSIONS AND RELEVANCE Tamoxifen, raloxifene, and aromatase inhibitors were associated with lower risk of primary invasive breast cancer in women but also were associated with adverse effects that differed between medications. Risk stratification methods to identify patients with increased breast cancer risk demonstrated low accuracy.

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Although periodic mammography screening is currently the main approach to early detection of primary breast cancer,[1] medications to reduce risk of breast cancer provide an additional prevention option for women at increased risk.[2] Clinical trials indicate that the selective estrogen receptor modulators raloxifene and tamoxifen[3] and the aromatase inhibitors anastrozole[4] and exemestene[5,6] are associated with reduced incidence of primary invasive breast cancer. However, these medications are also associated with adverse effects,[3] and candidates for risk-reducing medications need to be accurately identified to optimize potential benefits and minimize harms.

In 2013, the US Preventive Services Task Force (USPSTF) issued a B recommendation for clinicians to offer to prescribe risk-reducing medications for women at increased risk for breast cancer and low risk for adverse medication effects.[2] However, use of medications for breast cancer risk reduction is low in clinical practice[7-9] because of women's concerns about adverse effects and beliefs that benefits are not worth the harms,[3] difficulty in identifying candidates for therapy, and primary care physicians' unfamiliarity with tamoxifen and aromatase inhibitors because they are predominantly used for breast cancer treatment.[10] This review was conducted to update evidence on the efficacy and harms of risk-reducing medications and the accuracy of clinical risk assessment methods to select candidates for therapy to inform new USPSTF recommendations.

Methods

Scope of Review
Detailed methods are available in the full evidence report at http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-medications-for-risk-reduction1.[11] **Figure 1** shows the analytic framework, key questions (KQs), and contextual questions that guided the review. Contextual questions provide additional information for the USPSTF but are not systematically reviewed or represented in the analytic framework.

Data Sources and Searches
Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, Ovid EMBASE, and MEDLINE (January 1, 2013, to February 1, 2019) were searched for relevant English-language articles (eMethods 1 in the Supplement), and reference lists were manually reviewed. Studies published before 2013 were identified from prior systematic reviews for the USPSTF.[3,13]

Study Selection
Investigators reviewed abstracts and full-text articles using prespecified eligibility criteria.[11] A second reviewer independently confirmed results of the initial review; discrepancies were resolved by consensus.

Studies reporting discriminatory accuracy (ie, area under the receiver operating characteristic curve [AUC]) of risk assessment methods that could be used in primary care settings to identify women at higher than average risk for breast cancer were included for KQ1. For KQ2 and KQ4 (efficacy), only double-blind, placebo-controlled or head-to-head randomized clinical trials (RCTs) of

tamoxifen, raloxifene, or aromatase inhibitors for primary prevention of breast cancer that enrolled women without preexisting breast cancer and reported breast cancer incidence as a primary or secondary outcome were included. For KQ3 and KQ4 (harms), RCTs and observational studies of these medications that had non-user comparison groups or direct comparisons between the medications were included. All adverse outcomes at all reported follow-up times were considered in an effort to capture potential short- and long-term adverse effects. Studies reporting only intermediate outcomes rather than health outcomes, such as bone density rather than fractures, were not included.

Data Extraction and Quality Assessment
Investigators abstracted data from studies of risk assessment methods (study design; population characteristics; eligibility criteria; reference standards; risk factors included in the models; and performance measures) and trials of medications (study design; setting; population characteristics; eligibility criteria; interventions [dose and duration]; numbers enrolled and lost to follow-up; method of outcome ascertainment; and results for each outcome). A second investigator reviewed accuracy of abstracted data.

Two investigators independently applied criteria developed by the USPSTF[12] to rate the quality of each study as good, fair, or poor (eMethods 2 in the Supplement). Discrepancies were resolved through a consensus process. Individual study quality ratings are provided in eTables 1 and 2 in the Supplement.

Data Synthesis and Analysis
For all KQs, the overall quality of evidence was rated good, fair, or poor, based on study quality, consistency of results, precision of estimates, study limitations, risk of reporting bias, and applicability and was summarized in a table.[12]

Statistical Meta-analysis
Results of placebo-controlled trials were combined for each medication separately using meta-analysis that considered clinical and methodological differences. Estimates of risk ratios (RRs [rate ratio, hazard ratio, or relative risk]) and their standard errors were abstracted or calculated from each study and used as effect measures (additional information in eMethods 3 in the Supplement). Statistical heterogeneity was assessed using Cochrane χ^2 tests and the magnitude of heterogeneity using the I^2 statistic.[14] The RRs were combined by using a profile likelihood random-effects model to account for variation among studies.[15] All analyses were performed using Stata version 13.1 (StataCorp).

To determine outcomes for subgroups, analysis was performed by age (≤50 years; >50 years), family history of breast cancer (yes; no), use of menopausal hormone therapy (yes; no), menopausal status (pre; post), and body mass index (≤25; >25 [calculated as weight in kilograms divided by height in meters squared]), when at least 2 studies reported results. For outcomes of major adverse events, analyses were stratified by active vs posttreatment periods, although this was possible for tamoxifen only.

Estimating Number of Events Reduced or Increased
To interpret the clinical effect of medications, the numbers of events reduced for benefits or increased for harms compared

Figure 1. Analytic Framework: Medication Use for the Risk Reduction of Primary Breast Cancer in Women
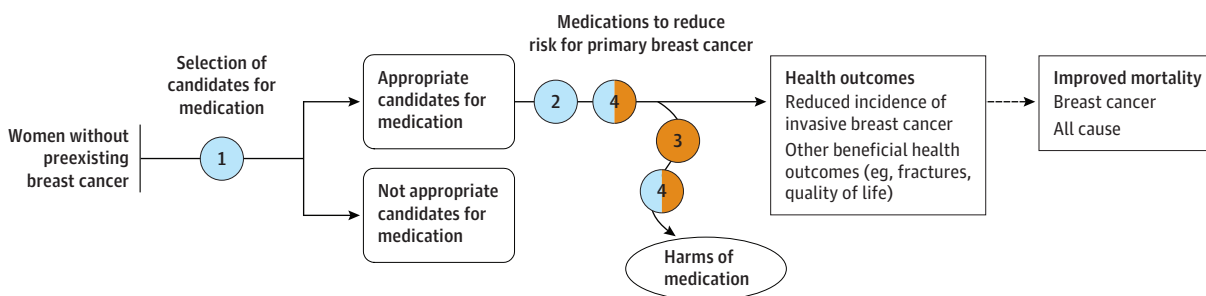
Key questions

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 (eg, 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, 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

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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display key questions addressed by the review to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions to outcomes. A dashed line indicates a health outcome that precedes subsequent outcomes. A circle that is half blue and half orange indicates a key question that pertains to both benefits and harms, such as key question 4. Refer to the USPSTF procedure manual for further details.[12]

with placebo per 1000 women, assuming 5 years of medication use, were estimated when the meta-analysis indicated a significant difference between treatment and placebo groups. Estimates used combined RRs from the meta-analyses and combined event rates from placebo groups of included trials. Combined event rates were determined from a meta-analysis of 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 follow-up. This analysis was performed using PROC NLMIXED in SAS version 9.4 (SAS Institute Inc). The 95% CIs were estimated using a simulation method that assumed that the logs of both the RRs and the event rates have normal distributions and then drew 10 000 random samples from the distribution.

The numbers of events reduced or increased were then estimated from each sample; 95% CIs were obtained by computing the 2.5% and 97.5% quantiles of the full sample.

Results

A total of 46 studies[4,16-60] (82 articles [>5 million participants]) met inclusion criteria for KQs (**Figure 2**), including 25 studies of discriminatory accuracy and 21 studies of the efficacy and harms of medications (20 RCTs; 1 observational study). In addition, 14 studies addressed the contextual question regarding clinician and patient attitudes and practices.[7,61-73]

Figure 2. Literature Search Flow Diagram: Medication Use for the Risk Reduction of Primary Breast Cancer in Women
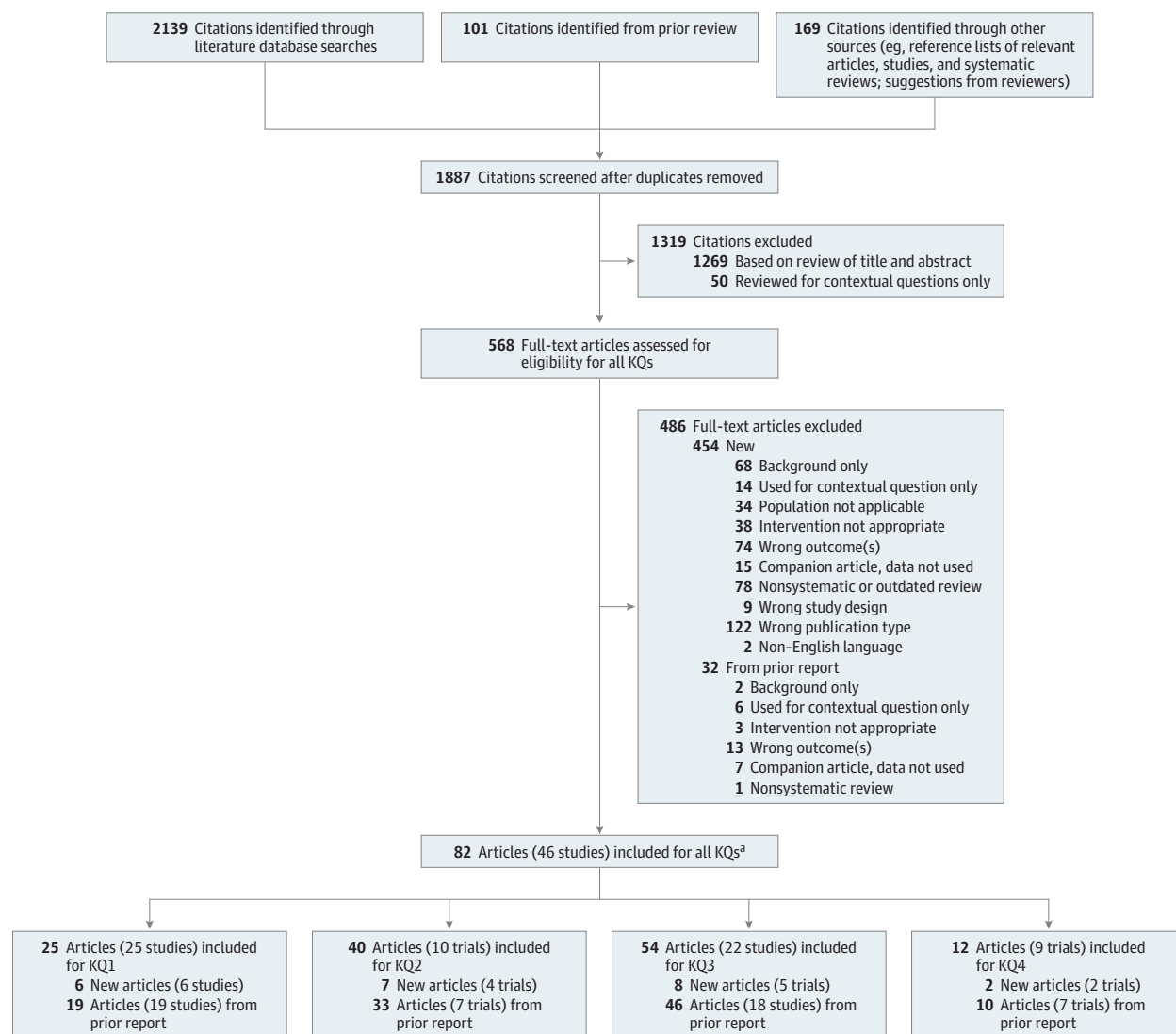
KQ indicates key question.

a Forty-six studies in 82 publications provided data; some addressed more than 1 KQ.

Accuracy of Breast Cancer Risk Assessment Methods

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?

A total of 25 studies reporting results of evaluations of 18 risk assessment methods based on data from more than 5 million women met inclusion criteria (**Table 1**; eTable 3 in the Supplement).[16-40] Although most methods shared common risk factors, they differed by including additional variables and using dissimilar reference populations. Three new studies expanded existing methods with new data by adding breast density to the Gail and Tyrer-Cuzick models[21]; modifying the Gail model for Asian Americans[31]; and adding benign breast disease to the Breast Cancer Surveillance Consortium (BCSC) model.[37] A fourth new study developed models to predict estrogen receptor–positive and estrogen receptor–negative breast

cancer.[30] No studies evaluated the optimal age or frequency of risk assessment (KQ1a and KQ1b).

Studies reported AUC values from 0.55 to 0.65, indicating low accuracy in predicting incidence of breast cancer in individual women.[16-39] Only 1 study reported AUC values above 0.70 for both the Gail-2 model (AUC, 0.74 [95% CI, 0.67-0.80]) and the Tyrer-Cuzick model (AUC, 0.76 [95% CI, 0.70-0.82]).[17] However, this study was small and did not include a primary care population, limiting its clinical applicability. One study determined how well the BCSC-Tice model stratified women into low- vs high-risk groups based on the risk threshold used in the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) and the Study of Tamoxifen and Raloxifene (STAR) trials (≥1.66% 5-year breast cancer risk).[36] Results indicated AUC values from 0.61 to 0.64.[36]

Table 1. Breast Cancer Risk Assessment Methods (Key Question 1)

Model	Age, y	Age at Menarche, y	Age at Birth of First Child, y	No. First-Degree Relatives With Breast Cancer	No. Previous Breast Biopsies	Other Factors	Summary of Accuracy, AUC (95% CI)[a]
Gail 2 (5-y risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	0; 1; ≥2 Atypical hyperplasia: 0; ≥1	Not included	0.55 (0.51-0.60)[16] 0.60[26] 0.58 (0.56-0.60)[34] 0.58[20] 0.59 (0.54-0.63)[27] 0.60[22] 0.61 (0.60-0.62)[36]
Gail 2 (10-y risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	0; 1; ≥2 Atypical hyperplasia: 0; ≥1	Not included	0.74 (0.67-0.80)[17] 0.54 (0.52-0.56)[21]
African American Gail (5-y risk)	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	0; 1; ≥2	African American race	0.56 (0.54-0.58)[28] 0.56 (0.51-0.60)[16]
Asian American Gail (5-y risk)	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	0; 1; ≥2	Asian American race	0.61 (0.59 to 0.64)[31]
Gail + breast density (10-y risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	Yes; no	Breast density (%); BMI	0.59 (0.57-0.61)[21]
Gail + breast density (5-y risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	0; 1; ≥2	Breast density (%); BMI	0.64[22]
BCSC (premenopausal; 1-y risk)	45-84 by 5-y groups	Not included	Not included	0; 1; ≥2; unknown	Yes; no; unknown	Breast density (BI-RADS)[b]	0.63 (0.60-0.66)[18]
BCSC (postmenopausal; 1-y risk)	45-84 by 5-y groups	Not included	<30; ≥30; no children; unknown	0; 1; ≥2; unknown	0; ≥1; unknown	Breast density (BI-RADS), prior false-positive mammogram, BMI, menopause type, hormone therapy, race or ethnicity	0.62 (0.62-0.63)[18]
BCSC (5-y risk)	45-84 by 5-y groups	Not included	Not included	Yes; no	Yes; no	Breast density (BI-RADS), race or ethnicity	0.66 (0.65-0.66)[36] 0.664[37]
BCSC + benign breast disease (5-y risk)[c]	45-84 by 5-y groups	Not included	Not included	Yes; no	Yes; no	Breast density (BI-RADS), race or ethnicity, benign breast disease	0.665[37]
Rosner-Colditz[d]	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	Yes; no	Not included	BMI, benign breast disease, menopause type, menopause age, hormone therapy use and duration, height, alcohol use, parity	0.57 (0.55-0.59)[33] 0.64 (0.63-0.66) (ER+/PR+)[25] 0.61 (0.58-0.64) (ER−/PR−)[25]
Rosner-Colditz 2[d]	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	Yes; no	Atypical hyperplasia: 0; ≥1	Benign breast disease presence or type	0.63 (0.61-0.65)[33] 0.64 (type)[33]
Tyrer-Cuzick (10-y risk)	<50; ≥50	≤12; >12	≤30; >30; no children	1; 2; ≥3	0; 1; ≥2 Lobular carcinoma in situ: 0; ≥1	BMI, height, menopause age, family history of ovarian or other cancer, age of cancer onset, bilateral or male breast cancer	0.76 (0.70-0.82)[17] 0.54 (0.42-0.65)[19] 0.57 (0.55-0.59)[21]
Tyrer-Cuzick + breast density (10-y risk)	<50; ≥50	≤12; >12	≤30; >30; no children	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 (0.58-0.63)[21] 0.62[40]

(continued)

Table 1. Breast Cancer Risk Assessment Methods (Key Question 1) (continued)

Model	Age, y	Age at Menarche, y	Age at Birth of First Child, y	No. First-Degree Relatives With Breast Cancer	No. Previous Breast Biopsies	Other Factors	Summary of Accuracy, AUC (95% CI)[a]
Italian 1 (5-y risk)	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	Not included	Age of relative at breast cancer diagnosis, diet score, alcohol use, BMI, hormone therapy, physical activity	0.59 (vitamin)[20] 0.60 (diet)[20]
Italian 2 (20-y risk)[e]	<50; ≥50	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; 1; ≥2	0; 1; ≥2	Occupational and leisure physical activity, education, alcohol use, BMI	0.62 (0.56-0.69) (age <50 y)[32] 0.57 (0.52-0.61) (age ≥50 y)[32]
Chlebowski (5-y risk)	50-59; 60-69; 70-79	<12; 12-13; ≥14	<20; 20-24; 25-29; ≥30; no children	0; ≥1	0; 1; ≥2	BMI, menopause age, hormone therapy use and duration, race, alcohol use, parity, breastfeeding, smoking status, physical activity	0.61 (0.59-0.63)[23] 0.62 (0.60-0.64) (ER+)[23] 0.53 (0.47-0.58) (ER−)[23]
Chlebowski-simplified (5-y risk)	<50; ≥50	Not included	Not included	0; ≥1	0; 1; ≥2	Not included	0.58 (0.56-0.60) (ER+)[23]
Model$_{ER+}$	Not included	<12; 12; 13; 14; >14	≤20; 20.1-25; 25.1-30; 30.1-35; >35	Not included	Not included	BMI, menopause status and age, alcohol use, hormone therapy use, breast-feeding duration, parity	0.59 (0.58 to 0.60)[30]

Abbreviations: AUC, area under the receiver operating characteristic curve; BCSC, Breast Cancer Surveillance Consortium; BI-RADS, Breast Imaging–Reporting and Data System; BMI, body mass index; ER−, estrogen receptor–negative; ER+, estrogen receptor–positive.

[a] From studies of discriminatory accuracy for invasive breast cancer unless otherwise indicated.

[b] BI-RADS categories include 0 (unknown), 1 (entirely fat), 2 (scattered fibroglandular densities), 3 (heterogeneously dense), 4 (extremely dense).

[c] Includes nonproliferative, proliferative without atypia, proliferative with atypia, and lobular carcinoma in situ.

[d] Invasive and noninvasive breast cancer.

[e] Included an Italian population and used incidence rates from the Italian multicenter case-control study of diet and breast cancer and from Italian cancer registries.

Benefits of Risk-Reducing Medications

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 ductal carcinoma in situ), breast cancer mortality, all-cause mortality, and other beneficial outcomes (such as reduced fractures caused by certain medications and improved quality of life)?

Ten RCTs (40 articles) provided results for KQ2, including 7 new publications. These included updated long-term results of the International Breast Cancer Intervention Study (IBIS-I) trial of tamoxifen,[74] a placebo-controlled trial of low-dose tamoxifen,[41] and placebo-controlled trials of anastrozole[4,75,76] and exemestane.[44,77]

Trials include the STAR head-to-head trial of tamoxifen and raloxifene[49,78,79]; 5 placebo-controlled trials of tamoxifen, including IBIS-I,[42,74,80] NSABP P-1,[46,81,82] Royal Marsden Hospital Trial,[47,83] Italian Tamoxifen Prevention Study,[43,84-87] and the Hormone Replacement Therapy Opposed by Low-dose Tamoxifen (HOT) study[41]; 2 placebo-controlled trials of raloxifene, the Multiple Outcomes of Raloxifene Evaluation (MORE) with long-term follow-up in the Continuing Outcomes Relevant to Evista (CORE) study[45,88-102] and the Raloxifene Use for the Heart (RUTH) trial[48,103]; and 2 placebo-controlled trials of aromatase inhibitors, the International Breast Cancer Intervention Study II (IBIS-II) of anastrozole[4,75,76] and the Mammary Prevention.3 trial (MAP.3) of exemestane.[44,77] The most recent placebo-controlled tamoxifen trial, HOT, using a lower dose than the other trials (5 mg/d vs 20 mg/d), did not indicate reduction in invasive breast cancer risk (RR, 0.83 [95% CI, 0.42-1.62]; n = 1884) and was not included in the meta-analyses of tamoxifen trials (see eFigures 1-8 in the Supplement for other results).[41] Details of individual trials are provided in **Table 2** and the full report.[11] Trials met criteria for fair or good quality (eTable 2 in the Supplement).

Trials included large numbers of women, ranging in size from 1884[41] to 19 747,[49] primarily from North America, Europe, and the United Kingdom. Most 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, and only the placebo-controlled tamoxifen trials enrolled premenopausal women. The Italian trial of tamoxifen exclusively enrolled women who had undergone prior hysterectomy, including some with oophorectomy.[43] Participants used exogenous estrogen in the Italian (14% of women), Royal Marsden (15%-27%), IBIS-I (40%), and HOT (100%) tamoxifen trials. The raloxifene trials enrolled older women with osteoporosis[45,88-102] or increased cardiovascular risk.[45,88-102]

Results of the meta-analysis for KQ2 are summarized in **Table 3** and in eFigures 1-8 in the Supplement. In placebo-controlled trials, tamoxifen (RR, 0.69 [95% CI, 0.59-0.84]; 7 fewer cases per 1000 women over 5 years of use [95% CI, 4-12]; 4 trials [n = 28 421]), raloxifene (RR, 0.44 [95% CI, 0.24-0.80]; 9 fewer cases [95% CI, 3-15]; 2 trials [n = 17 806]), and the aromatase inhibitors exemestane and anastrozole (RR, 0.45 [95% CI, 0.26-0.70]; 16 fewer cases [95% CI, 8-24]; 2 trials [n = 8424]) (**Figure 3**) were associated with 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]; n = 19 747) after long-term follow-up. All medications were associated with reduced estrogen receptor–positive but not estrogen receptor–negative invasive breast cancer. Tamoxifen was associated with reduced noninvasive cancer in the NSABP P-1[82] and IBIS-I[74] trials but not in the meta-analysis of all 4 trials (RR, 0.72 [95% CI, 0.56-1.41]; 4 trials [n = 28 421]). Medications were not associated with reductions in breast cancer–specific and all-cause mortality.

In placebo-controlled trials, raloxifene (RR, 0.61 [95% CI, 0.53-0.73]; 2 trials [n = 16 929]) was associated with reduced vertebral fractures; tamoxifen was associated with reduced nonvertebral fractures in the NSABP P-1 trial (RR, 0.66 [95% CI, 0.45-0.98]; n = 13 388) and the aromatase inhibitors had no effect on fractures. Tamoxifen and raloxifene had similar effects on fracture incidence at multiple vertebral and nonvertebral sites in the STAR head-to-head trial.

Key Question 2a. Does the effectiveness of risk-reducing medications vary by timing of initiation or duration of use?

Eight trials reported similar breast cancer outcomes regardless of age, although age categories varied by trial. No studies specifically compared shorter vs longer regimens of medication use or initiation based on time since menopause. While most trials intended 5 years of medication use, mean exposure times varied across the trials from 3 to 5 years. However, trials of similar medications indicated general consistency in their associations with breast cancer risk reduction, despite exposure time.

Key Question 2b. Does the effectiveness of risk-reducing medications persist beyond discontinuation of use?

The IBIS-I[80] and Royal Marsden[83] trials provided results for invasive and estrogen receptor–positive breast cancer for both the active treatment (mean duration, 5 years) and the posttreatment (median follow-up, 13 and 16 years, respectively) periods. These results indicate continued associations with reduced risk after discontinuation of tamoxifen, providing point estimates of even larger reductions in invasive and estrogen receptor–positive breast cancer during the posttreatment period. For IBIS-I, the RR for invasive breast cancer was 0.74 (95% CI, 0.60-0.93) for the 0- to 10-year follow-up period and 0.70 (95% CI, 0.52-0.95) for the greater than 10 years follow-up period,[4] although the difference between periods was not statistically significant.

Harms of Risk-Reducing Medications

Key Question 3. What are the harms of using medications to reduce risk for primary breast cancer?

A total of 22 studies (54 articles) met inclusion criteria, including updated long-term results of the IBIS-I trial of tamoxifen,[74] a placebo-controlled trial of low-dose tamoxifen,[41] and placebo-controlled trials of anastrozole[4,75,76] and exemestane.[44,77]

For tamoxifen, information on adverse effects was confined to the 5 large placebo-controlled primary prevention trials[41-43,46,47,74,80-84,86,87,105-108] and the STAR head-to-head trial.[49,78,79,109] 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.[41] For raloxifene, adverse effects were reported from the 2 large placebo-controlled trials, MORE/CORE and RUTH[88-94,104]; the STAR head-to-head trial[49,78,79]; 8 smaller trials

Table 2. Randomized Clinical Trials of Medications to Reduce Risk for Breast Cancer (KQ2, KQ3, KQ4)

Source	Group, No.[a] 1	2	Breast Cancer Risk Criteria	Participants, Setting	Age, Median, y	No. (%)[a] White	Posthyster-ectomy	Used Estrogen During Trial	Primary Outcomes	Median, y Follow-up	Exposure	Quality Rating
Tamoxifen (20 mg/d) vs Raloxifene (60 mg/d)												
STAR Vogel et al,[49] 2006 Land et al,[78] 2006 Vogel et al,[79] 2010	9872	9875	5-y predicted breast cancer risk ≥1.66% based on the modified Gail model[b]	Postmenopausal, aged ≥35 y, US-based with sites in North America	58.5[c]	18 204 (93.5)	10 027 (51.5)	0	Invasive breast cancer	3.9 initial; 6.8 long-term[c]	3.6-3.9[c]	Good
Tamoxifen (20 mg/d) vs Placebo												
IBIS-I Cuzick et al,[42] 2002 Cuzick et al,[80] 2007 Cuzick et al,[74] 2015	3573	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[d]	35-70 y, United Kingdom, Australia, New Zealand, Europe	50.8[c]	NR	2515 (35)	2844 (40)	Invasive and noninvasive breast cancer	4.2 initial; 8.0 long-term; 16 longer-term	5	Good
NSABP-P1 Fisher et al,[46] 1998 Fisher et al,[82] 2005 Day et al,[81] 2001	6576	6599	Age ≥60 y or 35-59 y with a 5-y predicted breast cancer risk ≥1.66% based on the modified Gail model or history of LCIS[b]	≥35 y, US-based with sites in North America	Median not reported; 5177 (39.3%) <50	12 706 (96.4)	4884 (37)	NR (<10)	Invasive and noninvasive breast cancer	4.6 initial; 7.0 long-term	4.0 when unblinded	Good
Royal Marsden Hospital Trial Powles et al,[47] 1998 Powles et al,[83] 2007	1238	1233	Family history of breast cancer[e]	30-70 y, United Kingdom	47	NR	NR	389 (15.6)	Invasive breast cancer	5.8 initial; 13.2 long-term	NR	Good
Italian Tamoxifen Prevention Study Veronesi et al,[43] 1998 Veronesi et al,[86] 2003 Veronesi et al,[84] 2007 Decensi et al,[87] 2005	2700	2708	None	35-70 y, Italy-based with sites 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%
Tamoxifen (5 mg/d) vs Placebo												
HOT DeCensi et al,[41] 2013	938	946	None	Postmenopausal, Italy-based	53[c]	NR	NR	100 (100)	Invasive breast cancer	6.2[c]	5[c]	Good
Raloxifene (60 or 120 mg/d) vs Placebo												
MORE and CORE Cauley et al,[89] 2001 Cummings et al,[90] 1999 Ettinger et al,[88] 1999 Barrett-Connor et al,[92] 2002 Delmas et al,[93] 2002 Delmas et al,[94] 2003 Grady et al,[96] 2004 Barrett-Connor et al,[91] 200 Silverman et al,[100] 2004 Johnell et al,[102] 2004; Martino et al,[45] 2004; Martino et al,[99] 2005 Duvernoy et al,[95] 2005 Keech et al,[97] 2005 Siris et al,[101] 2005 Lippman et al,[98] 2006	MORE: 5129l CORE: 2725	MORE: 2576; CORE: 1286	None	Postmenopausal, aged 31-80 y, with osteoporosis, US-based with sites in 25 countries; CORE includes a subset of MORE participants[f]	66.9	NR (96)	NR (23)	0	MORE: Incident radiographic vertebral fractures and clinical nonvertebral fractures; CORE: Breast cancer	MORE: 3, 4 CORE: 4, 8 (combines data)	NR	Good

Table 2. Randomized Clinical Trials of Medications to Reduce Risk for Breast Cancer (KQ2, KQ3, KQ4) (continued)

Source	Group, No.[a] 1	2	Breast Cancer Risk Criteria	Participants, Setting	Age, Median, y	No. (%)[a] White	Posthyster-ectomy	Used Estrogen During Trial	Primary Outcomes	Median, y Follow-up	Exposure	Quality Rating
RUTH Barrett-Connor et al,[48] 2006 Grady et al,[103] 2008 Ensrud et al,[104] 2008	5044	5057	None	Postmenopausal, aged ≥55 y, CHD or risk factors, US-based with sites in 26 countries[g]	67.5	8481 (84)	2319 (23)	0	Coronary events, invasive breast cancer	5.6	5.1	Good
Anastrozole (1 mg/d) vs Placebo												
IBIS-II Cuzick et al,[4] 2014 Sestak et al,[75] 2014 Spagnolo et al,[76] 2016	1920	1944	Increased risk for breast cancer: ages 45-60 y ≥2 times higher than the general population; ages 60-70 y 1.5 times higher; ages 40-44 y 4 times higher	Postmenopausal, aged 40-70 y, United Kingdom-based with sites in 18 countries	59.5	NR	1287 (33.3)	0	Invasive and noninvasive breast cancer	5	5	Good
Exemestane (25 mg/d) vs Placebo												
MAP.3 Goss et al,[44] 2011 Maunsell et al,[77] 2014	2285	2275	Risk factors for breast cancer: age ≥60 y; Gail risk score >1.66%; prior ADH, ALH, LCIS, or DCIS	Postmenopausal, age ≥35 y, US-based with sites in 4 countries	62.5	4261 (93.4)	NR	0	Invasive breast cancer	2.9	3	Good

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, International Breast Cancer Intervention Study; KQ, key question; LCIS, lobular carcinoma in situ; MAP.3, Mammary Prevention.3 trial; MORE, Multiple Outcomes of Raloxifene Evaluation; NR, not reported; NSABP-P1, National Surgical Adjuvant Breast and Bowel Project P-1; RUTH, Raloxifene Use for the Heart; STAR, Study of Tamoxifen and Raloxifene.

[a] At time of randomization.

[b] STAR and 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 biopsy results, 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.

[c] Values are means.

[d] IBIS: All criteria permit entry to trial at age 45 years: first-degree relative with breast cancer at 50 years or younger; first-degree relative with bilateral breast cancer (permits entry from age 40 years; if relative age ≤40 years, permits entry at age 35 years); 2 or more first-degree or second-degree relatives with breast cancer (permits entry from age 40 years if both developed breast cancer before age 50 years; permits entry at age 35

years if both relatives are first-degree and both relatives developed breast cancer before age 50 years); benign breast biopsy and first-degree relative with breast cancer; lobular carcinoma in situ (permits entry from age 35 years); atypical hyperplasia (permits entry from age 40 years); 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).

[e] Family history criteria, Royal Marsden Hospital Trial: 1 first-degree relative younger than 50 years with breast cancer, or 1 first-degree relative with bilateral breast cancer, or 1 affected first-degree of any age plus another affected first-degree or second-degree relative; benign breast biopsy result and a first-degree relative with breast cancer.

[f] MORE: study group 1, femoral neck or lumbar spine bone mineral density T-score less than −2.5; study group 2, low bone mineral density and 1 or more moderate or severe vertebral fractures or 2 or more milder vertebral fractures (20%-25% reduction in height); or 2 or more moderate fractures (25%-40% reduction from expected vertebral height), regardless of bone mineral density.

[g] Cardiovascular risk score of 4 or greater: established coronary heart disease (4 points), arterial disease of the leg (4 points), 70 years or older (2 points), diabetes mellitus (3 points), cigarette smoking (1 point), hypertension (1 point), and hyperlipidemia (1 point).

Table 3. Results of Randomized Clinical Trials of Risk Reducing Medications (KQ2 and KQ3)

Outcome	Tamoxifen vs Raloxifene (Single Trial)		Tamoxifen vs Placebo				Raloxifene vs Placebo				Aromatase Inhibitors vs Placebo			
	RR (95% CI)	No. of Events Reduced or Increased (95% CI)[a]	RR (95% CI)	No. of Trials[b]	Placebo Rate (SE)[c]	No. of Events Reduced or Increased (95% CI)[a]	RR (95% CI)	No. of Trials[b]	Placebo Rate (SE)[c]	No. of Events Reduced or Increased (95% CI)[a]	RR (95% CI)	No. of Trials[b]	Placebo Rate (SE)[c]	No. of Events Reduced or Increased (95% CI)[a]
Benefits														
Invasive breast cancer	1.24 (1.05-1.47)[d]	5 (1-9) fewer with tamoxifen	0.69 (0.59-0.84)	4	4.58 (0.96)	7 (4-12) fewer with tamoxifen	0.44 (0.24-0.80)	2	3.19 (0.59)	9 (3-15) fewer with raloxifene	0.45 (0.26-0.70)	2	5.90 (0.6)	16 (8-24) fewer with AIs
ER+ breast cancer	0.93 (0.72-1.24)[e]	NA	0.58 (0.42-0.81)	4	3.62 (0.76)	8 (4-13) fewer with tamoxifen	0.33 (0.15-0.70)	2	2.45 (0.42)	8 (4-13) fewer with raloxifene	0.37 (0.19-0.63)	2	4.55 (0.53)	15 (8-20) fewer with AIs
ER− breast cancer	1.15 (0.75-1.77)[e]	NA	1.18 (0.93-1.53)	4	NA	NA	1.25 (0.60-2.58)	2	NA	NA	0.79 (0.35-1.79)	2	NA	NA
Noninvasive breast cancer	1.22 (0.95-1.59)[d]	NA	0.72 (0.56-1.41)[f]	4	NA	NA	1.47 (0.61-3.85)	2	NA	NA	0.46 (0.16-1.42)	2	NA	NA
Breast cancer mortality	0.36 (0.08-1.21)[d]	NA	1.20 (0.79-1.79)	4	NA	NA	Not reported[g]	NA	NA	NA	Not reported	NA	NA	NA
All-cause mortality	0.84 (0.70-1.02)[d]	NA	1.07 (0.91-1.23)	4	NA	NA	0.90 (0.63-1.05)	2	NA	NA	1.02 (0.58-1.82)	2	NA	NA
Vertebral fracture	0.98 (0.65-1.46)[e]	NA	0.75 (0.48-1.15)[h]	1	NA	NA	0.61 (0.53-0.73)	2	3.45 (0.35)[i]	7 (5-9) fewer with raloxifene	1.28 (0.59-2.75)	2	NA	NA
Nonvertebral fracture	Not reported	NA	0.66 (0.45-0.98)[h]	1	1.55 (0.20)	3 (0.2-5) fewer with tamoxifen	0.97 (0.86-1.12)	2	NA	NA	1.05 (0.87-1.28)	2	NA	NA
Harms														
Venous thromboembolism[j]	0.75 (0.60-0.93)[d]	4 (1-7) more with tamoxifen	1.93 (1.33-2.68)	4	0.91 (0.19)	5 (2-9) more with tamoxifen	1.56 (1.11-2.60)	2	2.34 (0.25)	7 (0.3-17) more with raloxifene	1.24 (0.65-2.16)	2	NA	NA
DVT	0.72 (0.54-0.95)[d]	3 (1-5) more with tamoxifen	1.45 (0.73-2.59)	2	NA	NA	1.66 (0.79-5.14)	2	NA	NA	Not reported	NA	NA	NA
PE	0.80 (0.57-1.11)[d]	NA	2.69 (0.54-8.13)	2	NA	NA	2.11 (0.82-6.12)	2	NA	NA	Not reported	NA	NA	NA
CHD events	1.10 (0.85-1.43)[e]	NA	1.00 (0.75-1.30)	4	NA	NA	0.95 (0.80-1.10)	2	NA	NA	0.76 (0.41-1.49)	2	NA	NA
Stroke	0.96 (0.64-1.43)[e]	NA	1.36 (0.78-2.20)	4	NA	NA	1.04 (0.64-1.36)	2	NA	NA	0.98 (0.27-2.56)	2	NA	NA
Endometrial cancer	0.55 (0.36-0.83)[d]	5 (2-9) more with tamoxifen	2.25 (1.17-4.41)	3	0.62 (0.10)	4 (1-8) more with tamoxifen	1.14 (0.54-2.17)	2	NA	NA	0.60 (0.09-3.07)	1	NA	NA
Cataracts	0.80 (0.72-0.95)[d]	15 (8-22) more with tamoxifen	1.22 (1.08-1.48)	3	22.85 (0.75)[k]	26 (5-50) more with tamoxifen	0.93 (0.82-1.06)	2	NA	NA	0.94 (0.70-1.27)	1	NA	NA

Abbreviations: AI, aromatase inhibitor; CHD, coronary heart disease; DVT, deep vein thrombosis; ER−, estrogen receptor–negative; ER+, estrogen receptor–positive; KQ, key question; NA, not applicable; NSABP, National Surgical Adjuvant Breast and Bowel Project; PE, pulmonary embolism; RR, risk ratio; RUTH, Raloxifene Use for the Heart; SE, standard error; VTE, venous thromboembolism.

[a] Numbers of events reduced for benefits or increased for harms vs comparator per 1000 women assuming 5 years of use.

[b] Number of trials included in meta-analysis.

[c] Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the risk ratio estimate.

[d] Updated results from STAR (2010).[52]

[e] Initial results from STAR (2006).[50]

[f] Reduced in NSABP P-1 (2005) (60 vs 93 events; RR, 0.63 [95% CI, 0.45-0.89]).[57]

[g] Two breast cancer deaths in 7601 women for raloxifene vs 0 in 7633 women for placebo.[75,83]
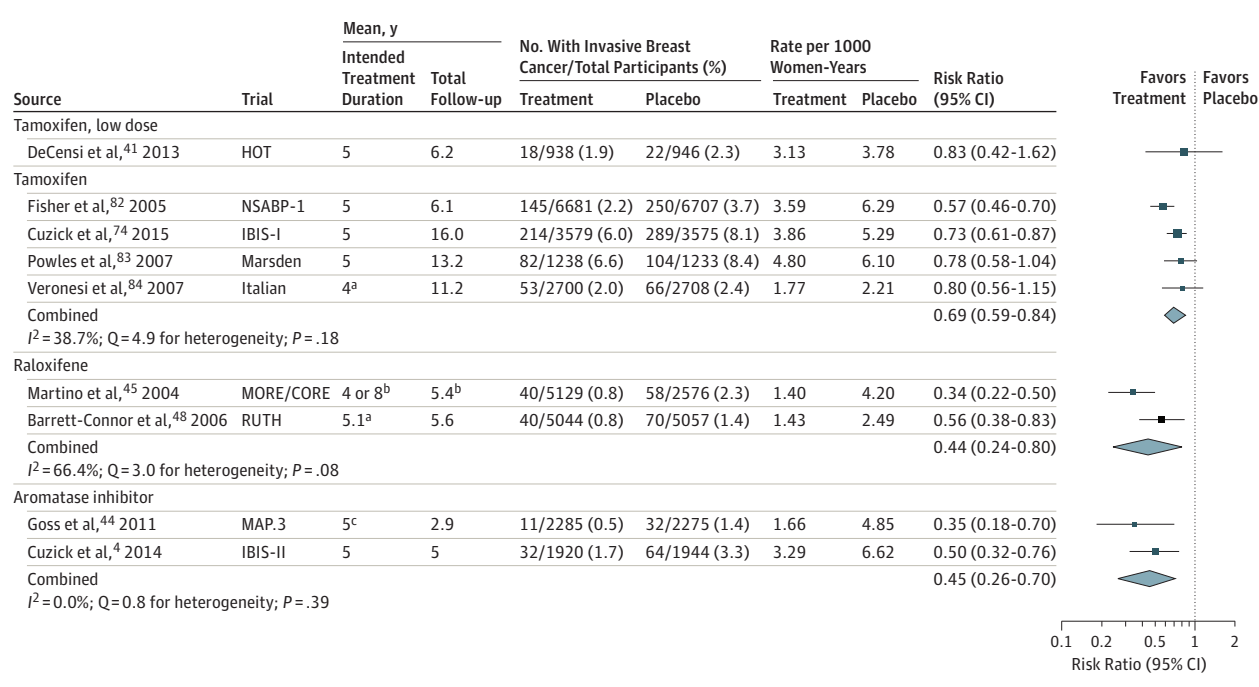
[h] NSABP P-1 (2007).[57]

[i] Estimated from the placebo group of the RUTH trial (2006).[82]

[j] Includes DVT and PE.

[k] Placebo rate was from NSABP P-1 (2005).[57]

Figure 3. Risk Reduction of Invasive Breast Cancer: Meta-analysis of Primary Prevention Trials

Source	Trial	Mean, y Intended Treatment Duration	Total Follow-up	No. With Invasive Breast Cancer/Total Participants (%) Treatment	Placebo	Rate per 1000 Women-Years Treatment	Placebo	Risk Ratio (95% CI)	Favors Treatment / Favors Placebo
Tamoxifen, low dose									
DeCensi et al,[41] 2013	HOT	5	6.2	18/938 (1.9)	22/946 (2.3)	3.13	3.78	0.83 (0.42-1.62)	
Tamoxifen									
Fisher et al,[82] 2005	NSABP-1	5	6.1	145/6681 (2.2)	250/6707 (3.7)	3.59	6.29	0.57 (0.46-0.70)	
Cuzick et al,[74] 2015	IBIS-I	5	16.0	214/3579 (6.0)	289/3575 (8.1)	3.86	5.29	0.73 (0.61-0.87)	
Powles et al,[83] 2007	Marsden	5	13.2	82/1238 (6.6)	104/1233 (8.4)	4.80	6.10	0.78 (0.58-1.04)	
Veronesi et al,[84] 2007	Italian	4[a]	11.2	53/2700 (2.0)	66/2708 (2.4)	1.77	2.21	0.80 (0.56-1.15)	
Combined I² = 38.7%; Q = 4.9 for heterogeneity; P = .18								0.69 (0.59-0.84)	
Raloxifene									
Martino et al,[45] 2004	MORE/CORE	4 or 8[b]	5.4[b]	40/5129 (0.8)	58/2576 (2.3)	1.40	4.20	0.34 (0.22-0.50)	
Barrett-Connor et al,[48] 2006	RUTH	5.1[a]	5.6	40/5044 (0.8)	70/5057 (1.4)	1.43	2.49	0.56 (0.38-0.83)	
Combined I² = 66.4%; Q = 3.0 for heterogeneity; P = .08								0.44 (0.24-0.80)	
Aromatase inhibitor									
Goss et al,[44] 2011	MAP.3	5[c]	2.9	11/2285 (0.5)	32/2275 (1.4)	1.66	4.85	0.35 (0.18-0.70)	
Cuzick et al,[4] 2014	IBIS-II	5	5	32/1920 (1.7)	64/1944 (3.3)	3.29	6.62	0.50 (0.32-0.76)	
Combined I² = 0.0%; Q = 0.8 for heterogeneity; P = .39								0.45 (0.26-0.70)	

0.1   0.2   0.5   1   2
Risk Ratio (95% CI)

The area of the square representing the risk ratio is proportional to the number of events in each subgroup. CORE indicates Continuing Outcomes Relevant to Evista; HOT, Hormone replaced therapy Opposed by low-dose Tamoxifen; IBIS, International Breast Cancer Intervention Study; MAP.3, Mammary Prevention.3; MORE, Multiple Outcomes of Raloxifene; NSABP-1, National Surgical Adjuvant Breast and Bowel Project P-1; RUTH, Raloxifene Use for the Heart.

[a] Veronesi (2007) and Barrett-Connor (2006) reported mean or median duration of the treatment period.

[b] Includes data from both MORE (4-year treatment) and CORE (4-year additional treatment); total follow-up time is averaged over both studies for 7705 participants.

[c] Intended treatment duration is 5 years or until a breast, neoplastic, cardiovascular, or toxicity event.

(in 11 publications) evaluating either bone density, biochemical profiles, or fractures[51-60,110]; and 1 observational study.[50] These additional studies contribute little to the evaluation of harms because they involve few women relative to the large primary prevention trials, although these results are generally consistent with those of the larger trials. Consequently, they were not included in the meta-analyses of raloxifene trials. For anastrozole and exemestane, information on adverse effects was based on the 2 large placebo-controlled primary prevention trials.[4,44] Similar to tamoxifen, no other RCTs or observational studies evaluated adverse effects of aromatase inhibitors in women without breast cancer.

Results of the meta-analysis for KQ3 are summarized in Table 3 and in eFigures 9-14 in the Supplement. In placebo-controlled trials, tamoxifen (RR, 1.93 [95% CI, 1.33-2.68]; 4 trials [n = 28 421]) and raloxifene (RR, 1.56 [95% CI, 1.11-2.60]; 2 trials [n = 17 806]) were associated with increased thromboembolic events. Raloxifene was associated with fewer thromboembolic events than tamoxifen in the STAR head-to-head trial (RR, 0.75 [95% CI, 0.60-0.93]; n = 19 490). Tamoxifen, raloxifene, and aromatase inhibitors were not associated with increased coronary heart disease events or strokes.

In placebo-controlled trials, tamoxifen was associated with increased incidence of endometrial cancer (RR, 2.25 [95% CI,

1.17-4.41]; 3 trials [n = 15 421]). In the STAR head-to-head trial, raloxifene was associated with fewer cases of endometrial cancer (RR, 0.55 [95% CI, 0.36-0.83]; n = 19 490) and endometrial hyperplasia (RR, 0.19 [95% CI, 0.12-0.29]; n = 19 490) and with fewer hysterectomies (RR, 0.45 [95% CI, 0.37-0.54]; n = 19 490) than tamoxifen. Tamoxifen was associated with increased incidence of cataracts (RR, 1.22 [95% CI, 1.08-1.48]; 3 trials [n = 22 832]) and cataract surgery compared with placebo. 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 were associated with adverse effects, such as vasomotor or musculoskeletal symptoms, that varied by medication.

Key Question 3a. Do the harms of risk-reducing medications vary by timing of initiation or duration of use?

The NSABP P-1 placebo-controlled trial of tamoxifen reported point estimates consistent with higher risks for deep vein thrombosis, pulmonary embolus, and stroke for women 50 years and older than for women younger than 50 years, although results were not statistically significant.[46] 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.[111] Age older than 60 years was also an important risk factor for venous thrombosis in the Italian trial.[87] The NSABP P-1 trial found that

endometrial cancer was more common among women 50 years and older than among women younger than 50 years (RR, 4.01 [95% CI, 1.70-10.90]; n = 7998 for those ≥50 years vs RR, 1.21 [95% CI, 0.41-3.60]; n = 5177 for those <50 years).[46] Initiation based on time since menopause was not reported.

Key Question 3b. Do the harms of risk-reducing medications persist beyond discontinuation of use?

Although tamoxifen was associated with increased thromboembolic events compared with placebo during the trials, risk returned to normal after discontinuation of tamoxifen in the 2 trials (IBIS-I[80] and Royal Marsden[83]) that reported posttreatment data (RR, 0.98 [95% CI, 0.48-1.80]; 2 trials; n = 10 130).[74] In the IBIS-I trial, risk for endometrial cancer was higher for tamoxifen compared with placebo during the first 5 years of follow-up (RR, 3.76 [95% CI, 1.20-15.56]) but declined after discontinuation (RR for 5- to 10-year follow-up, 0.64 [95% CI, 0.21-1.80]; RR for ≥10-year follow-up, 1.40 [95% CI, 0.38-5.61]).[74]

Outcomes in Subgroups

Key Question 4. Do the outcomes of using medications to reduce risk for primary breast cancer vary by population subgroups?

Studies included for KQ2 and KQ3 also provided results for KQ4. Medications were associated with lower risks for invasive breast cancer in all population subgroups evaluated based on menopausal status; 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 (eFigures 15-17 in the Supplement). Tamoxifen and anastrozole were associated with reduced risk, regardless of history of previous breast lesions (lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia) but demonstrated larger estimates of effect in women with previous lesions.

Clinician and Patient Attitudes and Practices

Factors associated with adherence and nonadherence in patient use of risk-reducing medications were examined in systematic reviews[7,69,72] and additional observational studies.[63,64,66-68,70,71,73] Factors associated with adherence included higher breast cancer risk; clinician recommendation; peers with good experiences using medications; belief that medications are effective; anxiety or worry about breast cancer; and history of an abnormal breast biopsy result. Factors associated with nonadherence included concern for adverse effects; estrogen contraindication; peers with poor experiences using medications; belief that medications are for treatment, not risk reduction; medication is a daily reminder of illness; preference for other risk-reducing approaches such as mastectomy; and knowledge of the benefits and harms of medication.

Prescribing risk-reducing medications is an uncommon practice among primary care physicians surveyed in 3 US studies.[61,62,65] Factors associated with prescribing included more breast cancer diagnoses in clinical practice; belief that benefits outweigh harms; patients asking about medications; personal experience with breast cancer in self or a relative; and belief that eligibility for medications is easy to determine. Barriers to prescribing included lack of training, experience, or comfort with medications; belief that benefit may not be worth harms; belief that patients lack interest in medications; preference that specialists prescribe medications; lack of com-

fort or certainty with identifying women eligible for medications; and time constraints.

Discussion

This evidence report reviewed trials of the efficacy and harms of medications to reduce the risk of primary invasive breast cancer and studies of the accuracy of clinical risk assessment methods to select patients for therapy. **Table 4** summarizes the evidence included in this review. Although most results are consistent with the 2013 USPSTF review,[3] this update provides additional evidence of the inaccuracy of risk assessment methods[21,30,31,37]; long-term follow-up of the IBIS-1 tamoxifen trial demonstrating persistent breast cancer risk reduction and normalization of endometrial cancer risk after discontinuation of tamoxifen[4]; and new trials of aromatase inhibitors.[4,44,75-77] In addition, a placebo-controlled trial of low-dose tamoxifen indicated no reduction in risk of invasive breast cancer.[41]

Results of 4 recently published studies of breast cancer risk assessment methods indicated low discriminatory accuracy in predicting the probability of breast cancer in individual women,[21,30,31,37] similar to previous studies. Most methods performed only slightly better than age alone as a risk predictor. Based on these studies, current practices of selecting women for risk-reducing medications according to a modified 5-year Gail score of 1.66% or higher, as used for inclusion criteria in primary prevention trials and US Food and Drug Administration approval of tamoxifen and raloxifene for risk reduction, are likely inaccurate. Most women 60 years and older without other risk factors would meet this threshold by age alone. Studies also provide no clinical guidance on optimal ages or frequencies for risk assessment because these components have not yet been evaluated.

Primary prevention trials of anastrozole[4,75,76] and exemestane[44,77] provide new evidence of the efficacy and harms of aromatase inhibitors for breast cancer risk reduction. However, no long-term follow-up data are available to determine whether harms demonstrated in treatment trials of women with noninvasive and early stage breast cancer, such as fractures and cardiovascular events, apply to risk reduction. An RCT of 2980 women with locally excised estrogen receptor–positive ductal carcinoma in situ compared anastrozole (1 mg/d) with tamoxifen (20 mg/d) for 5 years, with median follow-up of 7.2 years.[112] Results indicated increased risk of fractures (odds ratio, 1.36 [95% CI, 1.03-1.80]) and stroke (odds ratio, 3.36 [95% CI, 1.04-14.18]) with anastrozole and increased venous thromboembolic events with tamoxifen.[112] A meta-analysis of individual-level data from 31 920 postmenopausal women with estrogen receptor–positive early breast cancer in treatment RCTs of aromatase inhibitors vs tamoxifen also indicated associations with increased fractures for aromatase inhibitors but no differences for venous thromboembolic events or stroke.[113] Also, 7 RCTs that compared extended aromatase inhibitor treatment with treatment followed by placebo or no treatment showed associations with increased fractures and stroke for extended aromatase inhibitors and suggested increased cardiovascular events.[114] Although these trials imply associations of aromatase inhibitors with increased

Table 4. Summary of Evidence

Intervention	No. of Studies (No. of Participants)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Diagnostic Accuracy of Risk Assessment Methods						
Breast cancer risk assessment	25 discriminatory accuracy studies of 18 risk stratification methods (>5 000 000)	Methods have low discriminatory accuracy in predicting the probability of breast cancer in individuals (AUC, 0.55-0.65)	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
KQ1a: Optimal Age at Which to Begin Risk Assessment						
Breast cancer risk assessment	No studies	NA	NA	NA	Insufficient	NA
KQ1b: Optimal Frequency of Risk Assessment						
Breast cancer risk assessment	No studies	NA	NA	NA	Insufficient	NA
KQ2: Benefits of Risk-Reducing Medications						
Tamoxifen vs raloxifene	1 RCT (19 747)	Risk for invasive breast cancer was higher for raloxifene compared with tamoxifen (RR, 1.24 [95% CI, 1.05-1.47]; 5 more cases [95% CI, 1-9][a]) No differences for ER+, ER−, or noninvasive breast cancer; all-cause or breast cancer-specific mortality; or fractures	NA	None	High; 1 large definitive trial	High
Tamoxifen vs placebo	4 RCTs (28 193)	Tamoxifen was associated with reduced invasive breast cancer (RR, 0.69 [95% CI, 0.59-0.84]; 7 fewer cases [95% CI, 4-12][a]), ER+ breast cancer (RR, 0.58 [95% CI, 0.42-0.81]; 8 fewer cases [95% CI, 4-13][a]), and nonvertebral fractures (RR, 0.66 [95% CI, 0.45-0.98]; 3 fewer cases [95% CI, 0.2-5][a]) 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 1 trial)	High
Raloxifene vs placebo	2 RCTs (17 806)	Raloxifene was associated with reduced invasive breast cancer (RR, 0.44 [95% CI, 0.24-0.80]; 9 fewer cases [95% CI, 3-15][a]), ER+ breast cancer (RR, 0.33 [95% CI, 0.15-0.70]; 8 fewer cases [95% CI, 4-13][a]), and vertebral fractures (RR, 0.61 [95% CI, 0.53-0.73]; 7 fewer cases [95% CI, 5-9][a]) 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

(continued)

risk for fractures and stroke, it is unclear how well the results of treatment trials translate to women without cancer, particularly in the absence of true placebo comparison groups. For example, it is not known whether the increase in fractures reflects the direct harm of aromatase inhibitors or the protective effect of tamoxifen.

Future research to determine optimal candidates for risk-reducing medications should focus on the women mostly likely to benefit. Applying research findings to clinical selection criteria would improve identification of candidates in practice settings and clinical decision making. For example, no new studies and no studies in the 2013 review evaluated risk-reducing medications specifically in carriers of pathogenic *BRCA1/2* mutations. 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

Table 4. Summary of Evidence (continued)

Intervention	No. of Studies (No. of Participants)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Aromatase inhibitors (anastrozole; exemestane) vs placebo	2 RCTs (8424)	Aromatase inhibitors were associated with reduced invasive breast cancer (RR, 0.45 [95% CI, 0.26-0.70]; 16 fewer cases [95% CI, 8-24][a]) and ER+ breast cancer (RR, 0.37 [95% CI, 0.19-0.63]; 15 fewer cases [95% CI, 8-20][a]) compared with placebo No differences for ER− or noninvasive breast cancer, all-cause or breast cancer-specific mortality, or fractures	Consistent; precise	Trials used different medications and exposure durations	High for all outcomes	High
KQ2a: Benefits of Risk-Reducing Medications—Timing and Duration						
Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	9 RCTs (74 170)	No differences in breast cancer outcomes by age Despite variations in exposure times from 3-5 y, 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
KQ2a: Benefits of Risk-Reducing Medications—Persistence of Effects						
Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen (9610); no trials of other medications	Tamoxifen reduced invasive and ER+ breast cancer 8 y after discontinuation	Consistent; precise	Long term follow-up data are lacking from most trials	Moderate for tamoxifen; insufficient for other medications	High
KQ3: Harms of Risk-Reducing Medications						
Tamoxifen vs raloxifene	1 RCT (19 747)	Tamoxifen was associated with increased thromboembolic events (RR, 0.75 [95% CI, 0.60-0.93]; 4 more cases [95% CI, 1-7][a]), DVT (RR, 0.72 [95% CI, 0.54-0.95]; 3 more cases [95% CI, 1-5][a]), endometrial cancer (RR, 0.55 [95% CI, 0.36-0.83]; 5 more cases [95% CI, 2-9][a]), and cataracts (RR, 0.80 [95% CI, 0.72-0.95]; 15 more cases [95% CI, 8-22][a]) compared with raloxifene No differences for PE, CHD events, or stroke	NA	None	High; 1 large definitive trial	High
Tamoxifen vs placebo	4 RCTs (28 193)	Tamoxifen was associated with increased thromboembolic events (RR, 1.93 [95% CI, 1.33-2.68]; 5 more cases [95% CI, 2-9][a]), endometrial cancer (RR, 2.25 [95% CI, 1.17-4.41]; 4 more cases [95% CI, 1-8][a]), and cataracts (RR, 1.22 [95% CI, 1.08-1.48]; 26 more cases [95% CI, 5-50][a]) 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

(continued)

for 288 mutation carriers who developed breast cancer during the trial.[115] Of the 8 women with breast cancer who had *BRCA1* mutations, 5 received tamoxifen and 3 placebo (RR, 1.67 [95% CI, 0.32-10.70]). Of 11 women with breast cancer and *BRCA2* mutations, 3 received tamoxifen and 8 placebo (RR, 0.38 [95% CI, 0.06-1.56]). Also, 6 of 7 women (86%) with *BRCA1* mutations had estrogen receptor–negative breast cancer and 6 of 9 (67%) with *BRCA2* mutations had estrogen receptor–positive cancer. Tamoxifen is only effective in reducing risk for estrogen receptor–positive breast cancer.

Table 4. Summary of Evidence (continued)

Intervention	No. of Studies (No. of Participants)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Raloxifene vs placebo	2 RCTs (17 806)	Raloxifene was associated with increased thromboembolic events (RR, 1.56 [95% CI, 1.11-2.60]; 7 more cases [95% CI, 0.3-17][a]), endometrial cancer (RR, 2.25 [95% CI, 1.17-4.41]; 4 more cases [95% CI, 1-8][a]), and cataracts (RR, 1.22 [95% CI, 1.08-1.48]; 26 more cases [95% CI, 5-50][a]) compared with placebo No differences for DVT, PE, CHD events, stroke, endometrial cancer, or cataracts	Consistent; precise	Trials primarily designed for osteoporosis and cardiovascular outcomes; participants not selected based on breast cancer risk	High for all outcomes	High
Aromatase inhibitors (anastrozole; exemestane) vs placebo	2 RCTs (8424)	No differences between aromatase inhibitors and placebo for thromboembolic events, DVT, PE, CHD events, stroke, endometrial cancer, or cataracts	Consistent; precise	Trials used different medications and exposure durations; no long-term follow-up data	Low to moderate; follow-up inadequate for several outcomes	High
KQ3a: Harms of Risk-Reducing Medication—Timing and Duration						
Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen for thromboembolic events (18 583); 1 RCT of tamoxifen (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
KQ3a: Harms of Risk-Reducing Medication—Persistence of Effects						
Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs of tamoxifen for thromboembolic events (9610); 1 RCT of tamoxifen (7139) 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 follow-up data are lacking from most trials	Moderate for tamoxifen; insufficient for other medications	High
KQ4: Variability by Subpopulations						
Tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	2 RCTs with menopausal status (12 547); 5 RCTs with family history (56 136); 4 RCTs with BMI (26 230); 4 RCTs with breast lesions (41 346); 4 RCTs with risk categories (13 965); 1 RCT with reproductive factors (10 101)	Reduced risk for invasive cancer for tamoxifen for both premenopausal and postmenopausal women; tamoxifen and raloxifene for women with or without family history of breast cancer; raloxifene, anastrozole, and exemestane for all BMI categories Tamoxifen and anastrozole had more effects for women with previous breast lesions (LCIS, ADH, ALH) Risks were reduced for tamoxifen, raloxifene, and anastrozole in all modified Gail model risk categories and for raloxifene regardless of age at menarche, parity, or age at first live birth	Inconsistent; imprecise	Trials not designed for subgroup comparisons, and analysis of differences between groups may be underpowered	Low and insufficient	High

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; AUC, area under the receiver operating characteristic curve; BMI, body mass index; CHD, coronary heart disease; DVT, deep vein thrombosis; ER+, estrogen receptor–positive; ER–, estrogen receptor–negative; KQ, key question; LCIS, lobular carcinoma in situ; NA, not applicable; PE, pulmonary embolism; RCT, randomized clinical trial; RR, risk ratio.

[a] Per 1000 women over 5 years of use.

Limitations

This review had several limitations. First, there was potential publication bias as well as biases of the literature review process, such as including only English-language articles. Second, studies of risk assessment methods varied by size, study populations, reference groups, and methods. Third, RCTs were limited by clinical heterogeneity related to different eligibility criteria, exposure durations and follow-up, adherence, and ascertainment of outcomes. The trials

were not designed for subgroup analysis and may have been underpowered to demonstrate treatment effects. Furthermore, no trials directly compared the effects of timing and duration of medication use. Fourth, research is lacking for optimal doses, duration of use, persistence of effects after treatment for most medications, and outcomes in women who are nonwhite, premenopausal, have comorbidities, or are taking additional medications for other indications.

Conclusions

Tamoxifen, raloxifene, and aromatase inhibitors were associated with lower risk of primary invasive breast cancer in women but also were associated with adverse effects that differed between medications. Risk stratification methods to identify patients with increased breast cancer risk demonstrated low accuracy.

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