Use of Medications to Reduce Risk for Primary Breast Cancer: A Systematic Review for the U.S. Preventive Services Task Force

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Background: Medications to reduce risk for primary breast cancer are recommended for women at increased risk; however, use is low.

Purpose: To update evidence about the effectiveness and adverse effects of medications to reduce breast cancer risk, patient use of such medications, and methods for identifying women at increased risk for breast cancer.

Data Sources: MEDLINE and Cochrane databases (through 5 December 2012), Scopus, Web of Science, clinical trial registries, and reference lists.

Study Selection: English-language randomized trials of medication effectiveness and adverse effects, observational studies of adverse effects and patient use, and diagnostic accuracy studies of risk assessment.

Data Extraction: Investigators independently extracted data on participants, study design, analysis, follow-up, and results, and a second investigator confirmed key data. Investigators independently dual-rated study quality and applicability using established criteria.

Data Synthesis: Seven good- and fair-quality trials indicated that tamoxifen and raloxifene reduced incidence of invasive breast cancer by 7 to 9 cases in 1000 women over 5 years compared with placebo. New results from STAR (Study of Tamoxifen and Raloxifene) showed that tamoxifen reduced breast cancer incidence more than raloxifene by 5 cases in 1000 women. Neither reduced breast cancer–specific or all-cause mortality rates. Both reduced the incidence of fractures, but tamoxifen increased the incidence of thromboembolic events more than raloxifene by 4 cases in 1000 women. Tamoxifen increased the incidence of endometrial cancer and cataracts compared with placebo and raloxifene. Trials provided limited and heterogeneous data on medication adherence and persistence. Many women do not take tamoxifen because of associated harms. Thirteen risk-stratification models were modest predictors of breast cancer.

Limitation: Data on mortality and adherence measures and for women who are nonwhite, are premenopausal, or have comorbid conditions were lacking.

Conclusion: Medications reduced the incidence of invasive breast cancer and fractures and increased the incidence of thromboembolic events. Tamoxifen was more effective than raloxifene but also increased the incidence of endometrial cancer and cataracts. Use is limited by adverse effects and inaccurate methods to identify candidates.

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In 2002, the U.S. Preventive Services Task Force (USPSTF) recommended that clinicians discuss the potential benefits and harms of tamoxifen and raloxifene for reducing risk for primary breast cancer with women at high risk for breast cancer and low risk for adverse effects (1, 2). The USPSTF also recommended against routine use in women at low or average risk for breast cancer.

Clinical trials demonstrate the efficacy of several medications to reduce the risk for invasive breast cancer in women without preexisting cancer (3–8), but only tamoxifen citrate and raloxifene for 5 years of use are approved by the U.S. Food and Drug Administration (FDA) for this purpose (9). Raloxifene is approved for postmenopausal women only. In addition to beneficial effects, these medications may cause adverse health effects (7, 10, 11). In 2002, the USPSTF indicated that the risk for breast cancer within 5 years could be estimated by completing the National Cancer Institute Breast Cancer Risk Assessment Tool (Gail model). How to select patients for these medications in clinical practice has not been clear, however, and use of medications to reduce risk for breast cancer is low in the United States (12).

See also:

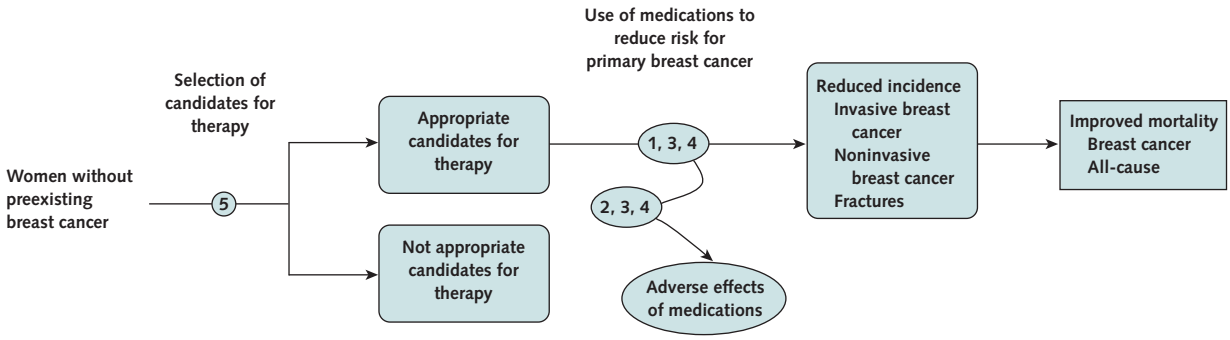
Web-Only
CME quiz

This report is an update for the USPSTF that was derived from a comprehensive comparative effectiveness review of the efficacy, adverse effects, and subgroup variations of medications to reduce risk for primary breast cancer in women (13). It also examines issues related to clinical effectiveness, such as patient choice, concordance, adherence, and persistence of use; and reviews methods to identify women at increased risk for breast cancer that are clinically applicable to determining candidacy for risk-reducing medications.

METHODS

We followed a standard protocol for this review consistent with the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program (14). Key questions were developed through the Effective Health Care Program and modified for the USPSTF. Investigators created an analytic framework incorporating the key questions and outlining the patient population, interventions, and outcomes (**Figure 1**). The target population includes

Figure 1. **Analytic framework.**



Key Questions:

1. In adult women without preexisting breast cancer, what is the comparative effectiveness of tamoxifen citrate and raloxifene when used to reduce risk for primary breast cancer on improving short- and long-term health outcomes, including invasive breast cancer; noninvasive breast cancer, including DCIS; breast cancer mortality; all-cause mortality; and osteoporotic fractures?
2. What are the harms of tamoxifen citrate and raloxifene when used to reduce risk for primary breast cancer?
3. How do outcomes vary by population subgroups?
4. How do benefits and harms affect decisions to use medications to reduce risk for primary breast cancer, concordance, adherence, and persistence?
5. What methods, such as clinical risk assessment models, have been used to identify women who could benefit from medications to reduce risk for primary breast cancer?

DCIS = ductal carcinoma in situ.

women without preexisting invasive or noninvasive breast cancer who are not known carriers of breast cancer susceptibility mutations. Interventions include FDA-approved medications to reduce risk for primary breast cancer. Health outcomes include signs, symptoms, conditions, or events as opposed to intermediate outcomes, such as laboratory test results. A technical report (15) details the methods and includes search strategies and additional evidence tables.

Data Sources

We searched MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from inception through 5 December 2012 for relevant English-language studies, systematic reviews, and meta-analyses (15). We manually reviewed reference lists of articles, citations in Web of Science and Scopus, and clinical trial registries. We requested scientific information packets from manufacturers of medications. (The only packet provided was for raloxifene.)

Study Selection

We developed selection criteria for studies based on the patient populations, interventions, outcome measures, and types of evidence. After an initial review of citations and abstracts, we 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. Results of the search and selection process are provided in the **Appendix Figure** (available at www.annals.org).

Inclusion criteria for studies of benefits, harms, and subgroup outcomes (key questions 1 through 3) have been fully described in previous publications (13, 15). For benefits, we included only double-blind, placebo-controlled or head-to-head, randomized, controlled trials (RCTs) of tamoxifen and raloxifene to reduce risk for breast cancer that enrolled women without preexisting breast cancer. We included trials that were designed and powered to demonstrate invasive breast cancer incidence as a primary or secondary outcome. For harms, we included RCTs and observational studies of tamoxifen and raloxifene in women without breast cancer that had a nonuser comparison group or direct comparisons between tamoxifen and raloxifene. We considered all adverse outcomes at all reported follow-up times to capture potential short- and long-term adverse effects.

We included RCTs, observational studies, and descriptive studies of decisions to use risk-reducing medications, concordance, adherence, and persistence of use (key question 4). Concordance occurs when a health care provider and patient reach a shared agreement about therapeutic goals after the patient is informed of the condition and options for treatment and becomes involved in the treatment decision (16). Adherence is the extent to which a patient acts in accordance with the prescribed interval and dose of a medication (17). Persistence is the duration of time from initiation to discontinuation of therapy (17).

We included studies of risk-stratification models that could be used in primary care settings to identify women at

higher-than-average risk for breast cancer (key question 5). Only studies reporting discriminatory accuracy 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, 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 (18). We also abstracted model calibration, a measure of how well predicted probabilities agree with actual observed risk in a population. In a perfect prediction model, the predicted risk in a population would equal the observed number of cases, such that the percentage expected divided by the percentage observed equals 1.0. We excluded studies of individual risk factors or laboratory tests as well as models designed primarily to evaluate risk for deleterious BRCA mutations.

Our search strategies also included systematic reviews that addressed our key questions and had similar scope, inclusion criteria, and analytic methods for meta-analysis. Other types of analyses and statistical models were not included (19).

Data Abstraction and Quality Assessment

An investigator abstracted details of the patient population, study design, analysis, follow-up, and results. A second investigator confirmed key data elements. Using predefined criteria (20), 2 investigators independently rated the quality of studies (good, fair, or poor) and resolved discrepancies by consensus. Investigators assessed applicability of trials using the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting (PICOTS) format (14).

Data Synthesis and Analysis

We updated the results of our previous meta-analysis of benefits and harms of tamoxifen and raloxifene for 2 outcomes (mortality and endometrial cancer for raloxifene) with new data using methods described in previous publications (13). As a group, investigators used methods developed by the USPSTF to assess the overall quality of the body of evidence for each key question (good, fair, or poor) on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence (20).

Role of the Funding Source

This research was funded by AHRQ. Investigators worked with AHRQ staff and a technical expert panel to define the scope, analytic framework, and key questions; resolve issues arising during the project; and review the final report to ensure that it met basic methodological standards for systematic reviews. The draft report was reviewed by content experts, USPSTF members, AHRQ program officers, and collaborative partners. The funding source had no role in the selection, critical appraisal, or synthesis of evidence. The investigators were solely responsible for the content and the decision to submit the manuscript for publication.

Results

Benefits and Harms of Tamoxifen and Raloxifene

Seven RCTs of tamoxifen or raloxifene in women without preexisting breast cancer provide breast cancer outcomes and data about mortality and fractures. These trials also provide estimates of harm, including thromboembolic events, cardiovascular disease events, uterine abnormalities, cataracts, and other adverse effects. Additional trials and an observational study describing harms of raloxifene were identified, but these studies were small, were methodologically limited, and did not contribute data to the meta-analysis.

Trials include a head-to-head comparison of tamoxifen and raloxifene, STAR (Study of Tamoxifen and Raloxifene) (21, 22); 4 placebo-controlled trials of tamoxifen, including the IBIS-I (International Breast Cancer Intervention Study) (23, 24), NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project) (8, 11, 25, 26), Royal Marsden Hospital trial (27, 28), and the Italian Tamoxifen Prevention Study (29–32); and 2 placebo-controlled trials of raloxifene, MORE (Multiple Outcomes of Raloxifene Evaluation) with long-term follow-up in the CORE (Continuing Outcomes Relevant to Evista) study (10, 33–46) and the RUTH (Raloxifene Use for the Heart) trial (7, 47). An updated analysis of STAR with an 81-month median follow-up provided most of the new findings for this review (22).

The tamoxifen trials were designed to determine breast cancer incidence as the primary outcome (8, 11, 23, 24, 27–32, 48). Inclusion criteria considered breast cancer risk in all but 1 trial (49). For raloxifene, breast cancer incidence was a primary outcome in RUTH and a secondary outcome in MORE. These trials were intended to evaluate the effect of raloxifene on reducing coronary heart disease events in RUTH (7) and preventing fractures in MORE (5, 40).

Trials varied by mean age at enrollment (47 to 50 years for the tamoxifen trials, 67 years for the raloxifene trials, and 59 years for STAR), estrogen use (23, 27, 29–32), and ascertainment of outcomes. For placebo-controlled trials of tamoxifen, median duration of treatment was approximately 4 years and follow-up was 7 to 13 years (8, 24). For raloxifene, results were reported after 3 and 4 years of treatment in the MORE trial (26–34, 36, 39), and results of CORE (a continuation study of MORE [44]) were reported for 4-year and combined 8-year outcomes (MORE and CORE) (37, 38, 40). The median duration of treatment in RUTH was 5.1 years (41). In

STAR, the mean duration of treatment was 3.8 years and median follow-up was 6.75 years (22).

All trials met criteria for fair or good quality and high applicability. The trials were multicenter, were relevant to primary care, and enrolled between 2471 (27) and 19 747 (48) women from clinics and communities predominantly in North America, Europe, and the United Kingdom.

In placebo-controlled trials, tamoxifen (risk ratio [RR], 0.70 [95% CI, 0.59 to 0.82]; 4 trials; 7 cases in 1000 women over 5 years) (8, 24, 28, 31) and raloxifene (RR, 0.44 [CI, 0.27 to 0.71]; 2 trials; 9 cases in 1000 women) (7, 44) reduced the incidence of invasive breast cancer (**Appendix Table 1**, available at www.annals.org). In STAR, more women receiving raloxifene had breast cancer than those receiving tamoxifen (RR for raloxifene, 1.24 [CI, 1.05 to 1.47]; 5 cases in 1000 women over 5 years) (22). Tamoxifen (8, 24, 28, 31) and raloxifene (7, 44) reduced estrogen receptor–positive but not estrogen receptor–negative or noninvasive cancer in placebo-controlled trials and had similar effects in STAR (21, 22, 48). Breast cancer–specific (8, 24, 28, 31, 50) and all-cause mortality rates (6–8, 24, 28, 31) were not reduced in placebo trials and were similar in STAR (22).

In placebo-controlled trials, raloxifene reduced incidence of vertebral fractures (RR, 0.61 [CI, 0.54 to 0.69]; 2 trials; 7 cases in 1000 women) (7, 37) and tamoxifen reduced incidence of nonvertebral fractures (RR, 0.66 [CI, 0.45 to 0.98]; 1 trial; 3 cases in 1000 women) (8). Tamoxifen and raloxifene had similar effects on incidence of vertebral fractures in STAR (48).

Thromboembolic event incidence was increased for tamoxifen (RR, 1.93 [CI, 1.41 to 2.64]; 4 trials; 4 cases in 1000 women) (11, 24, 28, 29) and raloxifene (RR, 1.60 [CI, 1.15 to 2.23]; 2 trials; 7 cases in 1000 women) compared with placebo (7, 10), and raloxifene caused fewer events than tamoxifen in STAR (RR, 0.75 [CI, 0.60 to 0.93]; 4 cases in 1000 women) (22). Coronary heart disease event or stroke incidence was not increased in placebo-controlled trials (7, 8, 24, 28, 31, 34) and did not differ in STAR (48), although women randomly assigned to raloxifene had a higher stroke mortality rate than that of those assigned to placebo in RUTH (RR, 1.49 [CI, 1.00 to 2.24]) (7).

Tamoxifen caused more cases of endometrial cancer (RR, 2.13 [CI, 1.36 to 3.32]; 3 trials; 4 cases in 1000 women) (11, 24, 28) and was related to more benign gynecologic conditions (24, 51); surgical procedures, including hysterectomy (24, 28, 51); and uterine bleeding (24, 51) than placebo. Raloxifene did not increase risk for endometrial cancer (7, 10, 52) or uterine bleeding (7, 35, 53–61). In STAR, raloxifene caused fewer cases of endometrial cancer (RR, 0.55 [CI, 0.36 to 0.83]; 5 cases in 1000 women), hyperplasia, and procedures than tamoxifen (22, 62). Women receiving tamoxifen had more cataract surgeries than those receiving placebo in NSABP P-1 (11). Raloxifene did not increase risk for cataracts or cataract surgery compared with placebo (7, 10) and caused fewer cataracts than tamoxifen in STAR (RR, 0.80 [CI, 0.72 to 0.95]; 15 cases in 1000 women) (22).

The most common side effects were vasomotor symptoms (11, 24, 28, 31) and vaginal discharge, itching, or dryness (11, 24, 28, 31) for tamoxifen and vasomotor symptoms (7, 35, 55, 56, 58) and leg cramps (7, 35, 58) for raloxifene. In STAR, raloxifene users reported more musculoskeletal problems, dyspareunia, and weight gain, whereas tamoxifen users had more gynecologic problems, vasomotor symptoms, leg cramps, and bladder control symptoms (62, 63).

Variability of Outcomes in Population Subgroups

In STAR, tamoxifen and raloxifene had similar effects on breast cancer outcomes regardless of age and family history of breast cancer (22). In NSABP P-1, cancer rates were highest and risk reduction greatest among women in the highest modified Gail model risk category (5-year risk >5%) and among women with previous atypical hyperplasia (8). Additional subgroup analyses of placebo-controlled trials indicated no differences for several factors (15, 43, 47). Thromboembolic events, strokes, and endometrial cancer were more common in older (>50 years) than younger women in NSABP P-1 (8). A recent meta-analysis of tamoxifen trials indicated that risks for endometrial cancer, deep venous thrombosis, and pulmonary embolism are low for women younger than 50 years (64).

Surveys of Medication Decisions and Concordance

Twelve studies described how women or physicians make decisions to use medications to reduce risk for primary breast cancer (**Appendix Table 2**, available at www.annals.org) (65–76). In an interview-based, cross-sectional study after an educational session about indications and adverse effects of tamoxifen, women indicated that breast cancer (69%), pulmonary embolism (67%), endometrial cancer (63%), and deep venous thrombosis (58%) were "very important" in making their decisions about use (69). Only 18% expressed interest in actually using tamoxifen. Another survey of eligible women indicated concerns for adverse effects, including endometrial cancer and thromboembolic events, lack of information, and reluctance to discontinue menopausal hormone therapy as reasons for not choosing tamoxifen (70). Two other studies also described concerns about adverse effects (67, 71).

In 2 similar studies, women reviewed online decision aids that provided their personal 5-year breast cancer risk and information about risk reduction with tamoxifen (73) or tamoxifen and raloxifene (74). Immediately after viewing the decision aid, 29% of women in the tamoxifen study were likely to seek more information, 30% were likely to discuss it with their physicians, 19% did not believe that tamoxifen would reduce their risk for breast cancer, and 6% were likely to take it in the next year (73). Three months after viewing the decision aid, 1% of

women had started taking tamoxifen, 6% had talked with their physicians, and 5% sought more information. Worry about side effects, belief that benefits were not worth the risks, and taking pills were cited as deterrents to use. Results were similar for the study considering both tamoxifen and raloxifene.

A study of women with elevated risk scores reported that 12% of women selected tamoxifen for breast cancer risk reduction, 77% declined, and 12% were undecided (68). Major adverse effects (61%) and small benefit from tamoxifen (32%) were the most common reasons for declining. However, 90% of women stated that they would take a medication with the same benefit as tamoxifen if it had no side effects, and one half would take a medication with the same side effects as tamoxifen if it could eliminate the chance of getting breast cancer.

In another study, 75% of women indicated that they would take a medication for an assumed 60% lifetime risk for breast cancer, although they overestimated their personal lifetime risk for breast cancer by 2- to 3-fold (75). Another survey indicated that 23% of responders interested in risk-reducing medications believed themselves to be at greater risk for breast cancer and were more worried about breast cancer than women who were not interested ($P < 0.050$) (66). A study about interest in using tamoxifen reported that more than 40% of women would be willing to take tamoxifen if they were determined to be at "high risk" (76). Asian women were more likely to take tamoxifen in this study (odds ratio, 3.0 [CI, 1.3 to 6.8]).

Of 350 physicians responding to a mailed survey, 27% had prescribed tamoxifen for breast cancer risk reduction within the previous 12 months (65). Prescribers were more likely than nonprescribers to have a family member with breast cancer (20% vs. 9%) and believed that the benefits of tamoxifen outweigh the risks (63% vs. 39%), colleagues are prescribing it (33% vs. 17%), it is easy to determine who is eligible (28% vs. 11%), and many female patients ask for information about it (15% vs. 5%). Physician prescribers and nonprescribers did not differ in their beliefs about whether the evidence for use of tamoxifen is controversial, it is too time-consuming to discuss in practice, and the risks for thromboembolic events and endometrial cancer are too great.

Three studies reported the concordance of physicians' recommendations and their patients' medication decisions (67, 71, 72). Women evaluated for benign breast findings in a breast clinic were provided with estimates of their breast cancer risks and the option of using tamoxifen for risk reduction (71). They were then asked to discuss tamoxifen use with their family physicians. For 31% of the women, the family physician's advice was an important influence in their decision (71). In another study, women whose physicians recommended enrollment in NSABP P-1 were 13 times more likely to enroll than women whose physicians recommended against enrollment ($P < 0.001$) (72). Women eligible for STAR who received recommendations for risk-reducing medications from their physicians were more likely to select treatment than those not getting recommendations (67).

Adherence and Persistence in Clinical Trials

Seven primary prevention trials of tamoxifen and raloxifene (7, 8, 10, 11, 24–43, 45–48, 63, 77, 78) and 6 additional trials of raloxifene (53, 57, 58, 79, 80) provided limited and heterogeneous data on adherence and persistence (**Appendix Table 3**, available at www.annals.org). Adherence was reported in 2 placebo-controlled trials of tamoxifen (28, 81) and 4 placebo-controlled trials of raloxifene (7, 36, 60, 79). Of trials reporting adherence, at least 70% of participants used the planned treatment dose. In NSABP P-1, 41% of participants took 100% of study medication and 79% took at least 76% of study medication at 36 months (81). Forgetting was the primary reason for nonadherence for 62% of women at 36 months. In the Royal Marsden Hospital trial, adherence was 8% lower with tamoxifen versus placebo ($P = 0.002$) (28). In RUTH, adherence was similar between groups; approximately 70% took at least 70% of the study medication (7). Adherence was not reported separately in MORE; 92% of the study population took at least 80% of the assigned study medication (36).

Persistence was measured as duration of treatment in STAR (48), 1 placebo-controlled trial of tamoxifen (31), and 3 placebo-controlled trials of raloxifene (7, 58, 79), and as completion of the planned course of treatment by 2 placebo-controlled trials of tamoxifen (24, 31) and 6 placebo-controlled trials of raloxifene (7, 57, 58, 60, 79, 80). Completion rates were similar between groups in STAR (71.5% for raloxifene vs. 68.3% for tamoxifen) (48), the Italian Tamoxifen Prevention Study (59.8% for tamoxifen vs. 61.8% for placebo) (31), IBIS-I (72% overall) (24), and RUTH (80% for raloxifene vs. 79% for placebo) (7). Additional trials of raloxifene reported 60% to 91% of participants completing the planned duration of treatment (57, 58, 60, 79, 80).

Methods to Identify Women at Increased Risk for Breast Cancer

Nineteen studies evaluating 13 risk-stratification models met inclusion criteria (**Appendix Table 4**, available at www.annals.org) (82–102). Of these, 15 met criteria for good quality (82–85, 87–90, 92–96, 99, 100). Four were rated as fair-quality because they inadequately described the population and follow-up (97), provided estimates for 1-year risks only (91), were not practical for primary care settings (86), or were based on small or narrowly defined populations (86, 98).

The Gail model, the first major breast cancer risk-stratification model to be used, was derived from multivariate logistic regression analysis of identified risk factors for breast cancer (82). In the original version of the model, breast cancer incidence rates and baseline hazard rates were determined for invasive cancer, ductal carcinoma in situ,

and lobular carcinoma in situ from a cohort of white women in the BCDDP (Breast Cancer Detection and Demonstration Project). The model was subsequently modified by using U.S. national data for invasive cancer from SEER (Surveillance, Epidemiology and End Results) (83). From these data, the model was developed to allow the prediction of individualized absolute risk (probability) of developing invasive breast cancer in women having annual screening mammography over 5 years. This version is called the Gail-2 model or the Breast Cancer Risk Assessment Tool.

Subsequent risk-stratification models use a similar approach but vary in their use of reference standards and the variables they include (**Appendix Table 5**, available at www.annals.org). 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 (82). Subsequent models include 1 or more of these variables in addition to other factors. These include race (87, 91, 92, 103), previous false-positive mammogram or benign breast disease (91, 96), body mass index or height (86, 87, 90, 91, 93, 97, 99, 100), estrogen and progestin use (86, 87, 91, 93), history of breastfeeding (87), menopause status or age (91, 93, 97), smoking (87), alcohol use (86, 87, 93), physical activity (86, 87, 100), education (100), mammographic breast density (90–92), and diet (86).

Studies of Calibration

Calibration was calculated for 7 of the 13 models (83, 85–88, 90–93, 97) (**Appendix Table 5**). For most models, the expected numbers of cases of breast cancer closely matched the observed numbers (expected–observed ratio, 0.90 to 1.10) (83, 85–88, 90–93, 97). Calibration varied in specialized populations (94, 95), for estrogen receptor–negative breast cancer (83), and when outdated breast cancer incidence rates were used in the model (104).

Studies of Discriminatory Accuracy

Most studies of risk models reported modest discriminatory accuracy estimates (c-statistic, 0.55 to 0.65) (**Appendix Table 5**) (83–92, 94–96, 98–100). Only 1 study reported levels greater than 0.70 for both the Gail-2 (c-statistic, 0.74 [CI, 0.67 to 0.80]) and the Tyrer–Cuzick models (c-statistic, 0.76 [CI, 0.70 to 0.82]) (98). However, this study had limited applicability because it enrolled high-risk women and included only 54 cases of breast cancer. The Tyrer–Cuzick results were not replicated in a subsequent study (c-statistic, 0.54 [CI, 0.42 to 0.65]) (99). Overall, models that included breast density had the highest accuracy (c-statistic, 0.63 to 0.66) (90–92).

Studies of Risk Thresholds

Some of the medication trials used individual risk scores for breast cancer as inclusion criteria (8, 11, 48). Three studies evaluated this approach to risk stratification by determining calibration or discriminatory accuracy based on risk quintiles (85, 87, 92), and 1 study determined these estimates based on a low (<1.67%) versus high (≥1.67%) 5-year risk threshold using the Gail model (92). The 1.67% threshold was used as inclusion criteria for NSABP P-1 and STAR, and is included in the FDA indication for the use of tamoxifen and raloxifene for risk reduction.

The BCSC (Breast Cancer Surveillance Consortium)–Tice model demonstrated high calibration (expected–observed ratio, 0.99 to 1.03) but modest discriminatory accuracy across risk quintiles (c-statistic, 0.61 to 0.64) (92). The Gail model showed high calibration in the higher risk quintiles despite a tendency to overpredict the number of invasive breast cancer cases, but inferior calibration in the lower quintiles with a tendency to underpredict (85, 87).

Discussion

The **Table** summarizes the evidence for all key questions in our review. Placebo-controlled primary prevention trials indicate that tamoxifen and raloxifene reduce the incidence of invasive breast cancer by 7 to 9 cases per 1000 women over a 5-year treatment period primarily by reducing estrogen receptor–positive breast cancer. New results from STAR show that tamoxifen has a greater effect than raloxifene by reducing invasive breast cancer by 5 fewer cases per 1000 women. Noninvasive breast cancer incidence and breast cancer–specific and all-cause mortality rates were not statistically significantly reduced by either medication, although trials were not powered for mortality. Both medications reduced fractures.

Although trials indicated that women at all levels of breast cancer risk had a reduction in breast cancer incidence with tamoxifen, those at highest risk (based on risk scores or preexisting atypical hyperplasia) derived the most benefit (8). Benefits for higher-risk women were also demonstrated in a recent observational study of 2459 women with atypical breast lesions (atypical ductal and lobular hyperplasia; lobular carcinoma in situ) in a large health system (105). Women who received tamoxifen, raloxifene, or exemestane had a 10-year breast cancer risk of 7.5% compared with women without treatment, who had a risk of 21.3% ($P < 0.001$). Risk was reduced for all types of atypia.

Beneficial effects of risk-reducing medications are countered by more thromboembolic events for both medications, with tamoxifen causing 4 more events per 1000 women than raloxifene in STAR. Tamoxifen also increases incidence of endometrial cancer and related gynecologic outcomes and cataracts compared with placebo and raloxifene. Many women have less serious adverse effects that

Table. **Summary of Evidence**

Studies	Design	Limitations	Consistency	Applicability	Overall Quality
Key question 1: Benefits of tamoxifen and raloxifene when used to reduce risk for primary breast cancer					
4 placebo-controlled trials of tamoxifen and 2 of raloxifene; 1 head-to-head trial	RCT	Trials are heterogeneous and lacked data on doses, duration, and timing of use	Consistent	High	Good
Findings: Tamoxifen and raloxifene reduced invasive breast cancer incidence by 30%–68% compared with placebo; tamoxifen had a greater effect than raloxifene in STAR. Noninvasive breast cancer incidence and mortality were not significantly reduced and did not differ between medications. Both reduced fracture incidence.					
Key question 2: Harms of tamoxifen and raloxifene when used to reduce risk for primary breast cancer					
4 placebo-controlled trials of tamoxifen; 14 trials and 1 study of raloxifene; 1 head-to-head trial	RCT and cohort	Trials are heterogeneous and lacked data on long-term effects	Consistent	High	Fair to good
Findings: Tamoxifen and raloxifene increased incidence of thromboembolic events compared with placebo; tamoxifen had a greater effect than raloxifene in STAR. Tamoxifen increased endometrial cancer incidence compared with placebo and raloxifene and increased incidence of cataracts compared with raloxifene. Both caused undesirable side effects for some women.					
Key question 3: Variability of outcomes in population subgroups					
4 placebo-controlled trials of tamoxifen and 2 of raloxifene; 1 head-to-head trial	RCT	Trials lacked data for women who are nonwhite, are premenopausal, or have comorbid conditions	Consistent	High	Fair
Findings: Risk reduction was greatest among women with >5% 5-y Gail model risk score or atypical hyperplasia for tamoxifen compared with placebo and raloxifene. Thromboembolic events and endometrial cancer were more common in women >50 y than younger women using tamoxifen.					
Key question 4: Medication decisions and concordance, adherence, and persistence					
Decisions: 11 studies; Adherence and persistence: 4 placebo trials of tamoxifen and 2 of raloxifene; 1 head-to-head trial	RCT and survey	Few decision studies included raloxifene; data on adherence and persistence were lacking	Could not determine	Unclear; data about decisions were descriptive and from small samples	Fair
Findings: Many women elect not to take tamoxifen because of harms. Trials provided limited data about adherence and persistence. Discontinuation rates for tamoxifen and raloxifene were generally slightly higher than placebo.					
Key question 5: Methods to identify women at increased risk for breast cancer					
19 studies of 13 models	Diagnostic accuracy	Studies varied by populations and risk parameters	Consistent	High	Good
Findings: Models have modest discriminatory accuracy in predicting the probability of breast cancer in a person (c-statistics between 0.55 and 0.65).					

RCT = randomized, controlled trial; STAR = Study of Tamoxifen and Raloxifene.

impact quality of life and adherence, such as vasomotor, genital, and musculoskeletal symptoms. In trials, older women had more adverse effects for some outcomes, such as endometrial cancer and thromboembolic events, than women younger than 50 years.

Small descriptive studies indicate that women make decisions to use tamoxifen to reduce breast cancer risk based on their concern for adverse effects as well as their risk for breast cancer. Many women overestimate their risk for breast cancer but weigh their physicians' recommendations highly when deciding whether to take tamoxifen. Similar data for raloxifene are lacking, and no studies about how women choose among several risk-reducing medications have been published. Comparisons of adherence and persistence rates across medications in trials are limited because not all trials reported them, measures varied, and trials were designed for different treatment purposes. From the few trials reporting data about discontinuation, rates for tamoxifen or raloxifene were generally higher than placebo, but differences were low (≤2% for adverse events and ≤4% for nonprotocol specified events).

Research on risk assessment relevant to identifying candidates for risk-reducing medications includes 13 risk-stratification models for use in clinical settings. Models considered several risk factors for breast cancer and predicted 1-year to lifetime risk estimates. Most risk models demonstrated high calibration but low to modest discriminatory accuracy in predicting the probability of breast cancer in a person. Most models performed only slightly better than age alone as a risk predictor (91, 94). Models that included breast density improved the predictive risk modestly (91), although breast density may be imprecise and unavailable in many clinical practices. Research evaluating the Gail model score that has been used as a risk threshold in trials and for the FDA indication for use (5-year risk ≥1.67%) found that it has low discriminatory accuracy in predicting the probability of breast cancer in a person. Most women aged 60 years or older without other risk factors would meet this threshold by age alone.

This review is limited by potential publication bias and biases of our literature review process, such as using only English-language reports. Trials of medications varied in their inclusion criteria, surveillance, and ascertainment of outcomes. Active surveillance ended with completion of therapy in most trials, and important long-term outcomes may have been underreported, particularly mortality. Con-

tinued follow-up of women enrolled in existing trials would provide needed data on long-term outcomes. Risks for some adverse outcomes and population subgroups were underestimated because of lack of statistical power. Data are lacking for nonwhite, premenopausal, or elderly women who have comorbid conditions or are taking additional medications for other indications. Studies of patient choice and use of medications are small, are descriptive, and may not apply to other populations. Measures of adherence and persistence in clinical trials may not be similar for patients in clinical practices.

Evidence gaps include determination of optimal doses, duration, and timing of use; persistence of effects after treatment; and outcomes in population subgroups. The ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial recently reported reduced recurrence of estrogen receptor–positive breast cancer and reduced breast cancer–specific and all-cause mortality rates in women with breast cancer after 10 versus 5 years of adjuvant therapy (106). Whether a longer course provides a more favorable benefit–harm tradeoff for risk reduction in women without breast cancer has yet to be determined.

Trials of other medications have also demonstrated reduction in breast cancer risk, including tibolone (5), lasofoxifene (3), and exemestane (4). Although they have not been FDA-approved for this purpose, they may expand clinical options. In the NCIC CTG MAP.3 (National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3) trial, exemestane reduced invasive breast cancer incidence by 65% after 3 years of therapy in postmenopausal women with increased risk for breast cancer, as determined by a Gail risk score greater than 1.66% or high-risk breast lesions (4). Hot flashes and arthritis were more common among women taking exemestane, but other adverse effects were not different from placebo.

Despite previous recommendations to identify women at increased risk for breast cancer and offer risk-reducing medications (2), use is low in the United States (65). It is not clear how to identify candidates for therapy. Although the trials indicate broad benefit, subgroup analysis and decision models (19) suggest that high-risk women, particularly those who had hysterectomies, may derive the most benefit with the least harms. Future research on clinical selection criteria reporting likelihood ratios of treatment thresholds would improve identification of candidates in practice settings and provide guidance for the appropriate use of risk-reducing medications.

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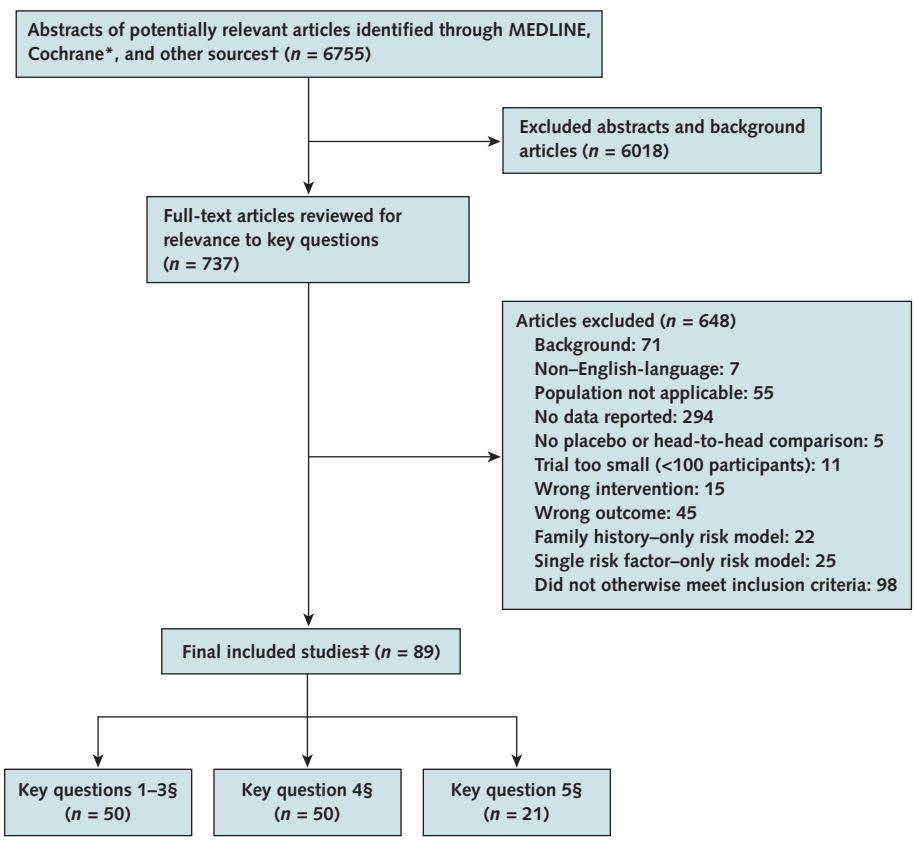
Appendix Figure. **Summary of evidence search and selection.**



* Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.
† Identified from reference lists, hand searching, and suggestions by experts.
‡ Studies that provided data and contributed to the body of evidence were considered "included."
§ Some studies are included in more than 1 key question.

Appendix Table 1. Results of Primary Prevention Trials

Outcome	Raloxifene vs. Tamoxifen		Tamoxifen vs. Placebo				Raloxifene vs. Placebo			
	RR (95% CI)	Events Reduced or Increased (95% CI), *n**	RR (95% CI)	Trials, *n*†	Placebo Rate (±SE)‡	Events Reduced or Increased (95% CI), *n**	RR (95% CI)	Trials, *n*†	Placebo Rate (±SE)‡	Events Reduced or Increased (95% CI), *n**
Benefits										
Invasive breast cancer	1.24 (1.05–1.47)§	5 (1–9) fewer with tamoxifen	0.70 (0.59–0.82)	4	4.70 ± 1.02	7 (4–12) fewer with tamoxifen	0.44 (0.27–0.71)	2	3.19 ± 0.59	9 (4–14) fewer with raloxifene
ER+ breast cancer	0.93 (0.72–1.24)‖	–	0.58 (0.42–0.79)	4	3.67 ± 0.78	8 (3–13) fewer with tamoxifen	0.33 (0.18–0.61)	2	2.45 ± 0.42	8 (4–12) fewer with raloxifene
ER− breast cancer	1.15 (0.75–1.77)‖	–	1.19 (0.92–1.55)	4	–	–	1.25 (0.67–2.31)	2	–	–
Noninvasive breast cancer	1.22 (0.95–1.59)§	–	0.85 (0.54–1.35)¶	4	–	–	1.47 (0.75–2.91)	2	–	–
Breast cancer mortality	0.36 (0.08–1.21)§	–	1.07 (0.66–1.74)	4	–	–	NR**		–	–
All-cause mortality	0.84 (0.70–1.02)§	–	1.07 (0.90–1.27)	4	–	–	0.84 (0.64–1.10)††	2	–	–
Vertebral fracture	0.98 (0.65–1.46)‖	–	0.75 (0.48–1.15)‡‡		–	–	0.61 (0.54–0.69)	2	3.45 ± 0.35§§	7 (5–9) fewer with raloxifene
Nonvertebral fracture	NR	–	0.66 (0.45–0.98)‡‡		1.55 ± 0.20	3 (0.2–5) fewer with tamoxifen	0.97 (0.87–1.09)	2	–	–
Harms										
Thromboembolic events‖‖	0.75 (0.60–0.93)§	4 (1–7) more with tamoxifen	1.93 (1.41–2.64)	4	0.91 ± 0.19	4 (2–9) more with tamoxifen	1.60 (1.15–2.23)	2	2.34 ± 0.25	7 (2–15) more with raloxifene
DVT	0.72 (0.54–0.95)§	3 (1–5) more with tamoxifen	1.45 (0.89–2.37)	2	–	–	1.91 (0.87–4.23)	2	–	–
PE	0.80 (0.57–1.11)§	–	2.69 (1.12–6.47)	2	0.19 ± 0.07	2 (0.1–6) more with tamoxifen	2.19 (0.97–4.97)	2	–	–
CHD events	1.10 (0.85–1.43)‖	–	1.00 (0.79–1.27)	4	–	–	0.95 (0.84–1.06)	2	–	–
Stroke	0.96 (0.64–1.43)‖	–	1.36 (0.89–2.08)	4	–	–	0.96 (0.67–1.38)	2	–	–
Endometrial cancer	0.55 (0.36–0.83)§	5 (2–9) more with tamoxifen	2.13 (1.36–3.32)	3	0.75 ± 0.15	4 (1–10) more with tamoxifen	1.11 (0.65–1.89)††	3	–	–
Cataracts	0.80 (0.72–0.95)§	15 (8–22) more with tamoxifen	1.25 (0.93–1.67)¶¶	3	–	–	0.93 (0.84–1.04)	2	–	–

CHD = coronary heart disease; DVT = deep venous thrombosis; ER− = estrogen receptor–negative; ER+ = estrogen receptor–positive; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; PE = pulmonary embolism; RR = risk ratio; RUTH = Raloxifene Use for the Heart; STAR = Study of Tamoxifen and Raloxifene.

* Numbers of events reduced for benefits or increased for harms compared with placebo or other comparator per 1000 women, assuming 5 y of use.

† If meta-analysis.

‡ Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.

§ Updated results from STAR (22).

‖ Initial results from STAR (48).

¶ Significantly reduced in NSABP P-1 (60 vs. 93 events; RR, 0.63 [CI, 0.45–0.89]) (8).

** 2 breast cancer deaths in 7601 women for raloxifene vs. 0 in 7633 women for placebo (Grady et al, 2010 [50]).

†† Updated meta-analysis.

‡‡ NSABP P-1 (8).

§§ Estimated from the placebo group of the RUTH trial (7).

‖‖ Includes DVT and PE.

¶¶ Significantly increased in NSABP P-1 (574 vs. 507 events; RR, 1.14 [CI, 1.01–1.29]) (11).

Appendix Table 2. **Descriptive Studies of Decisions to Use Risk-Reducing Medications**

Author, Year (Reference)	Method	Population	Response Rate	Enrolled, *n*	Decision to Use Medication		
					Accepted	Declined	Undecided
Armstrong et al, 2006 (65)	Mailed survey to physicians about rates and reasons for prescribing tamoxifen	Primary care physicians, including family medicine, obstetrics and gynecology, and general internal medicine	47%	350	96 (27%) prescribed with tamoxifen within previous 12 mo	NA	NA
Bastian et al, 2001 (66)	Telephone survey about interest in using medications for breast cancer risk reduction	Women aged 40–55 y enrolled in a Blue Cross/Blue Shield Personal Care Plan; 8% had Gail score ≥1.66%	59% (1287/2165)*	1287	NR	NR	NR
Bober et al, 2004 (67)	In-person survey with telephone follow-up of decision making about using medications at 2 and 4 mo follow-up times	Women aged ≥35 y with a 5-y risk for breast cancer ≥1.7%; mean age, 52 y	82% (129/158)	129	37 (29%) prescribed with tamoxifen; 35 (27%) STAR enrollment†	31 (24%)†	26 (20%)†
Fagerlin et al, 2010 (73)	Online survey with decision aid about interest in using tamoxifen for breast cancer risk reduction	Women with increased risk for breast cancer; Gail 5-y risk, ≥1.66%; mean Gail score, 2.56% (range, 1.7%–17.3%); mean age, 59 y (range, 40–74 y)	8896 invited; 1218 accessed Web site; 749 eligible; 663 consented; 632 completed posttest	632	3 (0.9%)‡	NR	NR
Fagerlin et al, 2011 (74)	Online survey with decision aid about interest in using tamoxifen or raloxifene for breast cancer risk reduction	Women with increased risk for breast cancer, Gail 5-y risk, ≥1.66%; mean Gail score, 2.67% (range, 1.7%–19.1%); mean age, 62 y (range, 46–74 y)	14 048 invited; 2340 accessed Web site; 1299 eligible; 1197 consented; 1039 completed posttest; 712 completed 3-mo survey; 382 used decision aid	712	2/382 (0.5%) prescribed with raloxifene; 0 prescribed with tamoxifen§	209/382 (54.7%)	171/382 (44.8%)
Kaplan et al, 2012 (76)	In-person brief description of tamoxifen and interview about risk knowledge and interest in using tamoxifen for breast cancer risk reduction	Women from 4 racial or ethnic groups identified in primary care clinics; mean age, 59 y (range, 50–80 y)	88%	417	Likely to take tamoxifen if at high risk for breast cancer: white, 24.5%; black, 28.3%; Hispanic, 28.2%; Asian, 57.1%	NA	NA
McKay et al, 2005 (68)	Mailed survey with decision guide about using tamoxifen for breast cancer risk reduction	Women with increased risk for breast cancer; mean Gail score, 3.7% (range, 1.7%–9.4%); mean age, 52 y	77% (30/39)§	51§	6 (11.8%)	38 (74.5%)	6 (11.8%)
Melnikow et al, 2005 (69)	Cross-sectional, mixed-methods interviews of attitudes and preferences for using tamoxifen for breast cancer risk reduction	Women at high risk for breast cancer; 32% aged 39–64 y, 44% aged 65–74 y, 25% aged ≥75 y	75% (255/341)	255	45 (17.6%)	206 (80.8%)	NR
Ozanne et al, 2010 (75)	Written questionnaire and in-person and phone interviews of interest in screening and prevention, including using medication for breast cancer risk reduction	Women at high risk for breast cancer at first visit to a cancer risk and prevention clinic; mean age, 40 y (range, 21–67 y)	83% (181/217) agreed to participate; 67% (146/217) completed all components	146	75% accepted medication for an assumed 65% lifetime risk	NA	NA

Continued on following page

Appendix Table 2—**Continued**

Author, Year (Reference)	Method	Population	Response Rate	Enrolled, *n*	Decision to Use Medication		
					Accepted	Declined	Undecided
Port et al, 2001 (70)	Education session with surveys before and after of patient interest and acceptance of using tamoxifen for breast cancer risk reduction	Women with increased risk for breast cancer; mean age, 52.8 y (range, 39–74 y)	NR	43	2 (4.7%)	15 (34.9%)	26 (60.5%)
Taylor and Taguchi, 2005 (71)	Telephone survey of interest in using tamoxifen for breast cancer risk reduction	Women with a Gail score >1.6%; age, 35–80 y	99% (88/89)	89	1/48 (2%) women who discussed with physician	47/48 (98%) women who discussed with physician	NA
Yeomans Kinney et al, 1998 (72)	In-person survey of the effect of a physician's recommendation to enroll in the NSABP P-1 trial	Women eligible for NSABP P-1 trial; mean age, 55 y; mean Gail score, 14.8%	75% (360/479) completed surveys; 23% (81/360) discussed tamoxifen with their physicians; 97% (175/181) reported their physicians' recommendations	360	89/175 (51%) enrolled	86/175 (49%) did not enroll	NA

NA = not applicable; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; STAR = Study of Tamoxifen and Raloxifene.
* After excluding ineligible women, completion rate was 76% and decline rate was 20%.
† 2-mo follow-up data.
‡ Medication decision at 3-mo follow-up. The denominator for the proportion was not provided in the publication.
§ 51 women were identified for participation and 39 agreed to participate. The 21 women who declined were included in the analysis as declining tamoxifen.

Appendix Table 3. Adherence and Persistence to Medications in Trials of Tamoxifen and Raloxifene

Outcomes	Raloxifene vs. Tamoxifen		Tamoxifen vs. Placebo							
	STAR (48)		NSABP P-1 (11)*		IBIS-I (24)		Royal Marsden (28)		Italian trial (31)	
Adherence	NR	NR	41% full†; 79% adequate		NR	NR	8% less than placebo (P = 0.002)		NR	NR
Duration of treatment	46.8 mo	43.5 mo	NR	NR	NR	NR	NR	NR	47.4 mo	48.9 mo
Completion of treatment	71.5%	68.3%	NR	NR	63.9% (2287/3579) for 5 y	71.9% (2574/3579) for 5 y	NR	NR	59.8% (1615/2700) for 5 y	61.8% (1674/2708) for 5 y
Discontinuation due to protocol specified event (major events)	NR	NR	NR	NR	NR	NR	NR	NR	7.6% (206/2700)	6.9% (188/2708)
Discontinuation due to non–protocol-specified event	NR	NR	23.7%	19.7%	NR	NR	NR	NR	26.7% (721/2700)	25.3% (686/2708)
Discontinuation due to adverse event	NR	NR	NR	NR	NR	NR	NR	NR‡	NR	NR

IBIS = International Breast Cancer Intervention Study; MORE = Multiple Outcomes of Raloxifene Evaluation; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; RUTH = Raloxifene Use for the Heart; STAR = Study of Tamoxifen and Raloxifene.

* Adherence was reported in Land et al (81) and discontinuation in Fisher et al (11).

† Adherence at 36 mo was defined as full adherence (taking 100% of medication) and adequate adherence (at least 76% of medication).

‡ An earlier report of the Royal Marsden Hospital trial before enrollment was completed stated that the most frequent side effects leading to discontinuation were hot flashes and gynecologic problems (Powles et al [27]).

§ Includes a treatment group using conjugated equine estrogen.

‖ 3-y study period.

¶ Reported completion of "study" rather than "treatment."

** Includes data relating to lasofoxifene.

†† 1-y study period.

‡‡ 2-y study period.

Appendix Table 3—Continued

Raloxifene vs. Placebo

RUTH (17)		MORE (36)		Cohen et al (53)		Goldstein et al (79)		Lufkin et al (57)		McClung et al (58)		Meunier et al (80)		Palacios et al (60)	
70% vs. 71% ($P = 0.62$)		92%		NR	NR	86% to 90%§		NR	NR	NR	NR	NR	NR	91.6%	87.4%
Median exposure, 5.05 y		NR	NR	NR	NR	Mean duration, 2.3 y‖		NR	NR	702 to 706 d**		NR	NR	NR	NR
80% vs. 79% ($P = 0.02$)¶		NR	NR	NR	NR	60%§		91% (130/143)††		67%**		84.5% (109/129)‡‡		89.2%	87.4%
NR	NR	NR	NR	NR	NR	NR	NR	0.7% (1/143)		NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	1.4% (2/143)		NR	NR	NR	NR	NR	NR
22% vs. 20% ($P = 0.01$)		0.6% (33/5129) hot flashes	0.1% (2/2576) hot flashes ($P < 0.001$)	13.9%		17.6%§		5.6% (8/143)		13.5% (22/163)	14.5% (12/83)	8% (7/87)	10% (4/40)	Nonsignificant differences between groups	

Appendix Table 4. **Studies of Risk-Stratification Models**

Author, Year (Reference)	Model	Population	Participants	Study Design	Comparison Group	Inclusion Criteria	Quality Rating
Adams-Campbell et al, 2007 (89)	Gail African American (invasive breast cancer)	BWHS; black women; aged ≥35 y from 1995–2003	725 case participants; 725 age-matched control participants	Validation; nested case–control; 8 y follow-up	SEER	Incident invasive breast cancer; must have complete data available	Good
Amir et al, 2003 (98)	Tyrer–Cuzick (10-y risk for invasive breast cancer)	Family history clinic at University Hospital of South Manchester, high-risk population; total population aged 21–73 y (median, 44 y); screened population age, 25–73 y (median, 46 y); from 1987–2001	64 case participants among 3150 women; subanalysis on screening population; 52 case participants among 1933-woman cohort	Women whose risk estimate could be derived by all the models were compared and only incident cases included	UK Northwest cancer registry	Complete risk data for all models being compared (Gail, Claus, Ford, Tyrer–Cuzick); excluded incomplete data	Fair*
Barlow et al, 2006 (91)	BCSC Barlow model (1-y risk for DCIS or invasive breast cancer)	BCSC; women without breast cancer; aged 35–84 y from 1996–2001	11 638 case participants from 2 392 998-woman cohort	Case participants within cohort of women being screened with mammography; 1 y follow-up	BCSC (compared with SEER)	DCIS or invasive breast cancer in women aged 35–84 y who had previous mammography within the last 5 y; no previous breast cancer, no breast augmentation; no previous mammography but detected breast cancer within 1 y of first mammography; if no data on menopause, excluded from subgroup analysis	Fair†
Boughey et al, 2010 (99)	Tyrer–Cuzick (10-y risk for invasive breast cancer)	Mayo benign breast disease cohort including women with benign breast biopsy results; 1967–1991: mean age, 58.1 y; 1967–2009: median follow-up, 14.6 y (86.7% >5 y)	331 case participants with atypical hyperplasia in 9376-woman cohort with benign breast disease	Validation; nested case–control	NR	Women aged 18–85 y with diagnosis of atypical hyperplasia at time of biopsy	Good
Boyle et al, 2004 (86)	Italian-1 (all breast cancer)	Derivation: Italian multicenter case–control study of diet and breast cancer, 1991–1994; age of case participants, 23–74 y (mean, 55 y); control participants, 20–74 y (mean, 56 y). Validation: Italian Tamoxifen Prevention Study, 1992–1997; age of case participants, 35–70 y (median age, 51 y)	Derivation: 2569 case participants with 2588 control participants Validation: 2700 participants taking tamoxifen, 2708 participants taking placebo	Derivation: case–control Validation: case participants in cohort	Regional Cancer Registry Data	Women admitted with breast cancer diagnosed within 1 y of the study interview with no previous history of cancer; no admissions for gynecologic, neoplastic, hormonal diseases or those related to increased risk for breast cancer in control participants	Fair‡
Chen et al, 2006 (90)	Gail plus breast density (invasive breast cancer)	BCDDP; primarily white women aged >40 y; invasive or noninvasive cancer vs. control; data collected 1973–1979	2852 case participants (1235 with mammography density); 3146 age-matched control participants (1656 with mammography density)	Case–control; follow-up through 1998	SEER	Case participants with missing data excluded	Good
Chlebowski et al, 2007 (87)	Expanded and simplified models vs. Gail-2; (ER+ vs. ER− invasive breast cancer)	WHI; aged 50–79 y (mean, 63 y)	3236 case participants; 363 excluded due to missing data; 2873 for subgroup analysis; 2412 ER+ case participants; 461 ER− case participants; 144 680 control participants	Derivation and validation; case–control; 5 y follow-up	SEER	Unlikely to move or die within 3 y; no history of breast cancer or mastectomy	Good

Continued on following page

Appendix Table 4—**Continued**

Author, Year (Reference)	Model	Population	Participants	Study Design	Comparison Group	Inclusion Criteria	Quality Rating
Colditz and Rosner, 2000 (93)	Rosner–Colditz, Model 2 (invasive breast cancer)	NHS; aged 35–70 y; 1980–1994	1761 case participants among 58 520 women	Derivation; case participants within cohort of NHS; 14 y follow-up	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 (95)	Rosner–Colditz, Model 2 (invasive breast cancer)	NHS; aged 35–79 y; 1980–2000	2096 case participants (1281 ER+/PR+, 417 ER−/PR−, 318 ER+/PR−, 80 ER−/PR+) among 66 145 women	Validation; case participants within cohort of NHS	NR	Invasive breast cancer with reported estrogen receptor status	Good
Costantino et al, 1999 (83)	Gail (invasive breast cancer)	BCPT; white women between 1992–1998	5969 women in placebo group of BCPT; 204 incident cases	Validation study of Gail-1 and -2 comparing BCDDP, CASH, NHS, BCPT cohorts; follow-up 1–70 mo (average 48.4)	BCDDP rates for invasive or noninvasive cancer (Gail-1); SEER data for invasive cancer (Gail-2)	10-y life expectancy, no history of breast cancer, negative mammogram within 180 d, negative clinical breast examination, no history of DCIS or LCIS	Good
Decarli et al, 2006 (85)	Italian–Gail Model§ (all breast cancer)	Derivation: Italian multicenter case–control study of diet and breast cancer; Florence European Prospective Investigation into Cancer and Nutrition; 1991–1994; age of case participants, 23–74 y (mean, 55 y); control participants, 20–74 y (mean, 56 y). Validation: age 35–64 y	Derivation: 2569 case participants with 2588 control participants Validation: 194 case participants in 10 031-woman cohort	Derivation: case–control Validation: case participants in cohort	Florence Cancer Registry	Women admitted with breast cancer diagnosed within 1 y of the study interview with no previous history of cancer. No admissions for gynecologic, neoplastic, hormonal diseases or those related to increased risk for breast cancer in control participants	Good
Gail et al, 1989 (82)	Gail (invasive breast cancer and LCIS)	BCDDP; white women aged 35–79 y with invasive and noninvasive cancer between 1973–1979	2582 case participants, 3146 control participants	Derivation; case–control; abstracted risk factor information from 80% of eligible case participants and 83% of eligible control participants; follow-up through 1998	243 221 white women in BCDDP registry	10-y life expectancy, no history of breast cancer, negative mammography within 180 d, negative clinical breast examination, no history of DCIS	Good
Gail et al, 2007 (88)	Gail African American (invasive breast cancer)	CARE: black women; aged 35–64 y; 1994–1998 and 1993–1998	1607 case participants; 1647 control participants; women matched for 5-y age group, location, and race; 14 059 from WHI	Derivation: CARE Validation: WHI case–control; WHI follow-up, 7.57 y	SEER	First primary incident invasive breast cancer in black women age 35–64 y; must have complete data available	Good

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Appendix Table 4—**Continued**

Author, Year (Reference)	Model	Population	Participants	Study Design	Comparison Group	Inclusion Criteria	Quality Rating
Petracci et al, 2011 (100)	Italian-2 (invasive breast cancer)	Florence registry of the EPIC study Derivation: age 23–74 y; 1991–1994 Validation: age 35–64 y; 1998–2004	Derivation: 2569 case participants, 2588 control participants Validation: 10 083 participants	Derivation: case–control Validation: cohort	Florence EPIC cohort	Women aged 23–74 y with invasive breast cancer served as case participants; women aged 20–74 y without breast cancer and admitted for acute conditions to hospitals in the same catchment areas as the case patients served as control participants	Good
Rockhill et al, 2001 (84)	Gail (5-yr risk for invasive breast cancer)	NHS; white women aged 45–71 y in 1992; study duration, 1992–1997	1354 case participants in 82 109-woman cohort	Validation; prospective cohort; follow-up 60 mo	SEER	White women with complete risk factor data	Good
Rockhill et al, 2003 (94)	Rosner–Colditz, Model (invasive breast cancer)	NHS; aged 45–73 y; 1992–1997	757 case participants among 45 210 women	Validation; case participants within cohort of NHS	NR	Invasive breast cancer; no previous cancer, natural menopause or hysterectomy without oophorectomy, complete data	Good
Tamimi et al, 2010 (96)	Rosner–Colditz, adapted to include category of benign breast disease (invasive breast cancer)	NHS; aged 35–79 y; 1980–2000	240 case participants; 1036 control participants	Nested case–control within cohort of NHS; derivation	NR	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 (92)	BCSC–Tice (invasive breast cancer)	BCSC; women without breast cancer aged 35–84 y; 71% white	1 095 484 women in cohort, 14 766 cases of invasive breast cancer; 629 229 for clinical risk factor analysis; 14 766 case participants	Case participants within cohort of women being screened with mammography; median follow-up, 5.3 y	SEER (BCSC vs. SEER, state tumor registries, and path databases)	Women aged ≥35 y with 1 previous mammography with BI-RADS measurement in BCSC; excluded women with diagnosis of breast cancer, women diagnosed within 6 mo of index mammography, and women with breast implants	Good
Tyrer et al, 2004 (97)	Tyrer–Cuzick (invasive breast cancer)	UK national statistics of breast cancer incidence rates in general population; BRCA risk tables from UK	NR	Derivation; data from other sources	UK rates of breast cancer and positive BRCA	NR	Fair‖

BCDDP = Breast Cancer Detection and Demonstration Project; BCPT = Breast Cancer Prevention Trial; BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging-Reporting Data System; BWHS = Black Women's Health Study; CARE = Women's Contraceptive and Reproductive Experiences; CASH = Cancer and Steroid Hormone Study; DCIS = ductal carcinoma in situ; EPIC = European Prospective Investigation into Cancer and Nutrition; ER− = estrogen receptor–negative; ER+ = estrogen receptor–positive; LCIS = lobular carcinoma in situ; NHS = Nurses' Health Study; NR = not reported; PR– = progesterone receptor–negative; PR+ = progesterone receptor–positive; SEER = Surveillance, Epidemiology and End Results; UK = United Kingdom; WHI = Women's Health Initiative.

* Small sample size from a non–primary care setting.

† Short follow-up (1 y).

‡ Not practical for primary care settings, small sample size.

§ Italian–Gail Model: 1 calibration varies from Gail by 1 ordinal value for 1 variable; another varies by using categorical rather than ordinal variables.

‖ Developed using secondary data sources with inadequate description of the population and duration of follow-up.

Appendix Table 5. **Risk-Stratification Models**

Model	Included Variables						Calibration Expected–Observed Cases Ratio (95% CI)* [Reference]	Discriminatory Accuracy c-Statistic (95% CI)* [Reference]
	Age, *y*	Age at Menarche, *y*	Age at Birth of First Child, *y*	First-Degree Relatives With Breast Cancer, *n*	Previous Breast Biopsy, *n*	Other Factors		
Gail model variations								
Gail-2 (5-y risk)	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Biopsy: 0; 1; ≥2; AH: 0; ≥1	Not included	1.03 (0.88–1.21) [83]; 0.94 (0.89–0.99) [84]; 0.96 (0.84–1.17) [85]; 0.79 [87]; 1.12 [86]	0.55 (0.51–0.60) [89]; 0.60 [83]; 0.58 (0.56–0.60) [84]; 0.58 [86]; 0.59 (0.54–0.63) [85]; 0.60 [90]; 0.61 (0.60–0.62) [92]
Gail-2 (10-y risk)	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Biopsy: 0; 1; ≥2; AH: 0; ≥1	Not included	0.69 (0.54–0.90) [94]	0.74 (0.67–0.80) [98]
African American Gail (5-y risk)	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	Biopsy: 0; 1; ≥2	African American race	1.08 (0.97–1.20) [103]	0.56 (0.54–0.58) [103]; 0.56 (0.51–0.60) [89]
Models with breast density								
Chen (5-y risk)	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Biopsy: 0; 1; ≥2	Breast density (%), BMI	NR	0.64 [90]
BCSC† (premenopausal; 1-y risk)	45–84, by 5-y groups	Not included	Not included	0; 1; ≥2; unknown	Biopsy: yes; no; unknown	Breast density (BI-RADS)‡	1.00 [91]	0.63 (0.60–0.66) [91]
BCSC† (postmenopausal; 1-y risk)	45–84, by 5-y groups	Not included	<30; ≥30; none; unknown	0; 1; ≥2; unknown	Biopsy: 0; ≥1; unknown	Breast density (BI-RADS), previous false-positive mammogram, BMI, menopause type, HT, race or ethnicity	1.01 [91]	0.62 (0.62–0.63) [91]
BCSC (5-y risk)	45–84, by 5-y groups	Not included	Not included	Yes; no	Biopsy: yes; no	Breast density (BI-RADS), race or ethnicity	1.01 (0.99–1.03) [92]	0.66 (0.65–0.66) [92]
Other models								
Rosner–Colditz†	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	Yes; no	Not included	BMI, benign breast disease, menopause type, menopause age, HT use and duration, height, alcohol use, parity	1.00 (0.93–1.07) [94]	0.57 (0.55–0.59) [94]; 0.64 (0.63–0.66) (ER+/PR+) [95]; 0.61 (0.58–0.64) (ER−/PR−) [95]
Rosner–Colditz-2†	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	Yes; no	AH: 0; ≥1	Benign breast disease presence or type	1.01 (0.94–1.09) [94]	0.63 (0.61–0.65) [94]; 0.64 (type) [94]
Tyrer–Cuzick (10-y risk)	<50; ≥50	≤12; >12	≤30; >30; none	0–1; 2; ≥3	Biopsy: 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	1.09 (0.85–1.41) [98]	0.76 (0.70–0.82) [98]; 0.54 (0.42–0.65) [99]

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Appendix Table 5—**Continued**

Model	Included Variables						Calibration Expected–Observed Cases Ratio (95% CI)* [Reference]	Discriminatory Accuracy c-Statistic (95% CI)* [Reference]
	Age, *y*	Age at Menarche, *y*	Age at Birth of First Child, *y*	First-Degree Relatives With Breast Cancer, *n*	Previous Breast Biopsy, *n*	Other Factors		
Italian-1§ (5-y risk)	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Not included	Age of relative at diagnosis, diet score, alcohol use, BMI, HT, physical activity	1.04 [86]	0.59 (vitamin) [86]; 0.60 (diet) [86]
Italian-2† (20-y risk)	<50; ≥50	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Biopsy: 0; 1; ≥2	Occupational and leisure physical activity, education, alcohol use, BMI	NR	0.62 (0.56–0.69) (age <50 y) [100]; 0.57 (0.52–0.61) (age ≥50 y) [100]
Chlebowski (5-y risk)	50–59; 60–69; 70–79	≤12; 12–13; ≥14	<20; 20–24; 25–29 or none; ≥30	0; ≥1	Biopsy: 0; 1; ≥2	BMI, menopause age, HT use and duration, race, alcohol use, parity, breastfeeding, smoking status, physical activity	NR	0.61 (0.59–0.63) [87]; 0.62 (0.60–0.64) (ER+) [87]; 0.53 (0.47–0.58) (ER−) [87]
Chlebowski, simplified (5-y risk)	<50; ≥50	Not included	Not included	0; ≥1	Biopsy: 0; 1; ≥2	Not included	NR	0.58 (0.56–0.60) (ER+) [87]

AH = atypical hyperplasia; 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; HT = hormone therapy; LCIS = lobular carcinoma in situ; NR = not reported; PR– = progesterone receptor–negative; PR+ = progesterone receptor–positive.

* For invasive breast cancer, other outcomes are specifically indicated.

† Invasive and noninvasive breast cancer.

‡ BI-RADS categories include: 0 = unknown; 1 = entirely fat; 2 = scattered fibroglandular densities; 3 = heterogeneously dense; and 4 = extremely dense.

§ Includes an Italian population and used incidence rates from an Italian multicenter case–control study of diet and breast cancer and Italian cancer registries.