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ASCO SPECIAL ARTICLE

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline

Kala Visvanathan, Patricia Hurley, Elissa Bantug, Powel Brown, Nananda F. Col, Jack Cuzick, Nancy E. Davidson, Andrea DeCensi, Carol Fabian, Leslie Ford, Judy Garber, Maria Katapodi, Barnett Kramer, Monica Morrow, Barbara Parker, Carolyn Runowicz, Victor G. Vogel III, James L. Wade, and Scott M. Lippman

Author affiliations appear at the end of this article.

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Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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ABSTRACT

Purpose
To update the 2009 American Society of Clinical Oncology guideline on pharmacologic interventions for breast cancer (BC) risk reduction.

Methods
A systematic review of randomized controlled trials and meta-analyses published from June 2007 through June 2012 was completed using MEDLINE and Cochrane Collaboration Library. Primary outcome of interest was BC incidence (invasive and noninvasive). Secondary outcomes included BC mortality, adverse events, and net health benefits. Guideline recommendations were revised based on an Update Committee's review of the literature.

Results
Nineteen articles met the selection criteria. Six chemoprevention agents were identified: tamoxifen, raloxifene, arzoxifene, lasofoxifene, exemestane, and anastrozole.

Recommendations
In women at increased risk of BC age ≥ 35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor (ER) –positive BC. In postmenopausal women, raloxifene (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) should also be discussed as options for BC risk reduction. Those at increased BC risk are defined as individuals with a 5-year projected absolute risk of BC ≥ 1.66% (based on the National Cancer Institute BC Risk Assessment Tool or an equivalent measure) or women diagnosed with lobular carcinoma in situ. Use of other selective ER modulators or other aromatase inhibitors to lower BC risk is not recommended outside of a clinical trial. Health care providers are encouraged to discuss the option of chemoprevention among women at increased BC risk. The discussion should include the specific risks and benefits associated with each chemopreventive agent.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published clinical practice recommendations for the use of pharmacologic interventions for breast cancer risk reduction in 1999.[1] ASCO guidelines are updated periodically at intervals determined by an Update Committee of the original Expert Panel, generally based on the release of new evidence. ASCO previously updated these guideline recommendations in 2002[2] and 2009.[3] These guideline recommendations are for use by medical oncologists, surgical oncologists, gynecologists, primary care physicians, and general practitioners.

Breast cancer is the most frequently diagnosed cancer worldwide (IARC Globocan), highlighting the need and potential global impact of effective breast cancer risk reduction strategies. This guideline is relevant to women without a personal history of breast cancer who are at increased risk of developing the disease. Risk of breast cancer may be determined by the Gail model,[4] the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool (which is a modified version of the Gail model, available at http://www.cancer.gov/bcrisktool), or other validated models[4-7] (including Tyrer-Cuzick),[8] or by the eligibility criteria used in the various breast cancer chemoprevention trials (Data Supplement Table DS8 at www.asco.org/guidelines.bcrr).

The guideline recommendations are limited to pharmacologic interventions. Evaluations of surgical and lifestyle interventions are not addressed.

GUIDELINE QUESTIONS

This guideline document focuses on three overarching clinical issues: whether pharmacologic interventions, tested in phase III randomized controlled trials (RCTs), reduce the risk of developing breast cancer (invasive or noninvasive) compared with no pharmacologic interventions; the comparative efficacy of the breast cancer chemoprevention agents; and what constitutes effective and responsible communication by physicians of issues regarding breast cancer risk reduction. This systematic review and the guideline recommendations address whether specific selective estrogen receptor (ER) modulators (SERMs) (ie, tamoxifen, raloxifene, lasofoxifene, arzoxifene) or aromatase inhibitors (ie, exemestane, anastrozole) reduce the risk of developing invasive breast cancer.

Table 1 provides a summary of the prior (2009) guidelines and updated recommendations. A Data Supplement, a patient guide, and other clinical tools and resources to help clinicians implement this

THE BOTTOM LINE

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline

Intervention

- Pharmacologic interventions for breast cancer risk reduction, including selective estrogen receptor (ER) modulators and aromatase inhibitors

Target Audience

- Medical oncologists, surgical oncologists, gynecologists, primary care physicians, general practitioners

Key Recommendations

- Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal or postmenopausal women age ≥ 35 years at increased risk of breast cancer or with lobular carcinoma in situ (LCIS). Tamoxifen is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack; during prolonged immobilization; or in women who are pregnant, may become pregnant, or are nursing mothers. Tamoxifen is not recommended in combination with hormone therapy.
- Raloxifene (60 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS. It should not be used for breast cancer risk reduction in premenopausal women. Raloxifene is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.
- Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to tamoxifen or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS or atypical hyperplasia. Exemestane should not be used for breast cancer risk reduction in premenopausal women.
- For tamoxifen and raloxifene, the most favorable risk-benefit profile is seen in women at greatest risk of developing breast cancer.
- Discussions with patients and health care providers should include both the risks and benefits of each agent under consideration.

Notes

Refer to Table 1 for the complete recommendations.

Increased risk is defined as a 5-year projected absolute risk of breast cancer ≥ 1.66% using the National Cancer Institute Breast Cancer Risk Assessment Tool or an equivalent measure.

Trials were not designed to assess mortality, and the impact of the agent on overall survival or breast cancer–specific survival has not been demonstrated in 10 years of follow-up.

Methods

- A systematic review of randomized controlled trials and meta-analyses published from June 2007 through June 2012 was completed using MEDLINE and the Cochrane Collaboration Library. An Update Committee was convened and reviewed the evidence to determine whether the 2009 ASCO clinical practice guideline recommendations needed to be updated.

Additional Information

- A Data Supplement and clinical tools and resources can be found on the ASCO Web site (http://www.asco.org/guidelines/bcrr).
- ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Table 1. Summary of Clinical Practice Guideline Recommendations

Agent	Old Recommendations (2009)[a]	New Recommendations[b]	Strength of Recommendation and Strength of Evidence[c]
Tamoxifen[d]	May be offered to reduce the risk of ER-positive invasive BC for premenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in premenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66%[e] or with LCIS. Risk reduction benefit continues for at least 10 years.[f]	Strong, evidence-based recommendation.
	May be offered to reduce the risk of ER-positive invasive BC for postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66%[e] or with LCIS. Risk reduction benefit continues for at least 10 years.[f]	Strength of evidence: Strong evidence, based on five RCTs with low risk of bias.
	Is not recommended for women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.	
	Combined use of tamoxifen for BC prevention and hormone therapy is currently not recommended.	Is not recommended in combination with hormone therapy.	
	Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter, with a timely workup of abnormal vaginal bleeding.	*Is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers.* Follow-up should include a timely workup of abnormal vaginal bleeding.	
	Risks and benefits should be given careful consideration during the decision-making process.	Discussions with patients and health care providers should include both the risks and benefits of tamoxifen in the preventive setting.[g]	
	Dosage: 20 mg per day for 5 years.	Dosage: 20 mg per day orally for 5 years.	
Raloxifene[h]	May be offered to reduce the risk of ER-positive invasive BC in postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66%[e] or with LCIS.[f]	Strong, evidence-based recommendation.
	May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit.	May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit.	
	Should not be used for BC risk reduction in premenopausal women.	Should not be used for BC risk reduction in premenopausal women.	Strength of evidence: Strong evidence, based on four RCTs with low risk of bias.
	Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.	
	Risks and benefits should be given careful consideration during the decision-making process.	Discussions with patients and health care providers should include both the risks and benefits of raloxifene in the preventive setting.[g]	
	Dosage: 60 mg per day for 5 years.	Dosage: 60 mg per day orally for 5 years.	

(continued on following page)

Table 1. Summary of Clinical Practice Guideline Recommendations (continued)

Agent	Old Recommendations (2009)[a]	New Recommendations[b]	Strength of Recommendation and Strength of Evidence[c]
Exemestane[i]	Use [of aromatase inhibitors] **is not recommended outside of the clinical trial setting to lower BC risk.**	*Should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women age ≥ 35 years with a 5-year projected absolute BC risk ≥ 1.66%[e] or with LCIS or atypical hyperplasia.*[ef]	Moderate, evidence-based recommendation.
		Should not be used for BC risk reduction in premenopausal women.	
		Discussions with patients and health care providers should include both the risks and benefits of exemestane in the preventive setting.[g]	Strength of evidence: Moderate evidence, based on one RCT with low risk of bias.
		Dosage: 25 mg per day orally for 5 years.	

NOTE. Editorial revisions to the 2009 recommendations that leave the substance unaltered have been made but are not indicated by font changes. Women with abnormal bleeding should be evaluated before starting tamoxifen or raloxifene. Fenretinide has been removed from the 2013 guideline update. The Update Committee concluded that the agent is no longer relevant for BC chemoprevention. Postmenopausal women include women who underwent natural or artificial menopause.

Abbreviations: ASCO, American Society of Clinical Oncology; BC, breast cancer; ER, estrogen receptor; FDA, US Food and Drug Administration; LCIS, lobular carcinoma in situ; NCI, National Cancer Institute; RCT, randomized controlled trial.

[a]Substantive deletions from the 2009 guideline appear in bold text.

[b]Substantive additions in the 2013 guideline appear as italicized text.

[c]Ratings based on ASCO strength of evidence and recommendations ratings (Data Supplement DS11, DS12, DS13).

[d]FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017970s054lbl.pdf.

[e]According to the NCI Breast Cancer Risk Assessment Tool or equivalent measures.

[f]Trials were not designed to assess mortality, and the impact of the agent on overall survival or breast cancer–specific survival has not been demonstrated in 10 years of follow-up.

[g]Risks and benefits may vary in postmenopausal women by specific risk factors including age, race, breast cancer risk, and history of hysterectomy.[27] Guideline text provides a more detailed discussion of risks and benefits.

[h]FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020815s018lbl.pdf.

[i]Exemestane is currently approved by the FDA only for the adjuvant treatment of early breast cancer and the treatment of advanced breast cancer, not for breast cancer risk reduction (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020753s009s011s012lbl.pdf).

guideline are available on the ASCO Web site (http://www.asco.org/guidelines/bcrr).

METHODS

Panel Composition

The ASCO Clinical Practice Guidelines Committee convened an Update Committee of experts in clinical medicine, public health, clinical research, health services, and related areas (ie, biostatistics, epidemiology, cancer prevention, patient-physician communication) with expertise in breast cancer prevention, along with a patient representative. The Update Committee members are listed in Appendix Table A1 (online only).

Guideline Development Process

The Update Committee held a teleconference in June 2012 to review the evidence and draft the guideline recommendations. Before the teleconference, the Update Committee members were sent evidence tables for review and were asked to complete an online survey about the content of the recommendations. During the teleconference, the Committee discussed the evidence and issues for each agent and the content of the recommendations. After the teleconference, a draft of the recommendations was sent to the entire Update Committee for comments. Any contentious comments or questions raised were addressed by e-mail until agreement was reached by the Committee. Additional work on the guideline document was completed through a steering group and by e-mail. All members of the Update Committee participated in the preparation of the draft guideline document and reviewed and approved the final guideline document. The guideline was submitted to *Journal of Clinical Oncology* for peer review. Feedback was also solicited from external reviewers. Before publication, the guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee.

Guideline Policy

This practice guideline is not intended to substitute for the independent professional judgment of the treating physician. This practice guideline does not account for individual variation among patients and may not reflect the most recent evidence, because it is bound by the date parameters of the systematic review. This guideline does not recommend any particular product or course of medical treatment. Use of this practice guideline is voluntary.

Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (Procedures, summarized at http://www.asco.org/guidelinescoi). Members of the Update Committee completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Revision Dates

At annual intervals, the Update Committee Co-Chairs and two Update Committee members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the Update Committee will be reconvened to discuss potential changes. When appropriate, the Update Committee will submit revised guideline recommendations to the ASCO Clinical Practice Guidelines Committee for review and approval.

Literature Review and Analysis

Literature search strategy. The Update Committee completed a systematic review and analysis of the literature published since the 2009 guideline update. The Update Committee's literature review focused attention on available systematic reviews and meta-analyses of published phase III RCTs on breast cancer risk reduction. Literature searches of MEDLINE and the Cochrane Collaboration Library were performed. Searches of the English-language literature from June 2007 through June 2012 were conducted to address each of the guideline recommendations. The searches were supplemented with the references of the selected articles as well as references provided by guideline Update Committee members. A summary of the literature review results is provided in a Quality of Reporting of Meta-Analyses (QUOROM) diagram in the online Data Supplement Table DS7 (available at http://www.asco.org/guidelines/bcrr).

Inclusion and exclusion criteria. Searches were limited to phase III RCTs, meta-analyses, systematic reviews, and existing clinical practice guidelines. Retrospective cohort studies were permitted if they were embedded within an RCT. Other study designs, including prospective or retrospective cohort studies and phase I or II trials, were excluded. English-language studies available in full text and published in peer-reviewed journals were eligible. Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the intervention consisted of one of the specified chemoprevention agents for the prevention of primary breast cancer; (2) participants were randomly assigned to a chemoprevention arm or a control arm (control arm could consist of no chemoprevention agent, a placebo, the same chemoprevention agent at an alternate dose/route, or a different chemoprevention agent); and (3) outcomes reported included at least one of the following: breast cancer incidence, breast cancer–specific mortality, overall mortality, net health benefits, or quality of life. The primary outcome of interest was incidence of invasive and noninvasive breast cancer (including ductal carcinoma in situ). The guideline is limited to pharmacologic interventions, and therefore, evaluations of surgical and lifestyle interventions were excluded from consideration. The Update Committee Co-Chairs reviewed the title lists of included and excluded abstracts, and full text articles were obtained for each included abstract.

Data extraction. Data were extracted from each article that met the inclusion criteria for patient and study characteristics, study quality, interventions, outcomes, and adverse events. Evidence tables were developed based on data extracted from these studies. A Data Supplement, which includes additional tables and figures, may be found online at www.asco.org/guidelines/bcrr. Data were extracted by one reviewer and subsequently checked independently for accuracy by a second reviewer. Disagreements were resolved by discussion and/or by consultation with Update Committee Co-Chairs, if necessary.

Study quality and limitations of the literature. Although all of the trials were RCTs, there was heterogeneity across them on key elements, such as participant and disease characteristics. Table DS10 in the online Data Supplement presents a summary of key quality and design elements and a rating of the overall risk of bias for each study. The overall risk of bias for all of the studies was considered low.

RESULTS

A summary of the literature search results is provided in a QUOROM diagram in Figure DS7 in the online Data Supplement. Preliminary searches identified 723 potential articles. Data were extracted from 19 articles in total that met the a priori criteria for inclusion (Data Supplement Table DS9). Six chemoprevention agents were identified in the literature for consideration by the Update Committee for breast cancer chemoprevention: four SERMs (ie, tamoxifen, raloxifene, arzoxifene, and lasofoxifene) and two aromatase inhibitors (ie, exemestane and anastrozole). These chemoprevention agents and their indications are summarized in Table 2.

Table DS8 in the online Data Supplement summarizes the characteristics of the breast cancer chemoprevention trials that met the selection criteria and that are addressed in the Literature Review and Analysis sections. Tables 3 through 5 summarize the most recent findings from the studies. These tables and the QUOROM diagram are available at http://www.asco.org/guidelines/bcrr.

GUIDELINE RECOMMENDATIONS

Table 1 provides the guideline recommendations. After reviewing the evidence, the Update Committee concluded that recommendations from the 2009 guideline still applied for tamoxifen and raloxifene, with some refinements as indicated in Table 1. The Committee felt that a stronger statement recommending the use of tamoxifen and raloxifene was needed given the weight of evidence from phase III randomized trials demonstrating a reduction in breast cancer risk for both tamoxifen and raloxifene. The phrase "may be offered" was replaced by "should be discussed as an option" in women at increased breast cancer risk. Second, the recommendation stating that baseline gynecologic examination before initiation of treatment and annually thereafter was necessary for women taking tamoxifen was removed. The Committee felt that there was little evidence that annual gynecologic examinations led to an earlier detection of uterine cancer, specifically among women taking tamoxifen, and therefore, it should not be part of the recommendation. The timely workup of abnormal vaginal bleeding continues to be part of the recommendation, and women should be encouraged to have annual gynecologic examinations as part of their routine medical care. No upper age limit was specified in the recommendations. It was felt that this decision should be individualized and should be left to the treating physician based on the general health of the patient. A recommendation for the aromatase inhibitor exemestane is new to this guideline update.

The following text is divided broadly into SERMs and aromatase inhibitors. For each agent, the recommendation is provided, along with a brief summary of the key clinical findings. Specific findings from the trials can be found in Tables 3 through 5.

CLINICAL QUESTION

Which pharmacologic interventions reduce the risk of developing breast cancer in women not previously diagnosed with breast cancer?

SERMs

TAMOXIFEN RECOMMENDATION

Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal women who are age $\geq$ 35 years with a 5-year projected absolute breast cancer risk $\geq$ 1.66%, according to the NCI Breast Cancer Risk Assessment Tool (or equivalent measures), or with lobular carcinoma in situ (LCIS). The risk reduction benefit continues for at least 10 years in both premenopausal and postmenopausal women. Tamoxifen is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Tamoxifen is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers.

Table 2. Summary of Agent Indications and Associated Chemoprevention Trials

Agent	Indication	Trials
SERMs		
Tamoxifen	FDA approved for the treatment of metastatic breast cancer and adjuvant treatment of breast cancer and to reduce the risk of invasive breast cancer in premenopausal or postmenopausal women with DCIS and/or women at high risk of developing breast cancer.	Tamoxifen-placebo: IBIS-I,[9-12] Italian,[13-16] NSABP-P1,[17-22] and Royal Marsden[16] Tamoxifen-raloxifene: STAR (NSABP-P2)[23,24] FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017970s054lbl.pdf
Raloxifene	FDA approved for the treatment and prevention of osteoporosis in postmenopausal women and to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis and/or postmenopausal women at increased risk of breast cancer.	Raloxifene-placebo: Royal Marsden,[16] MORE,[25-27] CORE,[25,28-30] and RUTH[31-33] Tamoxifen-raloxifene: STAR (NSABP-P2)[19,23,24,34-37] FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf
Arzoxifene	Not FDA approved for any indication but has been evaluated for breast cancer prevention and the treatment of osteoporosis in postmenopausal women. Development has been discontinued by the manufacturer.	Arzoxifene-placebo: GENERATIONS[38] FDA label: not applicable
Lasofoxifene	Not approved by the FDA for any indication. It is approved in Europe by the European Medicines Agency under the brand name Fablyn (Ligand Pharmaceuticals, La Jolla, CA) for the treatment of osteoporosis in postmenopausal women. Lasofoxifene has also been evaluated for breast cancer prevention in postmenopausal women with osteoporosis.	Lasofoxifene-placebo: PEARL[39-41] FDA label: not applicable
Aromatase inhibitors		
Exemestane	FDA approved for the adjuvant treatment of ER-positive early breast cancer in postmenopausal women and for treatment of ER-positive advanced breast cancer in postmenopausal women whose disease has progressed after tamoxifen therapy or in combination with everolimus after failure of treatment with letrozole or anastrozole. Exemestane is not approved by the FDA for breast cancer prevention.	Exemestane-placebo: MAP.3[42,43] FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020753s009s011s012lbl.pdf
Anastrozole	FDA approved for adjuvant treatment of hormone receptor–positive early breast cancer in postmenopausal women, for first-line treatment of postmenopausal women with hormone receptor–positive or hormone receptor–unknown locally advanced or metastatic breast cancer, and for the treatment of advanced breast cancer in postmenopausal women with disease progression after tamoxifen therapy. Anastrozole is not FDA approved for breast cancer prevention.	Anastrozole-placebo: IBIS-II[44] FDA label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020541s026lbl.pdf

Abbreviations: CORE, Continuing Outcomes Relevant to Evista; DCIS, ductal carcinoma in situ; FDA, US Food and Drug Administration; IBIS, International Breast Intervention Study; MORE, Multiple Outcomes of Raloxifene Evaluation; NSABP, National Surgical Adjuvant Breast and Bowel Project; PEARL, Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene; RUTH, Raloxifene Use for the Heart; SERMs, selective estrogen receptor modulators; STAR, Study of Tamoxifen and Raloxifene.

Tamoxifen is not recommended in combination with hormone therapy. Follow-up while on tamoxifen should include a timely workup of abnormal vaginal bleeding. Discussions with patients by health care providers should include both the risks and benefits of tamoxifen.

RALOXIFENE RECOMMENDATION

Raloxifene (60 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women who are age $\geq$ 35 years with a 5-year projected absolute breast cancer risk $\geq$ 1.66%, according to the NCI Breast Cancer Risk Assessment Tool (or equivalent measures), or with LCIS. Raloxifene may be used longer than 5 years in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit. Raloxifene should not be used for breast cancer risk reduction in premenopausal women and is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Discussions with patients by health care providers should include both the risks and benefits of raloxifene.

LITERATURE REVIEW RESULTS FOR SERMs

Tamoxifen Versus Placebo

Four phase III randomized placebo-controlled trials have prospectively evaluated tamoxifen for breast cancer risk reduction in premenopausal and postmenopausal women ranging in age from 30 to 70 years. These trials include: NSABP-P1 (National Surgical Adjuvant Breast and Bowel Project P-1 or BCPT), IBIS-I (International Breast Cancer Intervention Study), the Royal Marsden Tamoxifen Prevention Trial, and the Italian Randomized Tamoxifen Prevention Trial. Data Supplement Table DS8 summarizes the characteristics of these trials. (The Update Committee urges readers to refer to the online Data Supplement.)

For the NSABP-P1 trial, there were two publications since the previous guideline update that met the selection criteria; one reported findings from subset analyses on time to diagnosis of ER-positive breast cancer versus ER-negative breast cancer,[17] and another reported findings from a nested case-control study on the impact of *CYP2D6* on breast cancer incidence in NSABP-P1 and NSABP-P2 (STAR [Study of Tamoxifen and Raloxifene]) trials.[18]

Since the systematic review for the 2009 guideline update, there were no new publications that provided updates from the IBIS-I, Italian, or Royal Marsden trial.

Additionally, there was one systematic review that reported on adverse effects among women age $<$ 50 years who participated in randomized trials comparing tamoxifen with placebo.[46]

Raloxifene Versus Placebo

Three phase III randomized placebo-controlled trials have prospectively evaluated the association of raloxifene and breast cancer

Table 3. Results From SERM Trials: Tamoxifen and Placebo

Characteristic	NSABP-P1[22]			IBIS-I[9]			Italian[14]			Royal Marsden[16]		
Follow-up, years	7			10			13			20		
Mean	6.2											
Median				8.0			11.2			13.2		
Sample size*												
TAM	6,597			3,579			2,700			1,238		
PLA	6,610			3,575			2,708			1,233		
	NSABP-P1[22]			IBIS-I[9]			Italian[14]			Royal Marsden[16]		
Variable	Incidence	RR	95% CI	Incidence	RR	95% CI	Incidence	RR	95% CI	Incidence	HR	95% CI
Breast cancer incidence												
All breast cancers												
TAM	NR	NR	NR	142	**0.73**	**0.58 to 0.91**	62	0.84	0.60 to 1.17	96	0.84	0.64 to 1.10
PLA	NR			195			74			113		
Invasive												
All												
TAM	145	**0.57**	**0.46 to 0.70**	124	**0.74**	**0.58 to 0.94**	53	0.80	0.56 to 1.15	82	0.78	0.58 to 1.04
PLA	250			168			66			104		
ER positive												
TAM	70	**0.38**	**0.28 to 0.50**	87	**0.66**	**0.50 to 0.87**	40	0.77	0.51 to 1.16	53	**0.61**	**0.43 to 0.86**
PLA	182			132			52			86		
ER negative												
TAM	56	1.31	0.86 to 2.01	35	1.00	0.61 to 1.65	21	1.10	0.59 to 2.05	24	1.4	0.7 to 2.6
PLA	42			35			19			17		
Noninvasive												
All												
TAM	60	**0.63**	**0.45 to 0.89**	NR	NR	NR	9	1.50	0.53 to 4.20	NR	NR	NR
PLA	93			NR			6			NR		
LCIS												
TAM	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PLA	NR			NR			NR			NR		
DCIS												
TAM	NR	NR	NR	17	0.63	0.32 to 1.20	NR	NR	NR	14	NR	NR
PLA	NR			27			NR			9		
Adverse events and effects												
Sample size*												
TAM		6,597			3,579			2,700			1,238	
PLA		6,610			3,575			2,708			1,233	

(continued on following page)

Table 3. Results From SERM Trials: Tamoxifen and Placebo (continued)

Variable	NSABP-P1[22]			IBIS-I[9]			Italian[14]			Royal Marsden[16]		
	Incidence	RR	95% CI	Incidence	RR	95% CI	Incidence	RR	95% CI	Incidence	HR	95% CI
Death												
TAM	126	1.10	0.85 to 1.43	65	1.18	0.81 to 1.73	36	0.96	0.61 to 1.52	54	0.99	0.68 to 1.44
PLA	114			55			38			54		
VTE												
All												
TAM	NR	NR	NR	117	**1.72**	**1.27 to 2.36**	44	**1.63**	**1.02 to 2.62**	8†	NR	NR
PLA	NR			68			28			3†		
DVT												
TAM	49	1.44	0.91 to 2.30	68	**1.84**	**1.21 to 2.82**‡	NR	NR	NR	NR	NR	NR
PLA	34			37			NR			NR		
PE												
TAM	28	**2.15**	**1.08 to 4.51**	§			NR	NR	NR	NR	NR	NR
PLA	13						NR			NR		
Cardiovascular												
All												
TAM	113	1.03	0.79 to 1.36	NR	NR	NR	NR	NR	NR	10†	NR	NR
PLA	109			NR			NR			12†		
Stroke												
TAM	71	1.42	0.97 to 2.08	15	1.25	0.55 to 2.93	6	3.11	0.63 to 15.4	7†	NR	NR
PLA	50			12			2			9†		
TIA												
TAM	31	0.91	0.54 to 1.52	17	0.77	0.39 to 1.52	6	1.24	0.38 to 4.08	NR	NR	NR
PLA	34			22			5			NR		
Endometrial cancer												
TAM	53	**3.28**	**1.87 to 6.03**	17	1.55	0.68 to 3.65	NR	NR	NR	13†	NR	NR
PLA	17			11			NR			5†		
Fracture												
TAM	116	0.68	0.51 to 0.92	240	1.02	0.86 to 1.21	NR	NR	NR	19†	NR	NR
PLA	80			235			NR			22†		
Cataract												
TAM	NR	**1.21**	**1.10 to 1.34**	67	1.24	0.87 to 1.77	NR	NR	NR	NR	NR	NR
PLA	NR			54			NR			NR		

NOTE. Bold font indicates statistical significance.

Abbreviations: DCIS, ductal carcinoma in situ; DVT, deep vein thrombosis; ER, estrogen receptor; HR, hazard ratio; IBIS, International Breast Intervention Study; LCIS, lobular carcinoma in situ; NR, not reported in published literature; NSABP, National Surgical Adjuvant Breast and Bowel Project; PE, pulmonary embolism; PLA, placebo; RR, relative risk; SERM, selective estrogen receptor modulator; TAM, tamoxifen; TIA, transient ischemic attack; VTE, venous thromboembolism.

*Sample size included in analyses.

†While receiving treatment.

‡DVT, PE, and retinal vein thrombosis combined.

§See DVT.

Table 4. Results From Other SERM Trials

Characteristic	CORE[25,29,30*]	MORE[26,27,45*]	RUTH[31,33]	STAR[23,34,35]
Follow-up, years	4 + time in MORE trial	4	7	8
Median	7.9	.4	5.6	6.75
Sample size†				
RAL	5,129‡	5,111	5,044	9,754
PLA	2,576‡	2,571	5,057	
TAM				9,736

	CORE[25,29,30*]			MORE[26,27,45*]			RUTH[31,33]			STAR[23,34,35]		
Variable	Incidence	HR	95% CI	Incidence	RR	95% CI	Incidence	HR	95% CI	Incidence	RR	95% CI
Breast cancer incidence												
All breast cancers		**0.42**	**0.29 to 0.60**		**0.38**	**0.24 to 0.58**		**0.67**	**0.47 to 0.96**		NR	NR
RAL	56			NR			52			NR		
PLA	65			NR			76					
TAM										NR		
Invasive												
All		**0.33**	**0.21 to 0.49[25]**		**0.28**	**0.17 to 0.46**		**0.56**	**0.38 to 0.83**		**1.24**	**1.05 to 1.47**
RAL	37			NR			40			310		
PLA	55			NR			70					
TAM										247		
ER positive		**0.24**	**0.15 to 0.40**		**0.16**	**0.09 to 0.30**		**0.45**	**0.28 to 0.72**		0.94	0.72 to 1.24
RAL	22			NR			25			109		
PLA	44			NR			55					
TAM										115		
ER negative		1.06	0.43 to 2.59		NR	NR		1.44	0.61 to 3.36		1.15	0.75 to 1.77
RAL	15			NR			13			51		
PLA	7			NR			9					
TAM										44		
Noninvasive												
All		1.12	0.46 to 2.73		NR	NR		NR	NR		1.22	0.95 to 1.59
RAL	16			NR			NR			137		
PLA	7			NR			NR					
TAM										111		
LCIS		NR	NR		NR	NR		NR	NR		1.02	0.61 to 1.70
RAL	NR			NR			NR			34		
PLA	NR			NR			NR					
TAM										33		
DCIS		NR	NR		NR	NR		2.17	0.75 to 6.24		1.22	0.88 to 1.69
RAL	NR			NR			11			86		
PLA	NR			NR			5					
TAM										70		
Adverse events and effects												
Sample size†												
RAL		2,725			5,129			5,044			9,754	
PLA		1,286			2,576			5,057				
TAM											9,736	

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Table 4. Results From Other SERM Trials (continued)

Variable	CORE[25,29,30*]			MORE[26,27,45*]			RUTH[31,33]			STAR[23,34,35]		
	Incidence	HR	95% CI	Incidence	RR	95% CI	Incidence	HR	95% CI	Incidence	RR	95% CI
Death		*P* = .27			0.61	0.36 to 1.03		0.92	0.82 to 1.03		0.84	0.70 to 1.02
RAL	47			NR			554			202		
PLA	29			NR			595					
TAM										236		
VTE												
All		*P* = .094			NR	NR		**1.44**	**1.06 to 1.95**		**0.75**	**0.60 to 0.93**
RAL	47			NR			103			154		
PLA	13			NR			71					
TAM										202		
DVT		*P* = .32			***P* = .002**			1.37	0.94 to 1.99		**0.72**	**0.54 to 0.95**
RAL	31			NR			65			86		
PLA	10			NR			47					
TAM										118		
PE		***P* = .05**			3.97	0.91 to 17.3		1.49	0.89 to 2.49		0.080	0.57 to 1.11
RAL	17			NR			36			68		
PLA	2			NR			24					
TAM										84		
Cardiovascular												
All		NR	NR		NR	NR		NR	NR		1.10	0.85 to 1.43
RAL	NR			NR			NR			126		
PLA	NR			NR			NR					
TAM										114		
Stroke		NR	NR		0.68	0.43 to 1.07		1.10	0.92 to 1.32		0.96	0.64 to 1.43
RAL	NR			NR			249			51		
PLA	NR			NR			224					
TAM										53		
TIA		NR	NR		NR	NR		NR	NR		1.21	0.79 to 1.88
RAL	NR			NR			NR			50		
PLA	NR			NR			NR					
TAM										41		
Endometrial cancer		*P* = .75			0.69	0.22 to 2.18		*P* = .53			**0.55**	**0.36 to 0.83**
RAL	7			NR			21			37		
PLA	4			NR			17					
TAM										65		

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Table 4. Results From Other SERM Trials (continued)

Variable	CORE[25,29,30*]			MORE[26,27,45*]			RUTH[31,33]			STAR[23,34,35]		
	Incidence	HR	95% CI	Incidence	RR	95% CI	Incidence	HR	95% CI	Incidence	RR	95% CI
Fracture			***P* > .05**[30]		**0.66**§	**0.55 to 0.81**					0.92	0.69 to 1.22
Vertebral								**0.65**	**0.47 to 0.89**			
Nonvertebral								0.96	0.84 to 1.10			
RAL	NR			64						96		
Vertebral							64					
Nonvertebral							428					
PLA	NR			97								
Vertebral							97					
Nonvertebral							438					
TAM										104		
Cataract		NR	NR		NR	NR			*P* = .56		**0.80**	**0.72 to 0.89**
RAL	NR			NR			374			603		
PLA	NR			NR			391					
TAM										739		

NOTE. Bold font indicates statistical significance.

Abbreviations: CORE, Continuing Outcomes Relevant to Evista; DCIS, ductal carcinoma in situ; DVT, deep vein thrombosis; ER, estrogen receptor; HR, hazard ratio; LCIS, lobular carcinoma in situ; MORE, Multiple Outcomes of Raloxifene Evaluation; NR, not reported in published literature; PE, pulmonary embolism; PLA, placebo; RAL, raloxifene; RR, relative risk; RUTH, Raloxifene Use for the Heart; SERM, selective estrogen receptor modulators; STAR, Study of Tamoxifen and Raloxifene; TAM, tamoxifen; TIA, transient ischemic attack.

*Published data pooled doses of raloxifene (60 and 120 mg per day) for analyses.

†Sample size included in analyses.

‡Over course of MORE and CORE studies combined.

§RR.

Table 5. Results From Other SERM Trials

Characteristic	PEARL[39-41]			GENERATIONS[38]		
Follow-up, years	5			4		
Median	4.96			NR		
Sample size*						
PLA	2,740			4,678		
LAS (0.25 mg)	2,729					
LAS (0.5 mg)	2,745					
ARZ				4,676		
	PEARL[39-41]			GENERATIONS[38]		
Variable	Incidence	HR	95% CI	Incidence	HR	95% CI
Breast cancer incidence						
All breast cancers					NR	NR
PLA	24			NR		
LAS (0.25 mg)	20	0.82	0.45 to 1.49			
LAS (0.5 mg)	5	**0.21**	**0.08 to 0.55**			
ARZ				NR		
Invasive						
All					**0.44**	**0.26 to 0.76**
PLA	20			NR		
LAS (0.25 mg)	16	0.79	0.41 to 1.52			
LAS (0.5 mg)	3	**0.15**	**0.04 to 0.50**			
ARZ				NR		
ER positive					NR	NR
PLA	18			NR		
LAS (0.25 mg)	9	0.50	0.22 to 1.11			
LAS (0.5 mg)	3	**0.17**	**0.05 to 0.57**			
ARZ				NR		
ER negative					NR	NR
PLA	3			NR		
LAS (0.25 mg)	8	2.55	0.67 to 9.65			
LAS (0.5 mg)	1	0.35	0.04 to 3.34			
ARZ				NR		
Noninvasive						
All					NR	NR
PLA	NR			NR		
LAS (0.25 mg)	NR	NR	NR			
LAS (0.5 mg)	NR	NR	NR			
ARZ				NR		
LCIS					NR	NR
PLA	NR			NR		
LAS (0.25 mg)	NR	NR	NR			
LAS (0.5 mg)	NR	NR	NR			
ARZ				NR		
DCIS					NR	NR
PLA	4			NR		
LAS (0.25 mg)	4	1.00	0.25 to 3.99			
LAS (0.5 mg)	2	0.50	0.09 to 2.73			
ARZ				NR		
Adverse events and effects						
Sample size*						
PLA		2,852			4,678	
LAS (0.25 mg)		2,852				
LAS (0.5 mg)		2,852				
ARZ					4,676	
Death						$P = .62$
PLA	65			98		
LAS (0.25 mg)	90	**1.38**	**1.00 to 1.89**			
LAS (0.5 mg)	73	1.12	0.80 to 1.56			
ARZ				105		

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Table 5. Results From Other SERM Trials (continued)

Variable	PEARL[39-41]			GENERATIONS[38]		
	Incidence	HR	95% CI	Incidence	HR	95% CI
VTE						
All						***P* < .001**
PLA	18			27		
LAS (0.25 mg)	48	**2.67**	**1.55 to 4.58**			
LAS (0.5 mg)	37	**2.06**	**1.17 to 3.61**			
ARZ				63		
DVT						***P* = .004**
PLA	NR			9		
LAS (0.25 mg)	NR	NR	NR			
LAS (0.5 mg)	NR	NR	NR			
ARZ				26		
PE						*P* = .06
PLA	2			7		
LAS (0.25 mg)	12	**5.98**	**1.34 to 26.7**			
LAS (0.5 mg)	9	**4.49**	**0.97 to 20.8**			
ARZ				16		
Cardiovascular						
All						*P* = .83
PLA	95			113		
LAS (0.25 mg)	73	0.76	0.56 to 1.03			
LAS (0.5 mg)	65	**0.68**	**0.50 to 0.93**			
ARZ				116		
Stroke						*P* = .59
PLA	50			42		
LAS (0.25 mg)	31	**0.61**	**0.39 to 0.96**			
LAS (0.5 mg)	32	**0.64**	**0.41 to 0.99**			
ARZ				47		
TIA					NR	NR
PLA	14			NR		
LAS (0.25 mg)	19	1.35	0.68 to 2.69			
LAS (0.5 mg)	14	1.00	0.48 to 2.09			
ARZ				NR		
Endometrial cancer		NR	NR			*P* = .16
PLA	3			4		
LAS (0.25 mg)	2					
LAS (0.5 mg)	2					
ARZ				9		
Fracture						
Vertebral					**0.61**	**0.48 to 0.77**
Nonvertebral					0.94	0.81 to 1.10
PLA						
Vertebral	262 of 2,744	NR	NR	179		
Nonvertebral	296 of 2,852	NR	NR	354		
LAS (0.25 mg)						
Vertebral	189 of 2,734	**0.69**	**0.57 to 0.83**			
Nonvertebral	269 of 2,852	0.90	0.76 to 1.06			
LAS (0.5 mg)						
Vertebral	156 of 2,748	**0.58**	**0.47 to 0.70**			
Nonvertebral	230 of 2,852	**0.76**	**0.64 to 0.91**			
ARZ						
Vertebral				109		
Nonvertebral				334		
Cataract		NR	NR		NR	NR
PLA	NR			NR		
LAS (0.25 mg)	NR					
LAS (0.5 mg)	NR					
ARZ				NR		

NOTE. Bold font indicates statistical significance.

Abbreviations: ARZ, arzoxifene; DCIS, ductal carcinoma in situ; DVT, deep vein thrombosis; ER, estrogen receptor; HR, hazard ratio; LAS, lasofoxifene; LCIS, lobular carcinoma in situ; NR, not reported in published literature; PE, pulmonary embolism; PEARL, Postmenopausal Evaluation and Risk Reduction With Lasofoxifene; PLA, placebo; RR, relative risk; SERM, selective estrogen receptor modulators; TIA, transient ischemic attack.

*Sample size included in analyses.

incidence in postmenopausal women age ≤ 80 years. These trials include: RUTH (Raloxifene Use for the Heart), MORE (Multiple Outcomes of Raloxifene Evaluation), and CORE (Continuing Outcomes Relevant to Evista). All of these trials included postmenopausal women only, and breast cancer incidence was not the primary end point of the RUTH and MORE trials. The RUTH trial included women with chronic heart disease, or women who were at increased risk of developing chronic heart disease, and the MORE and CORE trials only included women with osteoporosis. The CORE trial is a continuation of the MORE trial. Data Supplement Table DS8 summarizes the characteristics of each of these trials. (The Update Committee urges readers to refer to the online Data Supplement.)

In total, there were three new publications presenting data from the raloxifene-placebo trials, including two publications of post hoc subset analyses on combined MORE and CORE datasets; one examined breast cancer incidence by bone mass subgroups (ie, osteoporosis *v* low bone mass),[28] and the other[25] reported results from two post hoc analyses on cumulative incidence of invasive breast cancer by year and incidence of invasive breast cancer in women who continued with raloxifene for 8 years compared with women who discontinued raloxifene.

Findings from subgroup analyses of the RUTH trial have also been published that examined the incidence of breast cancer, including tumor characteristics and treatment duration.[31]

Tamoxifen Versus Raloxifene

The STAR trial is the only RCT to compare tamoxifen and raloxifene in terms of breast cancer risk reduction. The STAR trial examined the incidence of invasive breast cancer in postmenopausal women age ≥ 35 years who were at increased risk of developing breast cancer. Four new publications were identified with longer-term follow-up data from the STAR trial on the incidence of invasive and noninvasive breast cancer, adverse events,[34-36] and cognition and memory.[37] The impact of *CYP2D6* testing on breast cancer incidence in the STAR and NSABP-P1 trials has also been reported.[18]

Lasofoxifene Versus Placebo

Three new articles reported findings from the PEARL (Postmenopausal Evaluation and Risk Reduction With Lasofoxifene) trial, which examined the incidence of vertebral fractures, nonvertebral fractures, and ER-positive breast cancer in postmenopausal women age 59 to 80 years with osteoporosis. One article reported findings on the incidence of vertebral and nonvertebral fractures and the incidence of ER-positive breast cancer,[39] and another reported on the incidence of coronary heart disease.[40] Additionally, LaCroix et al[41] reported findings from a case-control study on incident breast cancers and ER-positive breast cancer.

Arzoxifene Versus Placebo

Data were also available from the GENERATIONS trial, a randomized trial that tested whether arzoxifene would safely reduce the risk of fractures and invasive breast cancer in postmenopausal women with low bone mass or osteoporosis compared with placebo.[38]

FINDINGS FROM BREAST CANCER PREVENTION TRIALS INVOLVING SERMs

This section summarizes the results from the breast cancer prevention trials that were published since the systematic review for the 2009 guideline. Tables 3 through 5 provide the most recent findings from these studies.

Breast Cancer Incidence

There were no new findings specific to tamoxifen-placebo trials. The results of these trials demonstrate a risk reduction in ER-positive breast cancer between 31% and 67% (Table 3). Initial findings from the STAR trial demonstrated that after a median follow-up of 4.6 years, tamoxifen and raloxifene were equally efficacious in reducing the incidence of breast cancer overall and of ER-positive invasive breast cancer in postmenopausal women.[23] The longer follow-up data from the STAR trial suggest that after a median follow-up of 6 years, tamoxifen has a more favorable risk-benefit profile compared with raloxifene.[34,35] Women taking raloxifene were 24% more likely to develop invasive breast cancer than women taking tamoxifen (relative risk [RR], 1.24; 95% CI, 1.05 to 1.47). It was also less effective than tamoxifen in reducing the risk of noninvasive breast cancer, although the difference was not statistically significant (RR, 1.22; 95% CI, 0.95 to 1.59). The results for women with a history of LCIS remain similar to those originally reported (RR, 1.13; 95% CI, 0.76 to 1.69). Despite these differences, it is important to note that both tamoxifen and raloxifene are effective in reducing breast cancer incidence and that the decision to take either drug should involve a discussion of their benefits and adverse effects.

Data from a post hoc analysis of the MORE and CORE trials, which involved women with osteoporosis, suggest that longer-term use of raloxifene is associated with reduction in breast cancer risk. A 58% reduction in breast cancer risk was observed in women who took raloxifene for a median of 7.9 years compared with placebo (hazard ratio [HR], 0.42; 95% CI, 0.29 to 0.60).[25]

Mortality

None of these studies demonstrated a reduction in breast cancer mortality for tamoxifen or raloxifene. However, it is important to note that these studies were not powered to detect differences in mortality, because a reduction in the incidence of breast cancer was considered in itself to be an important clinical end point.

Adverse Events and Adverse Effects

Tamoxifen. Serious adverse events associated with tamoxifen use include endometrial cancer, stroke, transient ischemic attack, venous thromboembolism, deep vein thrombosis, and pulmonary embolism (Tables 3 and 4). A systematic review and analysis of data from women in the NSABP-P1, IBIS-I, and Royal Marsden trials demonstrated that women age < 50 years who took tamoxifen for breast cancer prevention had a lower risk of endometrial cancer, deep vein thrombosis, and pulmonary embolism than women age ≥ 50 years. The risk decreased from the active phase to follow-up phase of treatment.[46] Vascular and vasomotor adverse effects were observed to decline post-treatment across all ages.[9,46] Two studies have also identified specific subgroups of women at increased risk of developing venous thromboembolism while on tamoxifen: women who are immobilized in the prior 3 months and/or women who have body mass index (BMI) > 25 kg/m^2.[10] Of note, women were not eligible to join the STAR trial if they had: increased risk of thromboembolic disease from uncontrolled

atrial fibrillation; uncontrolled diabetes; uncontrolled hypertension; or prior history of stroke, deep venous thrombosis, or pulmonary embolus.

Raloxifene. Raloxifene was associated with a more favorable adverse effect profile compared with tamoxifen in the STAR trial, including a significantly lower risk of thromboembolic disease (statistically significant only for deep vein thrombosis) and uterine cancer and lower incidence of benign uterine hyperplasia, cataracts, and cataract surgery[34] (Table 4).

A retrospective analysis of data from the NSABP-P1 and STAR trials on the incidence of gynecologic conditions in postmenopausal women demonstrated that women who received raloxifene also had a statistically significant lower incidence of ovarian cysts, endometrial polyps, hot flashes, vaginal discharge, and vaginal bleeding and had fewer gynecologic procedures performed compared with women who received tamoxifen.[36]

Results of a substudy, known as Co-STAR, to assess cognitive differences between women in the tamoxifen arm compared with the raloxifene arm were also published.[37] The analyses included follow-up data on two thirds of the patients at 1 year and one third at 2 years. No significant differences in mean cognitive scores between women taking tamoxifen and raloxifene were observed at baseline or during subsequent visits. The women who took part in this substudy were younger and it should be noted that they were more likely to have attended some college, undergone a hysterectomy, reported prior estrogen usage, and had hypertension or diabetes compared with women who did not participate in Co-STAR.

Quality of Life

There were no new publications addressing quality of life from any of the tamoxifen or raloxifene chemoprevention trials. Table DS11 in the online Data Supplement reports earlier findings from quality-of-life data for the STAR trial.[24] This table was also reported in the 2009 guideline.

Lasofoxifene and Arzoxifene

Lasofoxifene and arzoxifene have not been evaluated in phase III randomized controlled breast cancer prevention trials. Therefore, the Update Committee chose not make recommendations for these chemoprevention agents. Table 5 summarizes the key findings for breast cancer incidence and adverse events from the PEARL trial (lasofoxifene) and the GENERATIONS trial (arzoxifene), which were conducted in women with low bone mineral density and/or osteoporosis. Of note, arzoxifene is not approved by the US Food and Drug Administration, and in 2009, Lilly announced that it would discontinue further development of the agent and would not seek regulatory approval.

Net Health Benefits

Premenopausal women. For tamoxifen, there were no new publications evaluating the risk-benefit profile in premenopausal women. Gail et al[4] previously demonstrated, based on the NSABP-P1 data, that the greatest clinical benefit with the least adverse effects, for tamoxifen compared with placebo, occurred in younger women (between ages 35 and 50 years) who were at elevated risk of breast cancer.

Postmenopausal women. Freedman et al[47] conducted a post hoc retrospective analysis that included data from the STAR and NSABP-P1 trials. This study did not meet the systematic review selection criteria, but the Update Committee decided that the findings should be described here briefly, because they may be clinically important. In postmenopausal women, the risk-benefit profile for both tamoxifen and raloxifene was found to vary by age, race (ie, white non-Hispanic, black, and Hispanic), level of breast cancer risk, and history of hysterectomy. Overall, the most favorable risk-benefit profile is seen in women at greatest risk of developing breast cancer. Postmenopausal women with an intact uterus were found to have a better risk-benefit index for raloxifene compared with tamoxifen. For postmenopausal women without a uterus, the risk-benefit ratio was not statistically significant between the two chemoprevention agents. More detailed estimates of risk-benefit profiles stratified by age and race are available in their article (http://www.uspreventiveservicestaskforce.org/draftrec4figs.htm).[47,48]

Additionally, Cuzick et al[49] conducted a meta-analysis based on individual-level data from nine randomized trials that compared SERMs with placebo or another drug in women without breast cancer. Although this article was published outside of the date parameters of the systematic review for this guideline, the Update Committee felt it was important to mention the publication, because it is a meta-analysis that includes individual-patient data from nine randomized chemoprevention trials that evaluated SERMs (ie, tamoxifen, raloxifene, lasofoxifene, and arzoxifene). Eight of these trials were placebo-controlled trials, and one compared tamoxifen with raloxifene. Overall, there was a 38% reduction in breast cancer incidence, with 42 women needing to be treated to prevent one case of breast cancer, over a 10-year follow-up period. The largest risk reduction was observed in the first 5 years. There was also a significant increase in the incidence of thromboembolic disease with all SERMs (odds ratio [OR], 1.73; 95% CI, 1.47 to 2.05) and a significant reduction in the incidence of nonvertebral fractures (OR, 0.66; 95% CI, 0.59 to 0.73).

In summary, when considering tamoxifen and/or raloxifene as chemopreventive options, both the risks and benefits (Tables 3 and 4) should be discussed, and the discussion should be tailored to the individual patient. Providing information on net health benefits such as those described here can also be helpful in the decision-making process.

ADDITIONAL CLINICAL CONSIDERATIONS FOR USE OF SERMs FOR BREAST CANCER PREVENTION

Menopausal Hormone Therapy

There is insufficient evidence to recommend the use of hormone therapy for menopausal symptoms in women taking tamoxifen or raloxifene for breast cancer prevention. In the IBIS-I trial, there continues to be no difference in tamoxifen benefit among users of hormone therapy, when compared with nonusers. In the NSABP-P1 and STAR trials, women receiving estrogen and progesterone therapy were excluded.

Obesity

There is no direct evidence to suggest that women who are overweight or obese should not be offered tamoxifen or raloxifene for breast cancer prevention. BMI and breast cancer risk were stratified by treatment group in a post hoc analysis of the STAR and NSABP-P1 trials.[19] There was no significant interaction found between BMI, treatment group, and incidence of invasive breast cancer.

Comorbidities

Neither tamoxifen nor raloxifene is recommended for use in women with a personal history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or immobilization, because of the increased risk of adverse events in these women, as noted in the Adverse Events section.

Adherence

Factors that may affect adherence should be considered during the decision-making process. In a post hoc subset analysis of the NSABP-P1 trial of 11,064 women, tamoxifen adherence seemed to decline substantially over a 36-month period.[20] At 1 month, 91% of participants were considered adequately adherent (ie, 76% to 99% of pills were taken over previous 4 weeks). At 3 years, only 79% of participants were adequately adherent. Long-term positive predictors of increased adherence included having a college degree, older age, and higher breast cancer risk; factors associated with reduced adherence included smoking and tamoxifen use.

Testing for CYP2D6 Allelic Variants in the Prevention Setting

Since the last guideline, additional data have been generated on the relationship between functional allelic variants in cytochrome P450 2D6 gene (*CYP2D6*), use of CYP2D6 inhibitors including selective serotonin reuptake inhibitors, and breast cancer incidence. Data from the NSABP-P1 and STAR trials do not support the use of *CYP2D6* testing to identify women not likely to benefit from tamoxifen therapy for breast cancer prevention.[18,50] *CYP2D6* encodes the enzyme responsible for catalyzing the conversion of tamoxifen to endoxifen, and variants in *CYP2D6* are associated with lower levels of this active metabolite.[51] In a post hoc nested case-control study among NSABP-P1 and STAR trial participants, no significant association was observed between *CYP2D6* genotype, inhibitor use or metabolizer status, and breast cancer incidence.[18] In a post hoc case-only study of NSABP-P1 data, a borderline statistically significant association was observed with tamoxifen treatment and the *CYP2D6* C1111T polymorphism.[50]

AROMATASE INHIBITORS

Since the previous guideline update, results have been published for the MAP.3 randomized placebo-controlled trial on the use of exemestane for breast cancer prevention. The primary results from the IBIS-II randomized placebo-controlled trial on the use of anastrozole for breast cancer chemoprevention are not yet available. The characteristics of the MAP.3 and IBIS-II studies are summarized in Data Supplement Table DS8. Cognitive function of a subset of IBIS-II participants has been reported.[44] The findings for the MAP.3 trial are reported in Table 6.

EXEMESTANE RECOMMENDATION

Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age $\geq$ 35 years with a 5-year projected breast cancer absolute risk $\geq$ 1.66%, according to the NCI Breast Cancer Risk Assessment Tool (or equivalent measures), or with LCIS or atypical hyperplasia. Exemestane should not be used for breast cancer risk reduction in premenopausal women. Discussions with patients and health care providers should include both the risks and benefits of each agent under consideration.

Of note, exemestane is US Food and Drug Administration approved only for the adjuvant treatment of early breast cancer and the treatment of advanced breast cancer, not for breast cancer risk reduction (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020753s009s011s012lbl.pdf).

ANASTROZOLE RECOMMENDATION

The Update Committee concluded that there was insufficient evidence to provide a recommendation for anastrozole to guide clinical practice.

LITERATURE REVIEW RESULTS FOR AROMATASE INHIBITORS

Exemestane Versus Placebo

There is currently only one RCT on the use of exemestane for breast cancer prevention. The MAP.3 trial is a randomized placebo-controlled double-blind trial of exemestane for the primary prevention of breast cancer in postmenopausal women age $\geq$ 35 years and at increased risk of breast cancer. Participants were randomly assigned to one of three treatment groups: 25 mg of exemestane plus placebo, 25 mg of exemestane plus celecoxib, or placebo, administered daily. The median follow-up is 3 years. Data Supplement Table DS8 summarizes the characteristics of the MAP.3 trial.

The literature review found two articles that summarize findings from the MAP.3 trial.[42,43] Goss et al[42] reported findings from a median follow-up of 35 months on the incidence of invasive and preinvasive breast cancers, adverse events, and health-related and menopause-related quality of life. Cheung et al[43] reported on a nested substudy that examined the skeletal effects of exemestane after 2 years of follow-up in a subset of postmenopausal women who were eligible to participate in the MAP.3 trial. The primary end point of the substudy was percent change from baseline to 2 years in total volumetric bone mineral density at the distal radius by high-resolution peripheral quantitative computed tomography.

Anastrozole Versus Placebo

There is currently only one RCT on anastrozole in the breast cancer prevention setting. The IBIS-II trial is an ongoing randomized placebo-controlled trial on the use of anastrozole (1 mg per day orally for 5 years) to reduce the incidence of breast cancer in postmenopausal women at increased risk of developing breast cancer. Data Supplement Table D8 summarizes the characteristics of the IBIS-II trial. Only one publication with data on the IBIS-II met the study selection criteria for systematic review.[44] The article reports findings from a cognitive subprotocol of the IBIS-II trial on cognitive performance, including memory and attention.[44] The release of additional results from the IBIS-II trial, including breast cancer incidence and adverse events, is forthcoming.

Because there is no published evidence on the efficacy of anastrozole for breast cancer risk reduction, the Update Committee did not make a recommendation for the agent. The Committee will review the findings from the study when they become available to determine whether a recommendation is warranted.

Table 6. Results From Aromatase Inhibitor Trial (MAP.3)

Characteristic		MAP.3[42,43]	
Follow-up, years			
Median		3	
Range		0 to 63.4	
Sample size*			
EXE		2,285	
PLA		2,275	
Variable	Incidence	HR	95% CI
Breast cancer incidence			
All breast cancers		**0.47**†	**0.27 to 0.79**†
EXE	20		
PLA	44		
Invasive			
All		**0.35**	**0.18 to 0.70**
EXE	11		
PLA	32		
ER positive		**0.27**	**0.12 to 0.60**
EXE	7		
PLA	27		
ER negative		0.80	0.21 to 2.98
EXE	4		
PLA	5		
Noninvasive			
All		NR	NR
EXE	NR		
PLA	NR		
LCIS		0.36‡	0.11 to 1.12‡
EXE	4		
PLA	11		
DCIS		0.65	0.28 to 1.51
EXE	9		
PLA	14		
Adverse events and effects			
Sample size*			
EXE		2,240	
PLA		2,248	
Death		NR	NR
EXE	19		
PLA	19		
VTE			
All		NR	NR
EXE	11		
PLA	7		
DVT		NR	NR
EXE	NR		
PLA	NR		
PE		NR	NR
EXE	NR		
PLA	NR		
Cardiovascular			
All			$P = .78$
EXE	106		
PLA	111		
Stroke		NR	NR
EXE	13		
PLA	11		
TIA			
EXE	§		
PLA			

(continued in next column)

Table 6. Results From Aromatase Inhibitor Trial (MAP.3) (continued)

Variable	Incidence	HR	95% CI
Endometrial cancer		NR	NR
EXE	5		
PLA	8		
Fracture			$P = .72$
EXE	149		
PLA	143		
Cataract		NR	NR
EXE	NR		
PLA	NR		

NOTE. Bold font indicates statistical significance.
Abbreviations: DCIS, ductal carcinoma in situ; DVT, deep vein thrombosis; ER, estrogen receptor; EXE, exemestane; HR, hazard ratio; LCIS, lobular carcinoma in situ; NR, not reported in published literature; PE, pulmonary embolism; PLA, placebo; TIA, transient ischemic attack; VTE, venous thromboembolism.
*Sample size included in analyses.
†Invasive and DCIS combined.
‡Results for incidence of atypical ductal hyperplasia, atypical lobular hyperplasia, and LCIS combined.
§See Stroke.

FINDINGS FROM TRIAL INVOLVING EXEMESTANE

Because data on the use of aromatase inhibitors for breast cancer risk reduction are only available for exemestane, the following sections summarize and discuss findings for exemestane only. Table 6 summarizes the key findings from the MAP.3 trial.

Breast Cancer Incidence

Results from the MAP.3 trial demonstrate that after a median follow-up of 3 years, exemestane statistically significantly reduces the overall risk of invasive breast cancer and the risk of ER-positive invasive breast cancer in postmenopausal women at increased risk of breast cancer by up to 73%. The data do not show a reduction in the risk of ER-negative breast cancer or noninvasive breast cancers with exemestane use, compared with placebo. There is no evidence that switching treatment from SERMs (tamoxifen or raloxifene) to exemestane is associated with a greater reduction in breast cancer incidence, nor that the addition of exemestane after completing 5 years of tamoxifen or raloxifene is associated with greater benefit.

Mortality

Mortality rates were not statistically different in the exemestane and placebo arms. None of the deaths were considered treatment related; causes of death were breast cancer, other malignancies, cardiovascular events, and other causes.

Adverse Events and Adverse Effects

Table 6 summarizes the key findings for adverse events in the MAP.3 trial. Overall, more adverse events occurred in the exemestane group compared with the placebo group of the MAP.3 trial. There were no statistically significant differences in the incidence of serious adverse events including cardiovascular events, skeletal fractures, other cancers, or treatment-related deaths.[42] Statistically significant differences were observed for endocrine-related adverse events (ie, hot flashes, fatigue, sweating, insomnia), constitutional and GI events (ie, diarrhea and nausea), and joint and muscle pain.

Bone Mineral Density

Results from a post hoc nested substudy of the MAP.3 trial demonstrated a statistically significant reduction in bone mineral density and cortical thickness at the distal tibia and distal radius, lumbar spine, total hip, and femoral neck. Compared with placebo, 2 years of treatment with exemestane worsened age-related bone loss in postmenopausal women, despite calcium and vitamin D supplementation.[43]

Quality of Life

Minimal differences in quality-of-life outcomes were observed between the exemestane and placebo groups. There was a statistically significant increase in the incidence of vasomotor symptoms, bodily pain, and sexual problems in women who took exemestane compared with women in the placebo group.[42]

Net Health Benefits

The reported findings indicate that exemestane is a reasonable option for reducing the risk of invasive breast cancer in postmenopausal women at increased risk of breast cancer. In the MAP.3 trial, exemestane significantly reduced the incidence of invasive breast cancer, was not associated with serious adverse effects, and resulted in only minimal changes in health-related quality of life. The potential for bone loss should be mentioned when discussing the risks and benefits of exemestane for prevention. Women receiving exemestane should undergo bone monitoring and have adequate vitamin D and calcium supplementation. Longer-term follow-up is needed to further characterize both adverse effects and breast cancer outcomes.

OTHER PHARMACOLOGIC AGENTS FOR BREAST CANCER PREVENTION

Fenretinide has been removed from this guideline update. The Update Committee concluded that the agent is no longer relevant for breast cancer chemoprevention.

RISK REDUCTION FOR *BRCA1* AND *BRCA2* MUTATION CARRIERS

There are insufficient data on the efficacy of tamoxifen for breast cancer risk reduction in *BRCA1* and *BRCA2* mutation carriers to give reliable estimates of their effect in this setting. The 2009 guideline describes the findings from phase III randomized trials of tamoxifen use and breast cancer incidence among women with inherited mutations in *BRCA1* and *BRCA2*.[3] To date, there are no data from phase III randomized trials on the preventive effect of raloxifene and aromatase inhibitors specifically in *BRCA1* and *BRCA2* mutation carriers.

PATIENT AND CLINICIAN COMMUNICATION

Uptake of Pharmacologic Interventions for Breast Cancer Risk Reduction

The potential preventive benefit of tamoxifen and raloxifene in women at increased risk of breast cancer has been demonstrated for up to a decade.[21,22,34] It has been estimated that > 2 million women in the United States could benefit from chemoprevention agents.[52] Nevertheless, these agents are infrequently used by women for breast cancer risk reduction, even among those with a favorable risk-benefit profile.[23,53-56] In fact, based on a National Health Interview Survey, there has been little increase in the use of tamoxifen since 2000 and a slight shift toward raloxifene use in postmenopausal women since 2007, but no overall increase in the use of these agents.[53] There are many possible explanations for the low uptake of breast cancer chemoprevention agents, including concerns about adverse effects, lack of potential benefit, and lack of awareness among both women at increased risk and health care providers.[53]

Key issues related to improving the uptake of pharmacologic interventions for breast cancer prevention include: (1) decreasing the gap between a woman's perceived and actual risk, (2) creating new and innovative approaches to communicate risks and benefits related to chemoprevention agents in a more effective manner, (3) improving on the discriminatory accuracy of current breast cancer risk assessment tools, (4) encouraging the assessment of breast cancer risk in the primary care setting, (5) increasing awareness among high-risk women and health care providers about the potential health benefits and the reduction in breast cancer risk, and (5) identifying additional barriers that are associated with reduced uptake of proven chemoprevention agents.

Effective and Responsible Communication

Since the previous guideline publication, there are data from a large study that examine approaches to effective and responsible communication, specifically in women at increased risk of breast cancer.[57-61] More than 2,000 women at increased risk for breast cancer were recruited from two large health care systems. The women were randomly assigned to either the intervention arm, which involved a tailored decision aid that discussed both breast cancer risk and chemoprevention options (tamoxifen and/or raloxifene), or one of two controls arms: one included a questionnaire about chemoprevention and the implementation of a decision aid at the end of the 3-month study, and the other included only a decision aid at 3 months. The decision aid did not improve uptake, despite the fact that patients were only moderately concerned about taking the chemoprevention agents. The larger issue was that > 50% did not perceive that tamoxifen or raloxifene treatment would alter their breast cancer risk. This study did demonstrate that the benefit of graphs to explain statistics related to the risks and benefits of chemoprevention agents and that the order in which risk-benefit information is presented may affect women's risk perception.

Electronic and interactive tools are continuing to emerge as means to enable women to make well-informed and individualized decisions about options for breast cancer risk reduction.[60] Additionally, there are resources for health providers, including a summary of recommendations of how risks and benefits of chemoprevention agents should be communicated to patients, as outlined in the previous guideline and in a recent article by Fagerlin et al.[58,59] These, and other resources, may be useful for patients to refer to, particularly during their discussions with their health care providers (eg, www.cancer.net, www.cancer.org, http://effectivehealthcare.ahrq.gov/ehc/products/50/389/breast%20cancer%20medications%20consumer%20guide.pdf).

Discussions with patients should include the following key points:

- Assessment and discussion of individual risk of developing breast cancer
- Options for reducing the risk of developing breast cancer (ie, nonpharmacologic and pharmacologic)

- Potential impact of specific chemoprevention agents on the incidence of both invasive and noninvasive breast cancers
- Potential risks and adverse effects of chemoprevention agents
- Long-term effectiveness of chemoprevention agents
- Chemoprevention studies were not powered to detect differences in mortality, because it was considered that a reduction in incidence was itself an important clinical end point
- Accessibility, cost, and insurance coverage
- Resources and materials for consideration (eg, www.cancer.net, www.cancer.org, http://effectivehealthcare.ahrq.gov/ehc/products/50/389/breast%20cancer%20medications%20consumer%20guide.pdf)
- Plan for follow-up

HEALTH DISPARITIES

Health disparities are an important consideration in reducing the risk of breast cancer. Since the last guideline, equal access to health care, racially diverse participation in clinical trials, and improved risk assessment models continue to remain challenges in minimizing health disparities.[3]

This clinical practice guideline represents expert recommendations on the best practices in chemoprevention and aims to provide the highest level of evidence for efficacious care for all women at increased risk of breast cancer. However, it is important to note that there are disparities that exist and persist in the quality of health care provided in the United States. Racial, ethnic, and socioeconomic status may affect health outcomes and/or create barriers to access and use of chemoprevention agents to reduce the risk of breast cancer. Emerging data suggest that in addition to age and comorbidities, race is important when considering risk-benefit profiles.[47] Therefore, when available, race-specific estimates should be considered and incorporated into patient and clinician discussions regarding chemoprevention agents.[47] The NCI Breast Cancer Risk Assessment Tool provides racially specific baseline breast cancer incidence estimations when calculating the 5-year and lifetime risks of developing breast cancer (http://www.cancer.gov/bcrisktool/).

Members of racial and ethnic minorities, in general, tend to be diagnosed with cancer at more advanced stages and have worse outcomes.[62] There are complex and diverse reasons for these disparities, which include but are not limited to: financial and insurance status, access to medical attention, language-related barriers, education and awareness, culture, and religious beliefs.[32,63-65] Awareness of these disparities in quality of care and access to care should be considered in the context of this clinical practice guideline. Health care providers should strive to deliver the highest level of cancer care to all patients.

FUTURE DIRECTIONS

Research is needed to address the many unresolved issues related to the poor uptake of breast cancer chemoprevention agents in women who are at increased risk of breast cancer. This includes: (1) the design of effective tools and approaches to educate providers on the option of chemoprevention, (2) efficacious interventions that communicate to eligible women the risks and benefits of specific chemoprevention agents, (3) the development of tools that more accurately identify women at increased risk, and (4) a greater understanding of what disparities and barriers exist with regard to chemoprevention use among women at higher risk for breast cancer. The results from the IBIS-II RCT comparing anastrozole with placebo will add to our understanding of how best to use aromatase inhibitors for breast cancer prevention. The evaluation of novel chemoprevention agents to help prevent both ER-positive and ER-negative breast cancer such as bisphosphonates is also needed.

ADDITIONAL RESOURCES

A Data Supplement and clinical tools and resources can be found on the ASCO Web site (http://www.asco.org/guidelines/bcrr). Patient information is also available at http://www.asco.org/guidelines/bcrr and http://www.cancer.net.

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Affiliations

Kala Visvanathan, Johns Hopkins Medical Institutions; Elissa Bantug, Johns Hopkins Medicine and Sidney Kimmel Comprehensive Cancer Center, Baltimore; Leslie Ford and Barnett Kramer, National Cancer Institute, Bethesda, MD; Patricia Hurley, American Society of Clinical Oncology, Alexandria, VA; Powel Brown, MD Anderson Cancer Center, University of Texas, Houston, TX; Nananda F. Col, University of New England, Biddeford, ME; Jack Cuzick, Queen Mary University of London, London, United Kingdom; Nancy E. Davidson, University of Pittsburgh Cancer Institute and Medical Center Cancer Center, Pittsburgh; Victor G. Vogel III, Geisinger Medical Center Cancer Institute, Danville, PA; Andrea DeCensi, Ente Ospedaliero Ospedali Galliera, Genoa, Italy; Carol Fabian, University of Kansas Medical Center, Kansas City, KS; Judy Garber, Dana-Farber Cancer Institute, Boston, MA; Maria Katapodi, University of Michigan School of Nursing, Ann Arbor, MI; Monica Morrow, Memorial Sloan-Kettering Cancer Center, New York, NY; Barbara Parker and Scott M. Lippman, Moores Cancer Center, University of California, San Diego, San Diego, CA; Carolyn Runowicz, Herbert Wertheim College of Medicine, Florida International University, Miami, FL; and James L. Wade, Cancer Care Specialists of Central Illinois, Decatur, IL.

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Appendix

Table A1. Breast Cancer Risk Reduction Guideline Update Committee

Update Committee Member	Affiliation
Kala Visvanathan, MD, MHS, Co-Chair	Johns Hopkins Medical Institutions, Baltimore, MD
Scott M. Lippman, MD, Co-Chair	Moores Cancer Center, University of California, San Diego, San Diego, CA
Elissa Bantug, MHS	Johns Hopkins Medicine and Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
Powel Brown, MD, PhD	MD Anderson Cancer Center, University of Texas, Houston, TX
Nananda F. Col, MD, MPH	University of New England, Biddeford, ME
Jack Cuzick, PhD	Queen Mary University of London, London, United Kingdom
Nancy E. Davidson, MD	University of Pittsburgh Cancer Institute and Medical Center Cancer Center, Pittsburgh, PA
Andrea DeCensi, MD	Ente Ospedaliero Ospedali Galliera, Genoa, Italy
Carol Fabian, MD	University of Kansas Medical Center, Kansas City, KS
Leslie Ford, MD	National Cancer Institute, Bethesda, MD
Judy Garber, MD, MPH	Dana-Farber Cancer Institute, Boston, MA
Maria Katapodi, PhD, RN, FAAN	University of Michigan School of Nursing, Ann Arbor, MI
Barnett Kramer, MD, MPH	National Cancer Institute, Bethesda, MD
Monica Morrow, MD	Memorial Sloan-Kettering Cancer Center, New York, NY
Barbara Parker, MD	Moores Cancer Center, University of California, San Diego, San Diego, CA
Carolyn Runowicz, MD	Herbert Wertheim College of Medicine, Florida International University, Miami, FL
Victor G. Vogel III, MD	Geisinger Medical Center Cancer Institute, Danville, PA
James L. Wade, MD	Cancer Care Specialists of Central Illinois, Decatur, IL

