Final Recommendation Statement

Breast Cancer: Medication Use to Reduce Risk

September 03, 2019

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Update in Progress for Breast Cancer: Medication to Reduce Risk

Recommendation Summary

Population	Recommendation	Grade
Women at increased risk for breast cancer aged 35 years or older	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects.	**B**
Women not at increased risk for breast cancer aged 35 years or older	The USPSTF recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer.	**D**

Clinician Summary

Population	**Women aged ≥35 years at increased risk for breast cancer**	**Women aged ≥35 years not at increased risk for breast cancer**
Recommendation	**Offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors** **Grade: B**	**Do not routinely use risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors** **Grade: D**

Risk Assessment	Various methods are available to identify women at increased risk for breast cancer, including formal clinical risk assessment tools or assessing breast cancer risk factors without using a formal tool. The USPSTF does not endorse any particular risk-prediction tool. The National Cancer Institute Breast Cancer Risk Assessment Tool and the Breast Cancer Surveillance Consortium Risk Calculator are based on models tested in US populations and are publicly available. There is no single cutoff for defining increased risk for all women. Alternatively, clinicians may use combinations of risk factors to identify women at increased risk. Some examples of combinations of multiple risk factors in women at increased risk include (but are not limited to): age 65 years or older with 1 first-degree relative with breast cancer; age 45 years or older with more than 1 first-degree relative with breast cancer or 1 first-degree relative who developed breast cancer before age 50 years; age 40 years or older with a first-degree relative with bilateral breast cancer; presence of atypical ductal or lobular hyperplasia or lobular carcinoma in situ on a prior biopsy. When considering prescribing breast cancer risk-reducing medications, the potential benefit of risk reduction of breast cancer must be balanced against the potential harms of adverse medication effects
Risk-Reducing Medications	Tamoxifen, raloxifene, and aromatase inhibitors all reduce primary breast cancer risk in post-menopausal women. Use of raloxifene and aromatase inhibitors is indicated only in postmenopausal women; only tamoxifen is indicated for risk-reduction of primary breast cancer in premenopausal women.
Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for breast cancer and for risk assessment, genetic counseling, and genetic testing for *BRCA* genetic mutations.

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to http://www.uspreventiveservicestaskforce.org.

View the Clinician Summary in PDF

Additional Information

Evidence Summary (September 03, 2019)

Final Evidence Review (September 03, 2019)

Final Research Plan (July 20, 2017)

Recommendation Information

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Full Recommendation:

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Preface

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Rationale

Importance

Breast cancer is the most common nonskin cancer among women in the United States and the second leading cause of cancer death.[1,2] The median age at diagnosis is 62 years,[1] and an estimated 1 in 8 women will develop breast cancer at some point in their lifetime.[2] African American women are more likely to die of breast cancer compared with women of other races.[1]

Assessment of Breast Cancer Risk Status

The USPSTF found convincing evidence that available risk assessment tools can predict the number of cases of breast cancer expected to develop in a population. However, these risk assessment tools perform modestly at best in discriminating between individual women who will or will not develop breast cancer over time. Overall, the USPSTF determined that the net benefit of

taking medications to reduce risk of breast cancer is larger in women who have a greater risk for developing breast cancer.

Potential Benefits of Risk-Reducing Medications

The USPSTF found convincing evidence that risk-reducing medications (tamoxifen, raloxifene, or aromatase inhibitors) provide at least a moderate benefit in reducing risk for invasive estrogen receptor (ER)–positive breast cancer in postmenopausal women at increased risk for breast cancer (Table).

Both tamoxifen and raloxifene can reduce risk of some types of skeletal fractures, independent from the risk of breast cancer.

The USPSTF found that the benefits of taking tamoxifen, raloxifene, and aromatase inhibitors to reduce risk for breast cancer are no greater than small in women not at increased risk for the disease.

Potential Harms of Risk-Reducing Medications

The USPSTF found convincing evidence that tamoxifen and raloxifene are associated with small to moderate harms. Tamoxifen and raloxifene increase risk for venous thromboembolic events (VTEs); tamoxifen increases risk more than raloxifene (Table), and the potential for harms are greater in older women than in younger women. The USPSTF also found adequate evidence that tamoxifen, but not raloxifene, increases risk for endometrial cancer in women with a uterus. Tamoxifen also increases risk of cataracts. Vasomotor symptoms (hot flashes) are a common adverse effect of both medications.

The USPSTF found adequate evidence that the harms of aromatase inhibitors are also small to moderate. These harms include vasomotor symptoms, gastrointestinal symptoms, musculoskeletal pain, and possible cardiovascular events, such as stroke. Aromatase inhibitors do not reduce, and may even increase, risk of fractures.

USPSTF Assessment

The USPSTF concludes with moderate certainty that there is a moderate net benefit from taking tamoxifen, raloxifene, or aromatase inhibitors to reduce risk of invasive breast cancer in women at increased risk.

The USPSTF concludes with moderate certainty that the potential harms of taking tamoxifen, raloxifene, and aromatase inhibitors to reduce risk of breast cancer outweigh the potential benefits in women not at increased risk for the disease.

Clinicians should discuss the limitations of current clinical risk assessment tools for predicting an individual's future risk of breast cancer when discussing the benefits and harms of risk-reducing medications with women.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to asymptomatic women 35 years and older, including women with previous benign breast lesions on biopsy (such as atypical ductal or lobular hyperplasia and lobular carcinoma in situ). This recommendation does not apply to women who have a current or previous diagnosis of breast cancer or ductal carcinoma in situ (DCIS).

Assessment of Risk for Breast Cancer

Various methods are available to identify women at increased risk for breast cancer, including formal clinical risk assessment tools or assessing breast cancer risk factors without using a formal tool.

Numerous risk assessment tools, such as the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool,[5] estimate a woman's risk of developing breast cancer over the next 5 years. There is no single cutoff for defining increased risk for all women. Women at greater risk, such as those with at least a 3% risk for breast cancer in the next 5 years, are likely to derive more benefit

than harm from risk-reducing medications[6] and should be offered these medications if their risk of harms is low. Some women at lower risk for breast cancer have also been included in trials documenting reduced risk for breast cancer when taking tamoxifen, raloxifene, or aromatase inhibitors.[3,4] However, when balancing the harms associated with these medications, the net benefit will be lower among women at lower risk.

Alternatively, clinicians may use combinations of risk factors (including some risk factors not included in risk assessment tools but that would have permitted enrollment in some of the risk reduction trials) to identify women at increased risk. Some examples of combinations of multiple risk factors in women at increased risk include (but are not limited to) age 65 years or older with 1 first-degree relative with breast cancer; 45 years or older with more than 1 first-degree relative with breast cancer or 1 first-degree relative who developed breast cancer before age 50 years; 40 years or older with a first-degree relative with bilateral breast cancer; presence of atypical ductal or lobular hyperplasia or lobular carcinoma in situ on a prior biopsy.

Women with documented pathogenic mutations in the breast cancer susceptibility 1 and 2 genes (*BRCA1/2*) and women with a history of chest radiation therapy (such as for treatment of childhood or adolescent Hodgkin or non-Hodgkin lymphoma) are at especially high risk for breast cancer. The cumulative absolute risk of developing breast cancer in a woman who received chest radiation at age 25 years increases from an estimated 1.4% at age 35 years to an estimated 29% by age 55 years,[7] although this may vary by treatment regimen. Women who carry a *BRCA1* mutation have a cumulative risk for breast cancer of 72% by age 80 years; women who carry a *BRCA2* mutation have a 69% cumulative risk[8] (compared with a 12% lifetime risk in the general population[9]). Women who carry the *BRCA1* mutation tend to develop estrogen receptor (ER)–negative breast cancer,[10] while women who carry the *BRCA2* mutation tend to develop ER-positive breast cancer. However, the USPSTF was not able to find sufficient evidence on the benefits and harms of risk-reducing medications in women with *BRCA1/2* gene mutations or women with a history of chest radiation, and the comprehensive management of these risk factors is beyond the scope of this Recommendation Statement. Further information on comprehensive management strategies, including risk-reducing medications, for women with these conditions is available from other organizations.

Women not at increased risk for breast cancer, such as women younger than 60 years with no additional risk factors for breast cancer, or women with a low 5-year risk of breast cancer should not be routinely offered medications to reduce risk of breast cancer, since the risk of harms from these medications likely outweighs their potential benefit.

Although evidence on the best interval at which to reassess risk and indications for risk-reducing medications is not available, a pragmatic approach would be to repeat risk assessment when there is a significant change in breast cancer risk factors, for instance when a family member is diagnosed with breast cancer or when there is a new diagnosis of atypical hyperplasia or lobular carcinoma in situ on breast biopsy.

When considering prescribing breast cancer risk-reducing medications, potential benefit of risk reduction of breast cancer must be balanced against the potential harms of adverse medication effects. See below for more information on potential harms from risk-reducing medications.

Risk-Reducing Medications

A systematic review of trials conducted for the USPSTF found that compared with placebo, tamoxifen reduced the incidence of invasive breast cancer by 7 events per 1000 women over 5 years (95% CI, 4-12), and raloxifene reduced incidence by 9 events (95% CI, 3-15) per 1000 women over 5 years.[3,4] Given that the study participants in tamoxifen vs placebo and raloxifene vs placebo trials differed with respect to breast cancer risk and age, direct comparisons of effectiveness between tamoxifen and raloxifene cannot be made based on these placebo-controlled trials. However, the large Study of Tamoxifen and Raloxifene (STAR) trial, which directly compared tamoxifen with raloxifene, found that tamoxifen reduced breast cancer risk more than raloxifene after long-term follow-up[3] (Table). For women with a predicted 5-year breast cancer risk of 3% or greater, the absolute benefits are likely even higher. Tamoxifen and raloxifene have been found to reduce risk for nonvertebral and vertebral fractures, respectively.[3] However, use of tamoxifen and raloxifene is also associated with increased risk for VTEs and vasomotor symptoms. Tamoxifen also increases the risk for endometrial cancer and cataracts. These risks are increased in older women, although women who have had a hysterectomy are not at risk for endometrial cancer.

Aromatase inhibitors were found to reduce the incidence of invasive breast cancer by 16 events per 1000 women over 5 years (Table).[3] As with tamoxifen and raloxifene, these absolute benefits are likely even higher for women with a predicted breast cancer risk of 3% or greater. Harms of aromatase inhibitors include vasomotor symptoms, gastrointestinal symptoms, and musculoskeletal pain. Data on harms of aromatase inhibitors for the primary risk reduction of breast cancer are limited, especially long-term harms. A trend toward increased cardiovascular events (such as transient ischemic attack and cerebrovascular

accident) has been observed in some aromatase inhibitor trials for treatment of women with early-stage breast cancer (or DCIS).[3,11,12] Younger women with no risk factors for cardiovascular disease are less likely to have a cardiovascular event with aromatase inhibitor treatment. Aromatase inhibitors do not reduce, and may even increase, risk of fractures.

Tamoxifen, raloxifene, and aromatase inhibitors all reduce primary breast cancer risk in postmenopausal women. Use of raloxifene and aromatase inhibitors is indicated only in postmenopausal women; only tamoxifen is indicated for risk-reduction of primary breast cancer in premenopausal women.

Duration of Medication Use and Persistence of Effects

In trials, participants typically used risk-reducing medications for 3 to 5 years.[3] Benefits of tamoxifen have been found to persist up to 8 years beyond discontinuation,[13,14] whereas risk for VTEs and endometrial cancer return to baseline after discontinuation of tamoxifen.[15] Data on similarly long-term persistence of effects are not available for raloxifene or aromatase inhibitors.

Additional Approaches to Prevention

The USPSTF has made recommendations on screening for breast cancer[16] and for risk assessment, genetic counseling, and genetic testing for *BRCA* genetic mutations.[17] The NCI and the Centers for Disease Control and Prevention provide information about potential ways to reduce risk of cancer, including lifestyle and diet changes.[18,19]

Useful Resources

The USPSTF does not endorse any particular risk prediction tool. However, the NCI Breast Cancer Risk Assessment Tool[5] and the Breast Cancer Surveillance Consortium Risk Calculator[20] are based on models tested in US populations and are publicly available for clinicians and patients to use as part of the process of shared, informed decision-making about taking risk-reducing medications for breast cancer. Both tools have been calibrated in US populations, but their discriminatory accuracy of predicting which women will develop breast cancer may be more limited and there is no single cutoff for defining increased risk for all women.

Other Considerations

Implementation

Prescribing risk-reducing medications for breast cancer is an uncommon practice among primary care clinicians. Based on limited survey data, 10% to 30% (depending on medication type) of primary care clinicians report ever prescribing risk-reducing medications for primary prevention of breast cancer, and most have only done so a few times.[21-23] The reported use of risk-reducing medications among women is also relatively low; 1 meta-analysis of 26 studies found that overall, 16.3% of women at increased risk for breast cancer used risk-reducing medications.[24] Although only exploratory, a number of studies have suggested that even women who are well informed about the risks and benefits have relatively little interest in taking risk-reducing medications for breast cancer and are primarily concerned with potential harms.[25-29] When considering prescribing risk-reducing medications for breast cancer, clinicians should discuss each woman's personal values and preferences with respect to breast cancer risk reduction, in addition to what is known about her personal risk for breast cancer and the potential benefits and harms of medications.

Research Needs and Gaps

More research is needed to better identify which individual women at increased risk for breast cancer could best benefit from risk-reducing medications. In particular, studies are needed that evaluate how medications may reduce breast cancer risk in women who are carriers of pathogenic *BRCA1* or *BRCA2* mutations. Additionally, given the higher breast cancer mortality rates in African American women, studies that include sufficient numbers of African American women are needed to better understand

how medications may reduce risk in these women. Although currently available risk assessment tools can identify the number of cases of breast cancer expected to arise in a given population, better tools for predicting breast cancer risk in individual women are needed. Additionally, longer-term follow-up is needed for studies of raloxifene and aromatase inhibitors to better understand the persistence of both breast cancer risk reduction effects and potential harms from the medications. Longer-term data on harms of aromatase inhibitors for the risk reduction of primary breast cancer are also needed. This information could help clinicians weigh the benefits and harms of individual medications with their patients.

Discussion

Burden of Disease

Breast cancer is the most common nonskin cancer and the second leading cause of cancer death in women.[2] In 2018, an estimated 266,120 new cases of breast cancer were diagnosed in women in the United States, representing 30% of all new cancer cases in women.[2] An estimated 40,920 women in the United States died of breast cancer, representing 14% of all cancer deaths in women.[2] Based on data from 2008 to 2014, the 5-year survival rate of breast cancer is an estimated 89.7%, ranging from 98.7% when cancer is diagnosed at localized stages to 27% when diagnosis occurs in the context of distant metastases.[1] Although incidence rates are similar among white and African American women (128.6 vs 126.9 cases per 100,000 persons, respectively), mortality rates are higher among African American women (28.7 deaths per 100,000 African American persons vs 20.3 deaths per 100,000 white persons).[1] Incidence rates have increased among Asian/Pacific Islander, non-Hispanic African American, and Hispanic women but have remained stable among non-Hispanic white and American Indian/Alaskan Native women.[9]

Scope of Review

The USPSTF reviewed evidence on the accuracy of risk assessment methods to identify women who could benefit from risk-reducing medications for breast cancer, as well as evidence on the effectiveness, adverse effects, and subgroup variations of these medications (specifically, the selective ER modulators tamoxifen and raloxifene and the aromatase inhibitors exemestane and anastrozole).[3,4] The USPSTF reviewed evidence from randomized trials, observational studies, and diagnostic accuracy studies of risk stratification models in women without preexisting breast cancer or DCIS. Studies that included women with pathogenic *BRCA1/2* genetic mutations were included in the review criteria; however, studies to understand the benefits and harms in this population were limited.

Effectiveness of Risk Assessment Models

The USPSTF reviewed evidence from 25 good- and fair-quality studies on 18 risk stratification models (n >5,000,000).[3,4] Models reviewed included the Gail,[30-36] Breast Cancer Surveillance Consortium,[37-39] Rosner-Colditz,[40-43] Tyrer-Cuzick,[44-47] Chlebowski,[48] and Italian[49-51] models, as well as variations of these models that focus on specific subpopulations or that include newer data on breast density or benign breast disease.[3]

The original Gail model, the first model used clinically, includes age, age at first menstruation, age at first childbirth, family history of breast cancer in first-degree relatives, number of prior breast biopsies, and history of atypical hyperplasia.[30] The current version of the Gail model is used in the Breast Cancer Risk Assessment Tool, which is publicly accessible through the NCI website.[5] Expanding on the Gail model, newer models include race/ethnicity, prior false-positive mammography results or benign breast disease, body mass index or height, estrogen and progestin use, history of breastfeeding, menopause status or age, smoking, alcohol use, physical activity, education, breast density, and diet.

Several models have been tested in large US populations in good-quality studies that reported only low to modest accuracy. The Breast Cancer Surveillance Consortium model was derived from more than 11,638 breast cancer cases that developed among a cohort of almost 2.4 million women.[38] The Rosner-Colditz model was derived from 1761 breast cancer cases that developed among 58,520 participants in the Nurses' Health Study.[40] Chlebowski and colleagues[48] developed a model based on 3236 cases that developed in the Women's Health Initiative study. Models from Italy[49-51] and the United Kingdom[44-47] were also based on large populations but were not tested in the United States. Although these models demonstrate good calibration for predicting risk in a population (ie, the predicted number of breast cancer cases expected to arise in a population closely matched the

observed number of cases), their discriminatory accuracy to correctly classify individual women who will develop breast cancer over the next 5 years from those who will not is modest at best; the C statistic for most models ranged from 0.55 to 0.65.[3] Models that include breast density, postmenopausal hormone use, and a more extensive family history minimally improve predictive estimates.

Most models report performance slightly better than age alone as a risk predictor. No studies evaluated optimal ages or frequencies for risk assessment.[3]

Effectiveness of Risk-Reducing Medications

The USPSTF reviewed evidence from 10 trials that evaluated the effect of risk-reducing medications for breast cancer.[3,4] Four trials (n = 28,193) evaluated tamoxifen in premenopausal and postmenopausal women at increased risk for breast cancer[13-15,52-60] (in 1 additional trial of low-dose tamoxifen in postmenopausal women not at increased risk for breast cancer,[61] the low dose was not found to reduce risk of breast cancer and so was not considered further by the USPSTF); 2 trials (n = 17,806) evaluated raloxifene in postmenopausal women not at increased risk for breast cancer,[62-78] 1 trial (n = 19,747) directly compared raloxifene with tamoxifen in postmenopausal women at increased risk for breast cancer (STAR trial[79-81]), and 2 trials evaluated aromatase inhibitors (examestane[82,83] [n = 4560] and anastrozole[84-86] [n = 3864]) in postmenopausal women at increased risk for breast cancer. Each of the studies that targeted women at increased risk for breast cancer used different combinations of risk criteria, such as age, family history, previous abnormal but benign breast pathology, or predicted breast cancer risk as estimated by a risk tool (most commonly >1.66% 5-year predicted risk of breast cancer, as calculated by the Gail model) to recruit participants. Women in the raloxifene trials were older (median age, 67-67.5 years)[3] than women in the other trials, given that these trials targeted postmenopausal women not at increased risk for breast cancer (the primary aim was for outcomes other than breast cancer risk reduction). In contrast, women in the tamoxifen trials were slightly younger, given that these trials included premenopausal women (median age range, 47-53 years).[3] Most trials were multicenter and conducted in numerous sites across several countries, predominantly in the United States, the United Kingdom, and Europe. Most trial participants were white (84%-97% white in studies that reported this information).[3]

In trials, all 3 types of medications reduced invasive and ER-positive breast cancer but not ER-negative breast cancer.[3] Using pooled results of the placebo-controlled trials and projecting benefits over 5 years, the use of tamoxifen would result in 7 fewer cases of invasive breast cancer (risk ratio [RR], 0.69 [95% CI, 0.59-0.84]) and 8 fewer cases of ER-positive breast cancer (RR, 0.58 [95% CI, 0.42-0.81]) (unless otherwise stated, all numbers of cases are per 1000 women over 5 years of medication use).[3] Raloxifene use would result in 9 fewer cases of invasive breast cancer (RR, 0.44 [95% CI, 0.24-0.80]) and 8 fewer cases of ER-positive breast cancer (RR, 0.33 [95% CI, 0.15-0.73]).[3] Furthermore, in addition to reducing breast cancer risk, tamoxifen and raloxifene were also found to reduce risk for fractures: 3 fewer cases of nonvertebral fractures with tamoxifen (RR, 0.66 [95% CI, 0.45-0.98]) and 7 fewer cases of vertebral fractures with raloxifene (RR, 0.61 [95% CI, 0.53-0.70]).[3] Aromatase inhibitors would result in 16 fewer cases of invasive breast cancer (RR, 0.45 [95% CI, 0.26-0.70]) and 15 fewer cases of ER-positive breast cancer (RR, 0.37 [95% CI, 0.19-0.63]).[3] Risk reduction of both invasive and ER-positive breast cancer persisted up to 8 years after discontinuation of tamoxifen use in 2 trials[14,15] (data on similar length of long-term follow-up for raloxifene and aromatase inhibitors are not currently available). Effectiveness of medications (within trials) did not vary by age or menopausal status. One trial of tamoxifen[60] and 1 of anastrazole[84] found that risk reduction was greater for women with a history of breast abnormalities on biopsy, such as atypical hyperplasia or lobular carcinoma in situ. Most trials that reported on subpopulation results by 5-year predicted risk category (as determined by the Gail model) showed risk reduction across all risk categories,[3,60,78,80,83] and 1 study of tamoxifen also indicated that risk reduction may be greatest in the highest-risk groups.[3,60]

Although comparisons of effectiveness between the 3 medication types (tamoxifen, raloxifene, and aromatase inhibitors) cannot be made because of the different participant characteristics among the placebo-controlled trials, the large STAR trial directly compared tamoxifen with raloxifene for breast cancer risk reduction and found that tamoxifen provided a greater risk reduction for invasive breast cancer on long-term follow-up (5 fewer cases [95% CI, 1-9]).[3]

Potential Harms of Risk Assessment and Risk-Reducing Medications

The same 10 trials described above that reported on benefits of risk-reducing medications for breast cancer also reported harms.[3,4] When compared with placebo, tamoxifen was associated with 5 more cases of VTEs (RR, 1.93 [95% CI, 1.33-2.68]), 4 more cases of endometrial cancer (RR, 2.25 [95% CI, 1.17-4.41]), and 26 more cases of cataracts (RR, 1.22 [95% CI, 1.08-1.48]).[3] Vasomotor

symptoms were also increased with tamoxifen use. No significant differences were found with tamoxifen use on rates of deep vein thrombosis, pulmonary embolism, coronary heart disease (CHD) events, or stroke.[3]

When compared with placebo, raloxifene was associated with 7 more cases of VTE (RR, 1.56 [95% CI, 1.11-2.60]).[3] Vasomotor symptoms were also increased with raloxifene use. No significant differences were found with raloxifene use on rates of CHD events, stroke, endometrial cancer, or cataracts. Based on the STAR trial, more harms were reported with tamoxifen compared with raloxifene: 4 more cases of VTE (95% CI, 1-7), 3 more cases of deep vein thrombosis (95% CI, 1-5), 5 more cases of endometrial cancer (95% CI, 2-9), and 15 more cases of cataracts (95% CI, 8-22) with tamoxifen than with raloxifene.[3] Both aromatase inhibitor trials reported more vasomotor and musculoskeletal symptoms with aromatase inhibitors compared with placebo.[3,82-84] No significant differences in rates of VTEs, deep vein thrombosis, pulmonary embolism, CHD events, stroke, endometrial cancer, or cataracts were reported for aromatase inhibitors;[3,82-84] however, primary prevention studies were likely underpowered to detect any differences in these outcomes.

Other studies have evaluated the use of aromatase inhibitors for indications other than risk reduction of primary breast cancer. A recent meta-analysis of trials that evaluated extended aromatase inhibitor use for adjuvant treatment in women with early-stage ER-positive breast cancer suggests a potential increase in cardiovascular disease events (odds ratio [OR], 1.18 [95% CI, 1.00-1.40]; 7 studies; n = 16,349) with aromatase inhibitors compared with placebo or no treatment.[12] Another study that compared anastrozole with tamoxifen in treating women with DCIS found a significant increase in cerebrovascular events (OR, 3.36 [95% CI, 1.04-14.18]) and a nonsignificant increase in transient ischemic attacks (OR, 2.69 [95% CI, 0.90-9.65]) with anastrozole.[11] Another meta-analysis that evaluated studies of aromatase inhibitors compared with tamoxifen for treatment of early-stage breast cancer found no difference in VTEs, cerebrovascular events, or coronary artery disease events.[87] Literature from these other studies also suggest that aromatase inhibitors may increase the risk of fractures. Compared with tamoxifen (which reduces risk of fractures), more fractures were seen with aromatase inhibitors.[11,87] The meta-analysis that evaluated extended use of aromatase inhibitors compared with placebo or no treatment also found increased fractures associated with aromatase inhibitors (OR, 1.34 [95% CI, 1.16-1.55]); however, some of the participants who received placebo or no treatment in the extended treatment period may have received tamoxifen or raloxifene during the initial treatment period.[12] Given that these studies focused on treatment of women with breast cancer or DCIS and were often conducted in comparison with tamoxifen rather than placebo, it is unclear whether these findings are generalizable to a primary prevention population.

Estimate of Magnitude of Net Benefit

Whether risk-reducing medications provide a net benefit depends on a woman's risk for breast cancer, balanced with the potential for harms from the medications. Accordingly, the USPSTF recommendation for women at low risk for breast cancer is different than its recommendation for women at increased risk.

For women at increased risk for breast cancer, the USPSTF concludes with moderate certainty that taking medications to reduce risk for breast cancer confer a moderate net benefit. Tamoxifen is associated with a greater risk reduction of breast cancer compared with raloxifene but also with a greater risk of endometrial cancer (in women with a uterus), cataracts, and VTEs. These risks increase with age. Both tamoxifen and raloxifene decrease risk of fractures but increase risk of vasomotor symptoms. Aromatase inhibitors also decrease risk of breast cancer in women at increased risk for the disease. No studies are currently available that compare aromatase inhibitors with tamoxifen or raloxifene for risk reduction of primary breast cancer. Some trials of aromatase inhibitors used for the treatment of women with early-stage breast cancer or DCIS suggest that there may be a small increase in cardiovascular disease, such as stroke, with aromatase inhibitors; compared with tamoxifen, which reduces risk of fractures, aromatase inhibitors increase risk of fractures. Whether aromatase inhibitors increase risk of fractures compared with placebo or no treatment is unclear.

For women not at increased risk for breast cancer, the USPSTF found that tamoxifen, raloxifene, and aromatase inhibitors provide only a small benefit in reducing risk for breast cancer but are associated with moderate harms. Overall, the USPSTF concludes with moderate certainty that the potential harms of tamoxifen, raloxifene, and aromatase inhibitors outweigh the potential benefits in women at low risk of breast cancer.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from January 15 to February 11, 2019. In response to comments received, the USPSTF has clarified that the recommendation statement does not list every scenario in which medications could be considered but rather provides information on risk factors that clinicians could

consider in assessing breast cancer risk with their patients. Some examples are provided to help clinicians understand how to consider these risk factors, but these examples should not be interpreted as a definitive list. Some comments expressed concern that the USPSTF was recommending risk-reducing medications at a lower 5-year breast cancer risk threshold than previously. The USPSTF has not lowered its risk threshold for which it has found a net benefit with risk-reducing medications. Instead, the current recommendation acknowledges the uncertainty around relying on a specific threshold calculated by risk assessment tools to identify women who may benefit from risk-reducing medications and offers an alternative approach to risk assessment of women, which includes clinician consideration of clinical risk factors. Some comments also expressed concern that the USPSTF was no longer recommending "shared, informed decision making." As with all of its recommendations, the USPSTF encourages clinicians to discuss with patients the risks and benefits of clinical preventive services in the context of each individual's personal health values and preferences when considering a service. Language clarifying this has been added to the Clinical Considerations section. Last, as requested, additional information is provided on selection of medications and menopausal status, and information on harms of aromatase inhibitors has been clarified in the Clinical Considerations section.

How Does Evidence Fit With Biological Understanding?

Tamoxifen and raloxifene are selective ER modulators that inhibit ERs in breast tissue and reduce risk for ER-positive breast cancer by blocking the proliferation of estrogen-sensitive epithelial cells where breast cancer can develop. These medications have been approved by the US Food and Drug Administration for risk reduction of breast cancer. Aromatase inhibitors inhibit conversion of androgen to estrogen and can reduce risk of ER-positive breast cancer by decreasing the amount of estrogen available to bind to estrogen-sensitive epithelial cells. Aromatase inhibitors have been evaluated for risk reduction of breast cancer in clinical trials, although they are primarily used for treatment rather than risk reduction of primary cancer. Aromatase inhibitors are not currently approved by the US Food and Drug Administration for risk reduction of primary breast cancer.

Update of Previous USPSTF Recommendation

This recommendations is consistent with the 2013 USPSTF recommendation.[88] As before, the USPSTF recommends offering risk-reducing medications to women at increased risk for breast cancer and at low risk for adverse medication effects (B recommendation) and recommends against routine use of risk-reducing medications in women not at increased risk (D recommendation). The current recommendation now includes aromatase inhibitors among medications that can reduce risk of breast cancer.

Recommendations of Others

In 2013, the American Society of Clinical Oncology recommended discussing tamoxifen as an option to reduce risk of breast cancer in women at increased risk who are 35 years and older. It also recommended that raloxifene and exemestane be discussed as additional options for risk reduction in postmenopausal women.[89] The National Comprehensive Cancer Network recommends risk-reducing agents for women 35 years and older and tamoxifen for premenopausal women only; tamoxifen, raloxifene, anastrozole, or exemestane may be used in postmenopausal women.[90] The American College of Obstetricians and Gynecologists states that the risk-reduction agents tamoxifen and raloxifene (in postmenopausal women) may be considered for breast cancer risk reduction in *BRCA* mutation carriers.[91] Given the protective effects in other at-risk populations, aromatase inhibitors may be an alternative for women who cannot take tamoxifen.[91] Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia and cancer.[92] The American Academy of Family Physicians supports the 2013 USPSTF recommendation.[93] The American Cancer Society does not have formal recommendations on the use of risk-reducing medications for breast cancer.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Authors followed the policy regarding conflicts of interest described at https://www.uspreventiveservicestaskforce.org/Page/Name/conflict-of-interest-disclosures. Dr Barry reported receiving grants and personal fees from Healthwise, a nonprofit, outside the submitted work. All members of the USPSTF receive travel reimbursement and an honorarium for participating in USPSTF meetings.

Funding/Support: The USPSTF is an independent, voluntary body. The US Congress mandates that the Agency for Healthcare Research and Quality (AHRQ) support the operations of the USPSTF.

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Table. Benefits and Harms of Risk-Reducing Medications Estimated From Meta-Analysis of Randomized, Placebo-Controlled Trials

Outcome	Tamoxifen	Raloxifene	Aromatase Inhibitors
Benefits: Events Reduced (95% CI)[a]			
Breast cancer			
Invasive	7 (4-12)	9 (3-15)	16 (8-24)
ER+	8 (4-13)	8 (4-13)	15 (8-20)
ER-	ND	ND	ND
Noninvasive	ND	ND	ND
Mortality			
Breast cancer	ND	NR	NR
All-cause	ND	ND	ND
Fracture			
Vertebral	ND	7 (5-9)	ND
Nonvertebral	3 (0.2-5)	ND	ND
Harms: Events Increased (95% CI)[a]			
Vascular			
Venous thromboembolic event	5 (2-9)	7 (0.3-17)	ND
Deep vein thrombosis	ND	ND	NR
Pulmonary embolism	ND	ND	NR
Coronary heart disease events	ND	ND	ND

Other			
Endometrial cancer	4 (1-8)	ND	ND
Cataracts	26 (5-50)[b]	ND	ND

Note: See Nelson et al.[3,4] Trials included women whose 5-year risk of breast cancer may have been lower than 3%.

a Per 1,000 women over 5 years of use.

b Results from the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) trial.

Abbreviations: ER–, estrogen receptor–negative; ER+, estrogen receptor–positive; ND, no difference; NR, not reported.