U.S. Preventive Services Task Force

Medications for Risk Reduction of Primary Breast Cancer in Women: Recommendation Statement

This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

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A collection of USPSTF recommendation statements published in *AFP* is available at http://www.aafp.org/afp/uspstf.

Summary of Recommendations and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians engage in shared, informed decision making with women who are at increased risk of breast cancer about medications to reduce their risk. For women who are at increased risk of breast cancer and at low risk of adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene *(Table 1)*. **B recommendation.**

See the Clinical Considerations section for additional information about risk factors.

The USPSTF recommends against the routine use of medications, such as tamoxifen or raloxifene, for risk reduction of primary breast cancer in women who are not at increased risk of breast cancer. **D recommendation.**

Rationale

IMPORTANCE

Breast cancer is the most common nonskin cancer in women. An estimated 232,340 new cases will be diagnosed in 2013, and 39,620 women will die of the disease.[1] In the United States, mortality rates are highest among black women. Screening for breast cancer may allow for early detection but does not prevent the development of the disease.

Tamoxifen and raloxifene are selective estrogen receptor modulators that have been shown in randomized controlled trials to reduce the risk of estrogen receptor–positive breast cancer. They have been approved by the U.S. Food and Drug Administration for this indication.

ASSESSMENT OF BREAST CANCER RISK STATUS

Important risk factors for breast cancer include increasing age, family history of breast or ovarian cancer (especially among first-degree relatives and onset before 50 years of age), history of atypical hyperplasia or other nonmalignant high-risk breast lesions, previous breast biopsy, and extremely dense breast tissue. A history of these or other risk factors (see the Clinical Considerations) may prompt clinicians to conduct a formal breast cancer risk assessment.

Available risk assessment models can accurately estimate the number of breast cancer cases that may arise in certain study populations, but their ability to accurately predict which women will (and will not) develop the disease is modest. Only a small fraction of women are at increased risk of breast cancer; moreover, only a subset of those women will derive benefit from risk-reducing medications.

Information about the validity, feasibility, and effect of using risk assessment models to identify appropriate candidates for risk-reducing medications in primary care settings is limited.[2-4]

POTENTIAL BENEFITS OF MEDICATIONS FOR BREAST CANCER RISK REDUCTION

The USPSTF found adequate evidence that treatment with tamoxifen or raloxifene can significantly reduce the relative risk of invasive estrogen receptor–positive breast cancer in postmenopausal women who are at increased risk of breast cancer.

A systematic review of clinical trials found that tamoxifen and raloxifene reduced the incidence of invasive breast cancer by seven to nine events per 1,000 women over five years and that tamoxifen reduced breast cancer incidence more than raloxifene[5-7] (see table at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction). Tamoxifen also reduces the incidence of invasive breast cancer in premenopausal women who are at increased risk of the disease.

Table 1. Medications for Risk Reduction of Primary Breast Cancer in Women: Clinical Summary of the USPSTF Recommendation

Population	Asymptomatic women 35 years or older without a prior diagnosis of breast cancer who are at increased risk of the disease	Asymptomatic women 35 years or older without a prior diagnosis of breast cancer who are not at increased risk of the disease
Recommendation	Engage in shared, informed decision making and offer to prescribe risk-reducing medications, if appropriate. Grade: B	Do not prescribe risk-reducing medications. Grade: D
Risk assessment	Important risk factors for breast cancer include patient age, race/ethnicity, age at menarche, age at first live childbirth, personal history of ductal or lobular carcinoma in situ, number of first-degree relatives with breast cancer, personal history of breast biopsy, body mass index, menopause status or age, breast density, estrogen and progestin use, smoking, alcohol use, physical activity, and diet. Available risk assessment models can accurately predict the number of breast cancer cases that may arise in certain study populations, but their ability to accurately predict which women will develop breast cancer is modest.	
Preventive medications	The selective estrogen receptor modulators tamoxifen and raloxifene have been shown to reduce the incidence of invasive breast cancer in postmenopausal women who are at increased risk of the disease. The usual daily doses for tamoxifen and raloxifene are 20 and 60 mg, respectively, for five years.	
Balance of benefits and harms	There is a moderate net benefit from use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk of the disease.	The potential harms of tamoxifen and raloxifene outweigh the potential benefits for breast cancer risk reduction in women who are not at increased risk of the disease. Potential harms include thromboembolic events, endometrial cancer, and cataracts.
Other relevant USPSTF recommendations	The USPSTF has made recommendations on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer, as well as screening for breast cancer. These recommendations are available at http://www.uspreventiveservicestaskforce.org/.	

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

USPSTF = U.S. Preventive Services Task Force.

Women who are at increased risk of breast cancer are more likely to benefit from risk-reducing medications. In general, women with an estimated five-year risk of 3% or greater are, on the basis of model estimates,[8] more likely to benefit from tamoxifen or raloxifene (see figures at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction). The USPSTF found that the benefits of tamoxifen and raloxifene for breast cancer risk reduction are no greater than small in women who are not at increased risk of the disease.

In addition to breast cancer risk reduction, the USPSTF found adequate evidence that tamoxifen and raloxifene reduce the risk of nonvertebral and vertebral fractures, respectively, in postmenopausal women.

POTENTIAL HARMS OF MEDICATIONS FOR BREAST CANCER RISK REDUCTION

The USPSTF found adequate evidence that tamoxifen and raloxifene increase the risk of venous thromboembolic events by four to seven events per 1,000 women over five years and that tamoxifen increases the risk more than raloxifene[5-7] (see table at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction). The USPSTF found that the potential harms from thromboembolic events are small to moderate, with increased potential for harms in older women.

The USPSTF also found adequate evidence that tamoxifen but not raloxifene increases the risk of endometrial cancer (four more cases per 1,000 women). Potential

harms from tamoxifen-related endometrial cancer are small to moderate and depend on hysterectomy status and age. The potential risks of tamoxifen-related harms are higher in women older than 50 years and in women with a uterus. Tamoxifen may also increase the incidence of cataracts.

Vasomotor symptoms (hot flashes), a common adverse effect of both medications that is not typically classified as serious, may affect a patient's quality of life and willingness to use or adhere to these medications.

USPSTF ASSESSMENT

The USPSTF concludes with moderate certainty that there is a moderate net benefit from use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk of the disease. The USPSTF concludes with moderate certainty that the potential harms of tamoxifen and raloxifene outweigh the potential benefits for breast cancer risk reduction in women who are not at increased risk of the disease.

Clinical Considerations

PATIENT POPULATION

This recommendation applies to asymptomatic women 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ. Neither tamoxifen nor raloxifene should be used in women who have a history of thromboembolic events (deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack). The USPSTF has issued separate recommendations for women with *BRCA* gene mutations (available at http://www.uspreventiveservicestaskforce.org).

ASSESSMENT OF BREAST CANCER RISK

If a family history of breast cancer or a personal history of breast biopsy is found during the usual patient assessment, clinicians may consider further evaluation using a breast cancer risk assessment tool. Risk assessment tools specifically for family history of breast cancer are available elsewhere (http://www.uspreventiveservicestaskforce.org).

The National Cancer Institute has developed a Breast Cancer Risk Assessment Tool (available at http://www.cancer.gov/bcrisktool) that is based on the Gail model and estimates the five-year incidence of invasive breast cancer in women on the basis of characteristics entered into a risk calculator. This tool helps identify women who may be at increased risk of the disease. Other risk assessment models have been developed by the Breast Cancer Surveillance Consortium, Rosner and Colditz, Chlebowski, Tyrer and Cuzick, and others.[5-7]

Examples of risk factors elicited by risk assessment tools include patient age, race or ethnicity, age at menarche, age at first live childbirth, personal history of ductal carcinoma in situ or lobular carcinoma in situ, number of first-degree relatives with breast cancer, personal history of breast biopsy, body mass index, menopause status or age, breast density, estrogen and progestin use, smoking, alcohol use, physical activity, and diet.

These models are not recommended for use in women with a personal history of breast cancer, a history of radiation treatment to the chest, or a possible family history of mutations in the *BRCA1* or *BRCA2* genes. Only a small fraction of women are at increased risk of breast cancer. Most who are at increased risk will not develop the disease, and most cases will arise in women who are not identified as being at increased risk. Risk assessment should be repeated when there is a significant change in breast cancer risk factors.

There is no single cutoff for defining increased risk. Most clinical trials defined increased risk as a five-year risk of invasive breast cancer of 1.66% or greater, as determined by the Breast Cancer Prevention Trial. At this cutoff, however, many women would not have a net benefit from risk-reducing medications. Freedman and colleagues[8] developed risk tables that incorporate the Breast Cancer Prevention Trial estimate of a woman's breast cancer risk as well as her age, race or ethnicity, and presence of a uterus.

On the basis of the Freedman risk–benefit tables for women 50 years or older (see figures at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction), the USPSTF concludes that many women with an estimated five-year breast cancer risk of 3% or greater are likely to have more benefit than harm from tamoxifen or raloxifene, although the balance depends on age, race or ethnicity, the medication used, and whether the patient has a uterus.[8]

ASSESSMENT OF RISK FOR ADVERSE EFFECTS

In general, women receiving medications for breast cancer risk reduction are less likely to have a venous thromboembolic event if they are younger and have no other predisposition to thromboembolic events. Women with a personal or family history of venous thromboembolism are at higher risk of these adverse effects.

Women without a uterus are not at risk of tamoxifen-related endometrial cancer. Women with a uterus should have a baseline gynecologic examination before treatment with tamoxifen is started, with regular follow-up after the end of treatment.

MEDICATIONS FOR BREAST CANCER RISK REDUCTION

Selective estrogen receptor modulators (tamoxifen and raloxifene) have been shown to reduce the incidence

of invasive breast cancer in several randomized controlled trials. Tamoxifen has been approved for this use in women 35 years or older, and raloxifene has been approved for this use in postmenopausal women.

The usual daily doses for tamoxifen and raloxifene are 20 and 60 mg, respectively, for five years. Aromatase inhibitors (exemestane) have not been approved by the U.S. Food and Drug Administration for this indication and are therefore beyond the scope of this recommendation.

Tamoxifen is not recommended for use in combination with hormone therapy or hormonal contraception or in women who are pregnant, those who may become pregnant, or breastfeeding mothers.

OTHER APPROACHES TO PREVENTION

The USPSTF recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer can be found at http://www.uspreventiveservicestaskforce.org. Clinical trials of tamoxifen and raloxifene have not been conducted specifically in women who are *BRCA* mutation carriers.

OTHER RESOURCES

The National Cancer Institute provides information about potential ways to prevent cancer, including lifestyle and diet changes (available at http://www.cancer.gov/cancertopics/pdq/prevention/breast/Patient and http://www.cdc.gov/cancer/breast/basic_info/prevention.htm).

The USPSTF does not endorse any particular risk prediction model. However, the Breast Cancer Prevention Trial model (http://www.cancer.gov/bcrisktool) and the Breast Cancer Surveillance Consortium model (https://tools.bcsc-scc.org/BC5yearRisk) can be used by clinicians and patients as part of the process of shared, informed decision making. Both models have been calibrated in U.S. populations.

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The "Other Considerations," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction.

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