Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation on the use of medications for breast cancer risk reduction.

Methods: The USPSTF reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce the risk for breast cancer—specifically, the selective estrogen receptor modulators tamoxifen and raloxifene. The USPSTF also reviewed a meta-analysis of placebo-controlled trials to understand the relative benefits and harms of tamoxifen and raloxifene.

Population: This recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ.

Recommendation: The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at in-creased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to pre-scribe risk-reducing medications, such as tamoxifen or raloxifene. (B recommendation)

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 for breast cancer. (D recommendation)

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without 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.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene. (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 for breast cancer. (D recommendation)

See **Figure 1** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

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 African American 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 for estrogen receptor (ER)–positive breast cancer. They have been approved by the U.S. Food and Drug Administration (FDA) 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 (es-

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> Summary for Patients 1
>
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> Supplement
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CLINICAL GUIDELINE | Medications for Risk Reduction of Primary Breast Cancer in Women

Figure 1. Medications for risk reduction of primary breast cancer in women: clinical summary of U.S. Preventive Services Task Force recommendation.

Annals of Internal Medicine

U.S. Preventive Services
TASK FORCE
www.USPreventiveServicesTaskForce.org

MEDICATIONS FOR RISK REDUCTION OF PRIMARY BREAST CANCER IN WOMEN
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Asymptomatic women aged ≥35 years without a prior diagnosis of breast cancer who are at increased risk for breast cancer	Asymptomatic women aged ≥35 years without a prior diagnosis of breast cancer who are not at increased risk for breast cancer
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 estimate the number of breast cancer cases that may arise in certain study populations, but their ability to accurately predict which individual women will (and will not) 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 for the disease. The usual daily doses for tamoxifen and raloxifene are 20 mg and 60 mg, respectively, for 5 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 for 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 for 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 www.uspreventiveservicestaskforce.org.	

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

pecially among first-degree relatives and onset before age 50 years), 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 for 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 (RR) for invasive ER-positive breast cancer in postmenopausal women who are at increased risk for breast cancer.

A systematic review of clinical trials found that tamoxifen and raloxifene reduced the incidence of invasive breast cancer by 7 to 9 events per 1000 women over 5 years and that tamoxifen reduced breast cancer incidence more than raloxifene (**Table**) (5–7). Tamoxifen also reduces the incidence of invasive breast cancer in premenopausal women who are at increased risk for the disease.

Women who are at increased risk for breast cancer are more likely to benefit from risk-reducing medications. In general, women with an estimated 5-year risk of 3% or greater are, on the basis of model estimates (**Figures 2 to 5**) (8), more likely to benefit from tamoxifen or raloxifene.

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Table. Summary of Primary Prevention Trials*

Major Clinical Outcome	Raloxifene vs. Tamoxifen	Tamoxifen vs. Placebo	Raloxifene vs. Placebo
Events reduced (benefits)			
Invasive breast cancer	5 (1–9) fewer events per 1000 women with tamoxifen	7 (4–12) fewer events per 1000 women with tamoxifen	9 (4–14) fewer events per 1000 women with raloxifene
ER-positive breast cancer	No difference	8 (3–13) fewer events per 1000 women with tamoxifen	8 (4–12) fewer events per 1000 women with raloxifene
ER-negative breast cancer	No difference	No difference	No difference
Noninvasive cancer	No difference	No difference	No difference
All-cause mortality	No difference	No difference	No difference
Vertebral fracture	No difference	No difference	7 (5–9) fewer events per 1000 women with raloxifene
Nonvertebral fracture	Not reported	3 (0.2–5) fewer events per 1000 women with tamoxifen	No difference
Events increased (harms)			
Thromboembolic events	4 (1–7) more events per 1000 women with tamoxifen	4 (2–9) more events per 1000 women with tamoxifen	7 (2–15) more events per 1000 women with raloxifene
Coronary heart disease	No difference	No difference	No difference
Stroke	No difference	No difference	No difference
Endometrial cancer	5 (2–9) more events per 1000 women with tamoxifen	4 (1–10) more events per 1000 women with tamoxifen	No difference
Cataracts	15 (8–22) more events per 1000 women with tamoxifen	No difference	No difference

ER = estrogen receptor.
* Numbers in parentheses are 95% CIs.

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 for the disease.

In addition to breast cancer risk reduction, the USPSTF found adequate evidence that tamoxifen and raloxifene reduce the risk for 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 risk for venous thromboembolic events (VTEs) by 4 to 7 events per 1000 women over 5 years and that tamoxifen increases risk more than raloxifene (**Table**) (5–7). The USPSTF found that 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 risk for endometrial cancer (4 more cases per 1000 women). Potential harms from tamoxifen-related endometrial cancer are small to moderate and depend on hysterectomy status and age. The potential risks for 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 for 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 for the disease.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS). 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 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 (www.uspreventiveservicestaskforce.org).

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Figure 2. Benefit–risk indices for tamoxifen and raloxifene chemoprevention in white non-Hispanic women with uterus, by age group and level of 5-y projected risk for invasive breast cancer.

5-year projected risk of IBC (%)	Tamoxifen vs. Placebo (with uterus)			Raloxifene vs. Placebo (with uterus)		
	50–59	60–69	70–79	50–59	60–69	70–79
1.5	−133	−310	−325	21	−11	-15
2.0	−105	−283	−298	43	11	7
2.5	−78	−255	−271	65	33	29
3.0	−51	−228	−244	86	55	51
3.5	−25	−202	−217	108	76	71
4.0	3	−175	−190	128	97	93
4.5	29	−148	−164	150	119	115
5.0	56	−121	−137	172	140	136
5.5	83	−95	−111	193	161	157
6.0	109	−69	−84	214	183	179
6.5	135	−42	−58	236	204	199
7.0	162	−15	−32	256	225	221

5-year projected risk of IBC is ≥1.67%	Using BCPT data and WHI baseline rates	Combining RR from BCPT and STAR using WHI baseline rates

☐ Strong evidence of benefits outweighing risks
☐ Moderate evidence of benefits outweighing risks
☐ Benefits do not outweigh risks

On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, Freedman and colleagues assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event.) For example, in this table, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence (P > 0.9; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, Freedman and colleagues estimate chemoprevention would result in 25 excess life-threatening events (P < 0.6; gray).

BCPT = Breast Cancer Prevention Trial; IBC = invasive breast cancer; RR = relative risk; STAR = Study of Tamoxifen and Raloxifene; WHI = Women's Health Initiative. (Reproduced from Freedman and colleagues [8] with permission from the American Society of Clinical Oncology. This figure remains the property of the American Society of Clinical Oncology and is not part of the public domain.)

The National Cancer Institute has developed a Breast Cancer Risk Assessment Tool (available at www.cancer.gov /bcrisktool) that is based on the Gail model and estimates the 5-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 for the disease. Other risk assessment models have been developed by the Breast Cancer Surveillance Consortium (BCSC), 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 DCIS or LCIS, 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 for 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 5-year

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Figure 3. Benefit–risk indices for tamoxifen and raloxifene chemoprevention in white non-Hispanic women without uterus, by age group and level of 5-y projected risk for invasive breast cancer.

5-year projected risk of IBC (%)	Tamoxifen vs. Placebo (without uterus)			Raloxifene vs. Placebo (without uterus)		
	50–59	60–69	70–79	50–59	60–69	70–79
1.5	3	−53	−93	27	2	−4
2.0	31	−26	−66	49	23	18
2.5	57	2	−39	71	45	40
3.0	84	29	−12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	262	237	232

5-year projected risk of IBC is ≥1.67%	Using BCPT data and WHI baseline rates	Combining RR from BCPT and STAR using WHI baseline rates

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On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, Freedman and colleagues assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event.) For example, in this table, among 10,000 non-Hispanic white women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 114 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > 0.9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, Freedman and colleagues estimate chemoprevention would also result in the prevention of 111 life-threatening events ($P < 0.9$; blue). Among 10,000 non-Hispanic white women without a uterus, age 70 to 79 years, and with a 5-year IBC risk of 3.0%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P ≥ 0.6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, Freedman and colleagues estimate chemoprevention would result in 12 excess life-threatening events ($P < 0.6$; gray).

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risk for invasive breast cancer of 1.66% or greater, as determined by the BCPT (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 BCPT estimate of a woman's breast cancer risk as well as her age, race or ethnicity, and presence of uterus.

On the basis of the Freedman risk–benefit tables for women aged 50 years or older (**Figures 2 to 5**), the

USPSTF concludes that many women with an estimated 5-year breast cancer risk of 3% or greater are likely to have more benefit than harm from using 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 VTE if they

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Figure 4. Benefit–risk indices for tamoxifen and raloxifene chemoprevention in black women with uterus, by age group and level of 5-y projected risk for invasive breast cancer.

5-year projected risk of IBC (%)	Tamoxifen vs. Placebo (with uterus)			Raloxifene vs. Placebo (with uterus)		
	50–59	60–69	70–79	50–59	60–69	70–79
1.5	−144	−319	−349	−25	−68	−108
2.0	−117	−292	−322	−3	−46	−86
2.5	−89	−264	−294	19	−24	−64
3.0	−62	−237	−267	41	−3	−43
3.5	−36	−211	−241	62	19	−21
4.0	−9	−184	−214	83	40	−1
4.5	18	−157	−187	105	62	22
5.0	45	−130	−160	126	83	43
5.5	72	−105	−135	147	104	64
6.0	98	−78	−108	169	126	86
6.5	124	−51	−81	190	146	106
7.0	151	−25	−55	211	168	128

5-year projected risk of IBC is ≥1.67%	Using BCPT data and WHI baseline rates	Combining RR from BCPT and STAR using WHI baseline rates

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On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, Freedman and colleagues assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event.) For example, in this table, among 10,000 black women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P \geq 6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, Freedman and colleagues estimate chemoprevention would result in 36 excess life-threatening equivalent events ($P < 0.6$; gray).

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are younger and have no other predisposition to thromboembolic events. Women with a personal or family history of venous thromboembolism are at higher risk for these adverse effects.

Women without a uterus are not at risk for 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 aged 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 mg and 60 mg, respectively, for 5 years. Aromatase inhibitors (exemestane) have not been approved by the FDA 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.

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Figure 5. **Benefit–risk indices for tamoxifen and raloxifene chemoprevention in black women without uterus, by age group and level of 5-y projected risk for invasive breast cancer.**

5-year projected risk of IBC (%)	Tamoxifen vs. Placebo (without uterus)			Raloxifene vs. Placebo (without uterus)		
	50–59	60–69	70–79	50–59	60–69	70–79
1.5	−67	−111	−200	−21	−58	−101
2.0	−40	−84	−173	1	−36	−79
2.5	−12	−56	−145	23	−14	−57
3.0	15	−29	−118	45	8	−36
3.5	42	−3	−92	66	29	−14
4.0	69	25	−65	87	50	7
4.5	95	51	−38	109	72	29
5.0	122	78	−11	130	93	50
5.5	149	104	15	151	114	71
6.0	175	131	42	173	136	93
6.5	201	157	68	194	156	113
7.0	228	183	94	215	178	135

5-year projected risk of IBC is ≥1.67%   Using BCPT data and WHI baseline rates   Combining RR from BCPT and STAR using WHI baseline rates

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On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, Freedman and colleagues assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event.) For example, in this table, among 10,000 black women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 66 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P > 0.6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risk. If tamoxifen were used instead, Freedman and colleagues estimate chemoprevention would result in 42 life-threatening equivalent events being prevented, with moderate evidence of the benefits outweighing the risks ($P > 0.6$ but < 0.9; gold).

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Other Approaches to Prevention

The USPSTF recommendation on risk assessment, genetic counseling, and genetic testing for BRCA-related cancer can be found at 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 www.cancer.gov/cancertopics /pdq/prevention/breast/Patient and www.cdc.gov/cancer /breast/basic_info/prevention.htm).

The USPSTF does not endorse any particular risk prediction model. However, the BCPT model (www.cancer .gov/bcrisktool) and the BCSC 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.

OTHER CONSIDERATIONS
Implementation

In order to identify patients for whom the potential benefits of risk-reducing medications may outweigh the

potential risks, clinicians should first identify those who may be at increased risk for breast cancer (see Assessment of Breast Cancer Risk).

Clinicians may use this opportunity to educate all women about their risk for breast cancer. Studies have shown that women tend to overestimate their risk for the disease.

For women whose 5-year projected risk for breast cancer is 3% or greater, clinicians should identify those for whom the potential benefits of risk-reducing medications may outweigh the potential risks. In doing so, clinicians should consider the woman's age, comorbid conditions, presence of uterus, and risks for thromboembolic or medication-related adverse events. Clinicians may refer to risk–benefit tables to complement clinical assessment (**Figures 2 to 5**) (8, 9).

Clinicians should clearly discuss the potential benefits and risks of risk-reducing medications with women for whom the former may outweigh the latter. Clinicians should then strive to ensure that patients make a fully informed decision that incorporates their personal values and preferences, including their concerns about breast cancer and specific medication-related adverse events.

Research Needs and Gaps

Research to improve the ability to assess and accurately predict a woman's chance of developing breast cancer over a defined period is needed. The ideal candidates for risk-reducing medications are women who have not only a high probability of developing breast cancer over a defined period but also a low probability of thromboembolic and other medication-related adverse events. Models that can more precisely predict both of these events should be developed.

Clinical trials that provide more information about the safety and effectiveness of other medications for breast cancer risk reduction, such as aromatase inhibitors and tibolone, are needed. The aromatase inhibitor exemestane reduced the incidence of invasive breast cancer in postmenopausal women who were at moderately increased risk for the disease. There were no significant differences in the incidence of osteoporosis, cardiovascular events, other types of cancer, or death. However, these findings were reported from a randomized, clinical trial with a median follow-up of 3 years and will require long-term assessment. IBIS-II (International Breast Cancer Intervention Study II), an ongoing British study, is comparing the aromatase inhibitor anastrozole with placebo in women who are at increased risk for breast cancer.

Additional research could help clarify the optimum treatment duration, timing, and dose. Future studies should examine the benefits and harms of risk-reducing medications in racially diverse patient populations.

DISCUSSION

Burden of Disease

Breast cancer is the most common nonskin cancer in women. According to the National Cancer Institute, 12.4% (1 in 8) of women born today will be diagnosed with breast cancer during their lifetime (10). Between 2005 and 2009, the median age at diagnosis was 61 years, and the median age at death from the disease was 68 years. The age-adjusted mortality rate was 23.0 deaths per 100 000 women per year, with higher mortality rates among African American women (31.6 deaths per 100 000 women per year) (10).

Scope of Review

The USPSTF reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce the risk for breast cancer—specifically, the selective estrogen receptor modulators tamoxifen and raloxifene (5–7). The USPSTF reviewed randomized trials, observational studies, and diagnostic accuracy studies of risk stratification models in women without preexisting breast cancer, precursor conditions, or known breast cancer susceptibility mutations. The USPSTF also reviewed a meta-analysis of placebo-controlled trials to understand the relative benefits and harms of tamoxifen and raloxifene (7).

Effectiveness of Risk Assessment

To understand the effectiveness of breast cancer risk assessment, the USPSTF reviewed 13 breast cancer risk assessment models that can be used in primary care. The original Gail model, the first to be used clinically, includes age, age at menarche, age at first childbirth, family history of breast cancer in first-degree relatives, number of prior breast biopsies, and history of atypical hyperplasia. Expanding on the Gail model, newer models include race or 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 U.S. populations in studies that received good quality ratings but reported only modest accuracy. The BCSC Barlow model was derived from more than 11 638 breast cancer cases that developed among a cohort of almost 2.4 million women (11). The Rosner–Colditz model was derived from 1761 breast cancer cases that developed among 58 520 participants in the Nurses' Health Study (12). Chlebowski and colleagues developed a model based on 3236 cases that developed in the Women's Health Initiative study (13). Breast cancer risk assessment models from Italy and the United Kingdom were also based on large populations but were not tested in the United States.

All models predicted probabilities of breast cancer that were in general agreement with observed risk. Models had the best calibration in women older than 60 years, those who received annual breast cancer screening, and those

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with ER-positive breast cancer. However, most had a false-positive rate of 55% to 66%, indicating modest accuracy in predicting risk for individuals.

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).

Effectiveness of Risk-Reducing Medications

To understand the effectiveness of risk-reducing medications for breast cancer, the USPSTF reviewed 7 large randomized, controlled trials of breast cancer outcomes in women without preexisting breast cancer (5–7). Other relevant study outcomes included death, fractures, thromboembolic events, cardiovascular disease events, uterine abnormalities, cataracts, and other adverse effects.

STAR (Study of Tamoxifen and Raloxifene) was a head-to-head comparison of tamoxifen versus raloxifene with more than 9800 patients in each study group (14, 15). Four studies compared tamoxifen with placebo: NSABP-1 (National Surgical Adjuvant Breast and Bowel Project) (16–19), IBIS-I (20, 21), the Royal Marsden Hospital trial (22, 23), and the Italian Tamoxifen Prevention Study (24–27). Two studies compared raloxifene with placebo: the Multiple Outcomes of Raloxifene Evaluation study, with long-term follow-up in the Continuing Outcomes Relevant to Evista study (28–41), and the Raloxifene Use for the Heart trial (42, 43). These were all multicenter trials that were relevant to primary care. They enrolled between 2471 and 19 747 women, predominantly in North America, Europe, and the United Kingdom. All trials met criteria for fair or good quality as well as high applicability to the U.S. primary care population.

For STAR, eligibility criteria included having a 5-year predicted breast cancer risk of 1.66% or greater; median follow-up was 81 months (15). For the placebo-controlled trials involving tamoxifen, eligibility criteria and duration of follow-up varied. Eligibility criteria for NSABP-1 included having a 5-year predicted breast cancer risk of 1.66% or greater, and median follow-up was about 7 years (16). Eligibility criteria for IBIS-I included having an estimated 10-year risk of 5% or greater; median follow-up was 96 months (21). For the Royal Marsden Hospital (23) and Italian Tamoxifen Prevention (27) trials, eligibility criteria did not include a prespecified breast cancer risk threshold, and median follow-up was 13 and 11 years, respectively. For placebo-controlled trials involving raloxifene (Multiple Outcomes of Raloxifene Evaluation and Continuing Outcomes Relevant to Evista), eligibility criteria did not include a prespecified breast cancer risk threshold; together, these trials provided 8 years of follow-up (39).

In placebo-controlled trials, tamoxifen and raloxifene significantly reduced the risk for invasive breast cancer (tamoxifen RR, 0.70 [95% CI, 0.59 to 0.82] [16, 21, 23, 26, 39]; raloxifene RR, 0.44 [CI, 0.27 to 0.71] [39, 42]). In STAR, tamoxifen reduced breast cancer more than raloxifene (raloxifene RR, 1.24 [CI, 1.05 to 1.47]) (14).

Both medications reduced breast cancer in all subgroups studied, although trial data for racial subgroups were not available. Tamoxifen reduced breast cancer outcomes in subgroups based on age, menopausal status, estrogen use, family history of breast cancer, and history of LCIS or atypical ductal hyperplasia. In NSABP-1, tamoxifen was most effective in preventing invasive breast cancer in high-risk groups, including women with LCIS, atypical ductal hyperplasia, the highest Gail risk scores, and the greatest number of relatives with breast cancer (16). Raloxifene reduced breast cancer outcomes in subgroups based on age, age at menarche, parity, age at first live childbirth, and body mass index. Effect estimates for raloxifene were limited by small sample size for subgroups based on prior estrogen use, family history of breast cancer, and prior hysterectomy or oophorectomy. Specific risk factors may be more useful than risk calculators in certain clinical settings.

Both medications reduced breast cancer risk in postmenopausal women. Tamoxifen also reduced the incidence of invasive breast cancer in premenopausal women who were at increased risk for the disease. Risk reduction with tamoxifen was greatest in women with 3 or more first-degree relatives with breast cancer, LCIS, or atypical hyperplasia.

Reduction of invasive breast cancer continued for at least 3 to 5 years after discontinuation of tamoxifen in the 2 trials providing posttreatment follow-up data. Neither medication significantly reduced the risk for ER-negative breast cancer, noninvasive breast cancer, or all-cause mortality. In the placebo-controlled trials and STAR, raloxifene reduced vertebral fractures (RR, 0.61 [CI, 0.54 to 0.69]) (32, 42), whereas tamoxifen reduced nonvertebral fractures (RR, 0.66 [CI, 0.45 to 0.98]) (17). Tamoxifen and raloxifene had similar effects on vertebral fractures in STAR (44).

The USPSTF could not assess the effect of these medications on mortality attributed to breast cancer or other causes. The effects of tamoxifen and raloxifene on mortality were not statistically significant in the clinical trials, which did not have sufficient long-term follow-up for this outcome. Although there is convincing evidence that these medications can reduce the incidence of invasive breast cancer (predominantly ER-positive cancer), whether reductions in breast cancer incidence lead to a corresponding reduction in mortality is unclear.

The USPSTF also considered meta-analysis summary calculations of the number of events reduced per 1000 women in placebo-controlled trials, assuming 5 years of treatment (**Table**) (7). Both medications reduced the incidence of invasive breast cancer, with 7 fewer events per 1000 women for tamoxifen (4 trials) and 9 fewer events per 1000 women for raloxifene (2 trials). When compared head-to-head in STAR, tamoxifen reduced breast cancer incidence by 5 more events per 1000 women than ralox-

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ifene. Compared with placebo, raloxifene reduced the incidence of vertebral fractures by 7 events per 1000 women (2 trials), whereas tamoxifen reduced the incidence of nonvertebral fractures by 3 events per 1000 women (1 trial). There were no significant differences in vertebral fractures when the drugs were compared head-to-head in STAR.

Potential Harms of Risk Assessment and Preventive Medications

No studies reported on the potential harms of breast cancer risk assessment in primary care settings. Clinical trials provided evidence on the potential harms of tamoxifen and raloxifene (5–7). Study outcomes included thromboembolic events, uterine abnormalities, cardiovascular disease events, cataracts, and other adverse effects.

In most trials, both tamoxifen and raloxifene nearly doubled the risk for all VTEs compared with placebo (tamoxifen RR, 1.93 [CI, 1.41 to 2.64] [17, 21, 23, 24]; raloxifene RR, 1.60 [CI, 1.15 to 2.23] [42, 45]). Tamoxifen increased risk for VTEs more than raloxifene in STAR. Risk returned to normal after discontinuation of tamoxifen in the 2 trials providing posttreatment data.

Compared with placebo, tamoxifen was associated with more cases of endometrial cancer (RR, 2.13 [CI, 1.36 to 3.32]) (17, 21, 23); more benign gynecologic conditions (21, 46); surgical procedures, including hysterectomy (21, 23, 46); and uterine bleeding (21, 46). Women without a uterus are not at increased risk for tamoxifen-related endometrial cancer. Raloxifene did not increase risk for endometrial cancer or uterine bleeding. In STAR, raloxifene was associated with fewer cases of endometrial cancer than tamoxifen (RR, 0.55 [CI, 0.36 to 0.83]) (14).

Tamoxifen and raloxifene did not increase risk for coronary heart disease events or stroke (16, 21, 23, 26, 27, 42). However, in 1 trial that was specifically designed to ascertain cardiovascular outcomes in postmenopausal women who had or were at increased risk for coronary heart disease, stroke mortality was higher with raloxifene than placebo (absolute increase, 0.7 events per 1000 women per year) (42).

Compared with women receiving placebo, those receiving tamoxifen more frequently had cataract surgery in 1 trial (17), although cataract risk was not increased in a meta-analysis of 3 tamoxifen trials (RR, 1.25 [CI, 0.93 to 1.67]) (16, 21, 23). Raloxifene did not increase risk for cataracts or cataract surgery compared with placebo (42, 45) and caused fewer cataracts than tamoxifen in STAR (14).

The most commonly reported adverse effects in these trials were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen and vasomotor symptoms and leg cramps for raloxifene. In STAR, raloxifene users reported more musculoskeletal problems, dyspareunia, and weight gain, whereas tamoxifen users had more gynecologic problems, vasomotor symptoms, leg cramps, and bladder control symptoms.

The USPSTF also considered meta-analysis summary calculations of the number of adverse health events per 1000 women caused by these medications in placebo-controlled trials, assuming 5 years of treatment (**Table**) (7). Tamoxifen was associated with 4 VTEs per 1000 women (4 trials), whereas raloxifene was associated with 7 VTEs per 1000 women (2 trials). Tamoxifen increased thromboembolic events by 4 more events per 1000 women than raloxifene in STAR. Tamoxifen was also associated with 4 cases of endometrial cancer per 1000 women (3 trials).

Risk Perception and Decision Making

In studies describing how women decide whether to take medications to reduce risk for primary breast cancer, women had substantial concerns about potential serious adverse events, especially when they were informed of the medications' risks and benefits. In 1 study of women who were at increased risk for breast cancer, only 12% selected tamoxifen for risk reduction; most (77%) declined, primarily because of concerns about serious adverse events and small therapeutic benefit (3). Women who were interested in receiving risk-reducing medications often overestimated their own risk for breast cancer (that is, erroneously thought they were at high risk). Women placed great emphasis on recommendations from their physicians.

Estimate of Magnitude of Net Benefit

One breast cancer risk model found that for many women with an increased 5-year risk for breast cancer, the benefits of risk-reducing medication outweigh the potential harms (**Figures 2 to 5**) (8). Whether there is a net benefit depends on a woman's risk for breast cancer, age, and race and whether she has a uterus. Accordingly, the USPSTF's recommendations are different for women with low risk for breast cancer than for those with high risk.

The USPSTF concludes with moderate certainty that medications to reduce risk for breast cancer confer moderate net benefit in women who are at increased risk for the disease. Tamoxifen is associated with moderate benefit, with adequate evidence for risk reduction of invasive breast cancer. Raloxifene is associated with slightly smaller benefit for breast cancer risk reduction but no risk for endometrial cancer. The USPSTF found adequate evidence of small benefit for reduction of nonvertebral fractures with tamoxifen, whereas raloxifene reduces vertebral fractures.

The USPSTF found adequate evidence of small to moderate risk for medication-associated VTEs (depending on age), as well as small to moderate risk for medication-associated endometrial cancer with tamoxifen (depending on hysterectomy status and age).

The USPSTF concludes that both tamoxifen and raloxifene confer a benefit no greater than small, with moderate harms, for women who are not at increased risk for breast cancer.

How Does Evidence Fit With Biological Understanding?

Tamoxifen and raloxifene are selective estrogen receptor modulators. Because ER-positive cancer is believed to

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be more amenable to therapy than ER-negative cancer, these medications would not prevent the type of breast cancer that is most difficult to treat.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 16 April through 13 May 2013. In response to public comment and in consideration of FDA-approved indications, the USPSTF provided more information about the target patient population for this recommendation. The USPSTF clarified that the recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, DCIS, or LCIS. The final recommendation statement further clarifies that raloxifene has been approved for breast cancer risk reduction in postmenopausal women and that other groups of women should not use tamoxifen. The USPSTF reiterated that only a small fraction of women are candidates for and would derive benefit from risk-reducing medications.

The USPSTF also provided a more comprehensive list of breast cancer risk factors and links to additional resources in response to comments, as well as summary tables to help readers understand the risk–benefit balance of these medications, links to online breast cancer risk assessment models, and updated recommendations of other groups.

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

In 2002, the USPSTF issued a B recommendation for clinicians to discuss risk-reducing medications with women who are at high risk for breast cancer and at low risk for medication adverse effects. The USPSTF issued a D recommendation against the routine use of tamoxifen or raloxifene for breast cancer risk reduction in women who are at low or average risk.

This recommendation reaffirms the USPSTF's 2002 recommendation and provides updated evidence on the risks and benefits of risk-reducing medications for women who are at increased risk for breast cancer.

RECOMMENDATIONS OF OTHERS

In 2013, the American Society of Clinical Oncology recommended that tamoxifen should be discussed as an option to reduce risk for ER-positive breast cancer in women aged 35 years or older who are at increased risk for breast cancer. It also recommended that raloxifene and exemestane should be discussed as options for breast cancer risk reduction in postmenopausal women (47). In 2013, the National Institute for Health and Care Excellence recommended that clinicians offer tamoxifen or raloxifene for 5 years to postmenopausal women with a uterus who are at high risk for breast cancer unless they have a history of or may be at increased risk for thromboembolic disease or endometrial cancer (48). The guideline also included rec-

ommendations for different age and risk groups. In 2011, the American Cancer Society recommended that women who are considering medications for breast cancer risk reduction should discuss their personal health situations with their physicians (49). In 2001, the Canadian Task Force on Preventive Health Care recommended that women who are at high risk for breast cancer should receive counseling about the risks and benefits of tamoxifen for cancer prevention; it found fair evidence to recommend against the use of tamoxifen in women who are at low or normal risk for breast cancer (50).

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APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.