Role of Hormones in Cancer Prevention

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OVERVIEW

Risk for breast cancer can be easily and rapidly assessed using validated, quantitative models. Multiple randomized studies show that the selective estrogen response modifiers (SERMs) tamoxifen and raloxifene can safely reduce the risk of invasive breast cancer in both pre- and postmenopausal women. Treatment resulted in a 38% reduction in breast cancer incidence, and 42 women would need to be treated to prevent one breast cancer event in the first 10 years of follow-up. Reduction was larger in the first 5 years of follow-up than in years 5 to 10, but no studies treated patients for longer than 5 years. Thromboembolic events were significantly increased with all SERMs, whereas vertebral fractures were reduced. Tamoxifen provides net benefit to all premenopausal women who are at increased risk, whereas raloxifene reduces risk nearly as much in postmenopausal women and offers increased safety. Both tamoxifen and raloxifene reduce the incidence of in situ cancers. Lasofoxifene reduced the risk of breast cancer by 79% in postmenopausal women with osteoporosis. The MAP3 trial showed a 65% reduction in the annual incidence of invasive breast cancer in postmenopausal women who were at moderately increased risk for breast cancer who took the aromatase inhibitor exemestane. The IBIS-II trial showed a 53% reduction in the risk of invasive breast cancer in postmenopausal women aged 40 to 70 who took the aromatase inhibitor anastrozole. Of the 50 million white women in the United States aged 35 to 79, 2.4 million would have a positive benefit/risk index for chemoprevention.

Chemoprevention is the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the progression of premalignant lesions to invasive carcinoma. Four randomized prospective clinical trials have used tamoxifen as a chemopreventive agent for breast cancer. Two of the trials, the NSABP Breast Cancer Prevention Trial (BCPT) and the International Breast Cancer Intervention Study I (IBIS-I), showed a reduction in breast cancer risk with tamoxifen. The STAR trial was a randomized comparison of tamoxifen and raloxifene in high-risk, postmenopausal women. These results are shown in Table 1.

In the MAP3 trial conducted by NCI Canada, exemestane significantly reduced invasive breast cancers (p = 0.002) in postmenopausal women who were at moderately increased risk for breast cancer. A total of 4,560 women (median age 62.5, and median Gail risk score 2.3%) were randomly assigned to either exemestane or placebo. At a median follow-up of 35 months, 11 invasive breast cancers were detected in patients given exemestane and in 32 of patients given placebo, with a 65% relative reduction in the annual incidence of invasive breast cancer. The annual incidence of invasive plus noninvasive (ductal carcinoma in situ) breast cancers was 0.35% on exemestane and 0.77% on placebo (hazard ratio [HR] 0.47, 95% CI [0.27, 0.79]; p = 0.004). Adverse events occurred in 88% of the exemestane group and 85% of the placebo group with no significant differences between the two groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths. Minimal quality-of-life differences were observed.

The IBIS-II trial recruited postmenopausal women aged 40 to 70 to an international, double-blind, randomized placebo-controlled trial. Eligible women had an increased risk of breast cancer and were randomly assigned to receive 1 mg oral anastrozole or matching placebo every day for 5 years. The primary endpoint was histologically confirmed breast cancer (invasive cancers or noninvasive ductal carcinoma in situ); 1,920 women were randomly assigned to receive anastrozole 1 mg orally daily and 1,944 were assigned to placebo. After a median follow-up of 5 years, 2% of women in the anastrozole group 4% in the placebo group developed breast cancer (HR 0.47, 95% CI [0.32, 0.68]; p < 0.0001). The predicted cumulative incidence of all breast cancers after 7 years was 5.6% in the placebo group and 2.8% in the anastrozole group.

Cuzick and colleagues conducted a meta-analysis based on individual-level data from nine randomized trials that compared selective estrogen response modifiers (SERMs) with placebo or another drug in women without breast cancer. There were 83,399 women with 306,617 collective years of follow-up. Eight of these trials were placebo-controlled trials,
Overall, there was a 38% reduction in breast cancer incidence, with 42 women needing to be treated to prevent one case of breast cancer, over a 10-year follow-up period. The largest risk reduction was observed in the first 5 years. There was also a significant increase in the incidence of thromboembolic disease with all SERMs (odds ratio [OR] 1.73, 95% CI [1.47, 2.05]) and a significant reduction in the incidence of nonvertebral fractures (OR 0.66, 95% CI [0.59, 0.73]).

**OTHER SERMs**

In the PEARL trial postmenopausal women with low bone density and normal mammograms were randomly assigned to two doses of lasofoxifene (0.25 and 0.5 mg) or placebo.\textsuperscript{12} The primary endpoints of the trial were incidence of estrogen receptor (ER)-positive breast cancer and nonvertebral fractures at 5 years. Compared with placebo, 0.5 mg of lasofoxifene statistically significantly reduced the risk of total breast cancer by 79% (HR $= 0.21$, 95% CI [0.08 – 0.55]) and ER-positive invasive breast cancer by 83% (HR $= 0.17$, 95% CI [0.05 – 0.57]). The effects of 0.5 mg of lasofoxifene on total

### TABLE 1. Tamoxifen Chemoprevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Characteristics</th>
<th>Population</th>
<th>No. Randomly Selected</th>
<th>Intended Duration of Treatment (Years)</th>
<th>Total Breast Cancers (Invasive and Noninvasive)</th>
<th>Breast Cancer Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Prevention Trial (BREAST CANCERPT, NSABP P-1)</td>
<td>High breast cancer risk (age $\geq$ 60 yr or a combination of risk factors using the Gail model); 39% $&lt; 50$ yr</td>
<td>13,388</td>
<td>1.66% 5-yr risk</td>
<td>124 Overall: 49%</td>
<td>Placebo: 244 Ductal carcinoma-in-situ: 50%</td>
<td>With prior lobular carcinoma-in-situ: 55%</td>
</tr>
<tr>
<td>Royal Marsden Hospital Chemoprevention Trial</td>
<td>Family history of breast cancer $&lt; .50$ yr old or two or more affected first-degree relatives</td>
<td>2,494</td>
<td>5-8</td>
<td>Tamoxifen: 62 Overall: no reduction</td>
<td>Placebo: 75</td>
<td>With prior atypical hyperplasia: 86%</td>
</tr>
<tr>
<td>International Breast Intervention Study I</td>
<td>Women aged 35 to 70 yr who were at increased risk for breast cancer</td>
<td>7,152</td>
<td>5</td>
<td>Tamoxifen: 69 Overall: 32%</td>
<td>Placebo: 101</td>
<td></td>
</tr>
<tr>
<td>Italian Tamoxifen Prevention Study</td>
<td>Women with hysterectomy (48% bilateral oophorectomy); median age: 51 yr</td>
<td>5,408</td>
<td>5</td>
<td>Tamoxifen: 34 Overall: no reduction; In the high-risk subset$^a$: 82%</td>
<td>Placebo: 45</td>
<td></td>
</tr>
<tr>
<td>All tamoxifen prevention trials</td>
<td></td>
<td>28,442</td>
<td>Tamoxifen: 289 Overall: 38%</td>
<td>Placebo: 465</td>
<td>ER-positive invasive: 48%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ER, estrogen receptor.

$^a$The high-risk subset included women taller than 160 cm, with at least one functioning ovary, menarche at age 13, and no pregnancy before age 24.


### KEY POINTS

- Multiple randomized clinical trials have shown statistically significant reduction in the risk of breast cancer using selective estrogen receptor modulators (SERMs) including tamoxifen, raloxifene, and lasofoxifene.
- Tamoxifen increases the risk of uterine malignancy, whereas raloxifene does not; both drugs reduce the risk of vertebral fractures. Raloxifene causes fewer thromboembolic events than does tamoxifen.
- The aromatase inhibitors anastrozole and exemestane have been shown to reduce the risk breast cancer in postmenopausal women with an apparently greater safety profile, although no randomized comparisons for risk reduction have been done.
- No randomized trials have shown effectiveness of either SERMs or aromatase inhibitors in carriers of BRCA1/2 mutations.
- The ASCO 2013 Clinical Practice Guideline says that agents to reduce the risk of breast cancer should be offered to women who are at increased risk after a discussion of the risks and benefits.
breast cancer were similar regardless of Gail score. Lasofoxifene appeared to represent an advance in the progression of pharmacologic agents for reducing the risk of fractures in women with osteoporosis and the risk of breast cancer in postmenopausal women. The rate of invasive breast cancer in PEARL was more than six times higher than the stroke event rate in the placebo group; breast cancer incidence was decreased by 79% with lasofoxifene, whereas the stroke event rate also fell by 36% with lasofoxifene compared with placebo. Despite these data, the manufacturer decided, nevertheless, not to move forward with the development of this drug.

TOXICITIES
Tamoxifen increases the risk of endometrial carcinoma in postmenopausal women as well as the risk of thromboembolic events including stroke and deep vein thrombosis. Gail and colleagues demonstrated, using BCPT data, that the greatest clinical benefit with the least adverse effects, for tamoxifen compared with placebo, occurred in younger women (between ages 35 and 50) who were at elevated risk of breast cancer.

In postmenopausal women, the benefit/risk profile for both tamoxifen and raloxifene varies by age, race (i.e., white non-Hispanic, black, and Hispanic), level of breast cancer risk, and history of hysterectomy. Overall, the most favorable benefit/risk profile is seen in women at greatest risk of developing breast cancer. Postmenopausal women with an intact uterus were found to have a better benefit/risk index for raloxifene compared with tamoxifen. For postmenopausal women without a uterus, the benefit/risk ratio was not statistically significant between the two chemoprevention agents. More detailed estimates of benefit/risk profiles stratified by age and race are available online (www.uspreventiveservicestaskforce.org/draftrec4figs.htm).

RISKS AND BENEFITS
Freedman and colleagues conducted a post hoc retrospective analysis that included data from the STAR and BCPT trials. They developed a benefit/risk index to quantify both beneficial and adverse outcomes from chemoprevention with tamoxifen or raloxifene. This index helps decide whether to initiate chemoprevention by comparing the benefits and risks of raloxifene versus tamoxifen. Risks and benefits of treatment with raloxifene or tamoxifen depend on age, race, breast cancer risk, and history of hysterectomy. Over a 5-year period, postmenopausal women with an intact uterus have a better benefit/risk index for raloxifene than for tamoxifen. For postmenopausal women without a uterus, the benefit/risk ratio is similar. The benefits and risks of raloxifene and tamoxifen are described in tables (see Table 2 for an example) that can help identify groups of women for whom the benefits of chemoprevention outweigh the risks.

The number of women who experience serious adverse effects (risk) when taking a SERM is far smaller than the number of women who will avoid breast cancer (the major benefit) because of these drugs. For example, tamoxifen will prevent 20 invasive and 20 noninvasive breast cancers (based on the long-term data at an 81-month median follow-up [7 years]) in 1,000 women at the elevated 5-year risk of 4% (the average risk in STAR) versus causing 2.25 endometrial cancers (in women with an intact uterus at study entry) and 3.3 thromboembolic events in the same group of women over 7 years. Raloxifene will prevent 15 invasive and 16 noninvasive breast cancers over 7 years in 1,000 women at an elevated risk (4%) versus causing 2.47 thromboembolic events and no endometrial cancers in the same group over 7 years. For these major effects, tamoxifen causes 40 beneficial versus 5.55 adverse effects (benefit/risk ratio of 7.1) and raloxifene causes 31 beneficial versus 2.47 adverse effects (benefit/risk ratio of 13.1) over 7 years.

LACK OF USE OF SERMs FOR REDUCING THE RISK OF BREAST CANCER
In order for a preventive strategy to be both effective and efficient, we need an easily identified target population, criteria for identifying those who would benefit from a risk reduction strategy, a safe and effective agent, an informed group of practitioners who can provide care to the high-risk group, and an educated population of patients who understand the advantages and the risks of taking a drug to modify their risk.

Despite the compelling results of chemoprevention trials using SERMs for breast cancer risk reduction, there has been minimal use of either tamoxifen or raloxifene by women at risk for breast cancer. Studies monitoring SERM sales have shown that only 5% to 20% of women who matched the eligibility criteria of the breast cancer prevention trials opted for SERM therapy for breast cancer risk reduction. Additional studies reported that use actually decreased following publication of the favorable results reviewed here, with only 6% of women offered a SERM agreeing to take this medication. Furthermore, only a small proportion of these women filled the SERM prescription that they had verbally agreed to take.

A number of reasons have been put forth to explain why patients may not be willing to adopt a SERM for breast cancer risk reduction. Hormone replacement therapy (HRT) is still widely used by postmenopausal women, even after published results showed an associated increased risk for breast cancer, but its use is contraindicated with concurrent SERM therapy. Patients erroneously perceive the risks of SERM therapy to be greater than its benefits, and they perceive the risks of therapy-related side effects to be greater than their risk of breast cancer. This problem is confounded by the fact that they (and perhaps their physicians) are confused by the concept of probabilistic risk. Finally, they fear endometrial cancer out of proportion to its true tamoxifen-related risk and do not understand that there is no increased risk of uterine malignancy associated with raloxifene; we must hope that
lasofoxifene does not soon suffer the same fate of misinformation. Additional reasons not to adopt and initiate strategies to reduce the risk of breast cancer include the fear of adverse effects, medication costs, lack of reasonably accurate and feasible methods for assessing personal individual risk, and lack of established risk thresholds that maximize benefit and minimize harms.

A 2002–2004 survey of 350 primary care physicians who were members of the American Medical Association found that only 27% had prescribed tamoxifen for breast cancer risk reduction in the previous year.17 Concerns about serious side effects including endometrial cancer are important barriers, and a perceived weak or unfavorable benefit/risk ratio for an individual patient made taking a SERM for chemoprevention unacceptable.

Other factors that also may have contributed to limited use include a lack of a marker or condition to help monitor cancer risk reduction effects, cost, insufficient public and professional information, and patients’ unmet expectations. There have been concerns expressed about the accuracy of risk prediction models for individual women that can lead to doubt about an individual’s benefit when taking a SERM for cancer prevention. There also has been insufficient education of the medical profession and the public at large about the magnitude of the benefits and risks of SERM prevention.

### ASCO 2013 CLINICAL PRACTICE GUIDELINE ON THE USE OF PHARMACOLOGIC INTERVENTIONS FOR BREAST CANCER RISK REDUCTION

Clinical experts were convened by ASCO in 2013 to review the evidence presented here and to make recommendations for the management of breast cancer risk.18 These recommendations are summarized in Table 3. In women at increased risk of breast cancer who are younger than 35, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of ER-positive breast cancer. In postmenopausal women, raloxifene (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) should also be discussed as options for breast cancer risk reduction. Those at increased breast cancer risk are defined as individuals with a 5-year projected absolute risk of breast cancer greater than or equal to 1.66% based on the National Cancer Institute breast cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/), or an equivalent measure,19 or women diagnosed with lobular carcinoma in situ (LCIS). Use of other selective ER modulators or other aromatase inhibitors to lower breast cancer risk is not recommended outside of a clinical trial.

The risk reduction benefit with SERMs continues for at least 10 years in both premenopausal and postmenopausal women. Tamoxifen is not recommended for use in women

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**TABLE 2. Benefit/Risk Indices for Tamoxifen and Raloxifene Chemoprevention by Level of 5-Year Projected Risk for Invasive Breast Cancer for White Non-Hispanic Women without Uterus, by Age Group**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Tamoxifen versus placebo (without uterus)</th>
<th>Raloxifene versus placebo (without uterus)</th>
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<tbody>
<tr>
<td>5-yr projected risk of IBR (1.67%)</td>
<td>Using BREAST CANCERPT data and WHI baseline rates</td>
<td>Combining RR from BREAST CANCERPT and STAR using WHI baseline rates</td>
</tr>
</tbody>
</table>

1. 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 of chemoprevention. 

There also has been insufficient education of the medical profession and the public at large about the magnitude of the benefits and risks of SERM prevention.

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1. Benefits do not outweigh risks.
with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Tamoxifen is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers. Tamoxifen is not recommended in combination with HRT. Follow-up while on tamoxifen should include a timely workup of abnormal vaginal bleeding.

The 2013 ASCO Clinical Practice Guideline indicates that premenopausal women older than 35 with Gail model risks of breast cancer greater than 1.67% in 5 years or lobular carcinoma-in-situ should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal women who are age ≥ 35 with a 5-yr projected absolute breast cancer risk ≥1.66% or with LCIS. Risk reduction benefit continues for at least 10 yr.

<table>
<thead>
<tr>
<th>Agent</th>
<th>New Recommendations</th>
<th>Strength of Recommendation and Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal women who are age ≥ 35 with a 5-yr projected absolute breast cancer risk ≥1.66% or with LCIS. Risk reduction benefit continues for at least 10 yr.</td>
<td>Strong, evidence-based recommendation</td>
</tr>
<tr>
<td></td>
<td>Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is not recommended in combination with hormone therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up should include a timely workup of abnormal vaginal bleeding.</td>
<td></td>
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<tr>
<td></td>
<td>Discussions with patients and health care providers should include both the risks and benefits of tamoxifen in the preventive setting.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dosage: 20 mg per day orally for 5 yr</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women who are age ≥ 35 with a 5-yr projected absolute breast cancer risk ≥1.66% or with LCIS.</td>
<td>Strong evidence, based on five RCTs with low risk of bias</td>
</tr>
<tr>
<td></td>
<td>May be used longer than 5 yr in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Should not be used for breast cancer risk reduction in premenopausal women.</td>
<td>Strong evidence, based on four RCTs with low risk of bias</td>
</tr>
<tr>
<td></td>
<td>Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.</td>
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</tr>
<tr>
<td></td>
<td>Discussions with patients and health care providers should include both the risks and benefits of raloxifene in the preventive setting.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dosage: 60 mg per day orally for 5 yr</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>Should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 with a 5-yr projected absolute breast cancer risk ≥ 1.66% or with LCIS or atypical hyperplasia.</td>
<td>Moderate, evidence-based recommendation</td>
</tr>
<tr>
<td></td>
<td>Should not be used for breast cancer risk reduction in premenopausal women.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussions with patients and health care providers should include both the risks and benefits of exemestane in the preventive setting.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dosage: 25 mg per day orally for 5 yr</td>
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</tbody>
</table>
cinoma in situ should be offered tamoxifen 20 mg orally daily for the reduction of breast cancer risk. The guideline indicates that no study has evaluated the optimal age at which to begin tamoxifen to reduce breast cancer risk; premenopausal women at increased risk derive the greatest net benefit because of the absence of increased risks for either thromboembolic events or uterine cancer in this group. Because the risk of clotting increases with age, and because both stroke and pulmonary embolism are potentially life-threatening consequences of tamoxifen therapy, careful consideration must be given to risks versus benefits in older postmenopausal women who are considering tamoxifen for risk reduction.

Chemoprevention with a SERM may be particularly beneficial to women with atypical hyperplasia, a 5-year Gail model risk of more than 5%, lobular carcinoma in situ, or two or more first-degree relatives with breast cancer based on the published data reviewed in this chapter. There are no primary prevention studies to evaluate the optimum duration of tamoxifen therapy for reducing the risk of breast cancer, but completed clinical trials in the adjuvant therapy setting show that using tamoxifen for 10 years is more beneficial than only 5 years of use. No trials are being conducted or are planned to examine the ideal duration of therapy in the risk-reduction setting.

The ASCO Clinical Practice Guideline recommends that discussions with patients who are considering the use of SERMs to reduce their risk of breast cancer should include the following key points:

- Assessment and discussion of individual risk of developing breast cancer
- Options for reducing the risk of developing breast cancer (i.e., nonpharmacologic and pharmacologic)
- Potential effects of specific chemoprevention agents on the incidence of both invasive and noninvasive breast cancers
- Potential risks and adverse effects of chemoprevention agents
- Long-term effectiveness of chemoprevention agents
- Chemoprevention studies were not powered to detect differences in mortality, because it was considered that a reduction in incidence was itself an important clinical endpoint
- Accessibility, cost, and insurance coverage

### Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

### References

17. Ravdin PM. The lack, need, and opportunities for decision-making and...

