Several large, prospective trials have evaluated tamoxifen compared with placebo for breast cancer risk reduction in women at increased risk for breast cancer. Analysis of the large, prospective breast cancer risk-reduction trials that used tamoxifen estimated that tamoxifen decreased breast cancer incidence by 38% on average and estrogen receptor-positive tumors by 48%.

The single most important risk factor for breast cancer is age, and hormonally linked reproductive and anthropometric risk factors contribute to the etiology of the disease.[1-3] There is an increase in the risk of breast cancer among women who have benign breast disease, especially those with atypical ductal or lobular hyperplasia.[4,5] Lobular carcinoma in situ (LCIS) increases risk significantly, as do a history of breast cancer in first-degree relatives and the presence of BRCA1 or 2 mutations.[6] Surprisingly, and perhaps counterintuitively, diet, exercise, and environmental factors play a very small role in overall risk. Mammographic breast density increases relative risk fivefold among women with the highest density, and breast cancer risk is two to three times greater in women with elevated serum levels of estradiol or testosterone.[7] Multivariable risk models allow determination of composite relative risks along with cumulative lifetime risk, although improved models for African-American women are required.

As outlined in Figure 1, management of women at increased risk for breast cancer should include...
comprehensive quantitative risk assessment, counseling appropriate to the individual’s risk, the opportunity for genetic testing where appropriate, and a specific management prescription.[8-10] The latter should include discussion of the risks and benefits of screening, prophylactic surgery when indicated, and risk reduction using approved chemopreventive agents. Clinicians who counsel women about selective estrogen-receptor modulators (SERMs) in this context should strive to ensure that the patient makes a fully informed decision that incorporates her personal values and preferences. The counseling process should be interactive and sensitive to the patient’s educational level and cultural background.

Breast Cancer Risk Assessment

The model developed by Gail et al[11] is an accurate method of quantifying a woman’s risk of developing breast cancer. Only six factors need to be used as significant predictors of the lifetime risk of breast cancer:

1. Current age
2. Age at menarche
3. Number of breast biopsies
4. Age at first live birth (or nulliparity)
5. History of breast cancer in first-degree relatives
6. Race

A previous diagnosis of atypical lobular or ductal hyperplasia with atypia nearly doubles the estimated risk. The model accurately estimates the 5-year probability of developing breast cancer but slightly overestimates the risk for women classified in the higher quintiles of predicted 5-year risk and underestimates the risk for those in the lower quintiles.[12,13]

The Gail model works well for women at high risk, but other models may be required for women at only slightly increased risk or for whom age is the most important determinant of their risk. Risk-prediction models for breast cancer could possibly be improved by the addition of recently identified risk factors, including breast density and use of hormone therapy. Strategies for estrogen receptor (ER)-positive breast cancer risk reduction in postmenopausal women require screening of large populations to identify those with potential benefit. Age and age at menopause are statistically significantly associated with ER-positive but not ER-negative cancers.

A simpler model that includes only age, breast cancer in first-degree relatives, and previous breast biopsy examination performs similarly for ER-positive breast cancer prediction.[14] Importantly, postmenopausal women aged 55 years or older with either a previous breast biopsy examination or a family history of breast cancer show a 5-year breast cancer risk of 1.8% or higher, a widely accepted definition of being at “high risk” for breast cancer. This simplified model may be easier to use than the Gail model for identifying women who are at increased risk for breast cancer.

Tamoxifen Prevention Trials

Breast Cancer Prevention Trial

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, or NSABP P-1) commenced in 1992 with the primary aim of evaluating whether tamoxifen, administered for at least 5 years, prevented invasive breast cancer in women at increased risk.[15] It represents the largest, prospective controlled trial of tamoxifen’s risks and benefits in high-risk women.

Women were considered at increased risk (as defined by the Gail model[11]) and eligible to enter the study if they were 60 years of age or older; were 35 to 59 years old with a 5-year predicted risk for
breast cancer of ≥ 1.66% using the Gail model; or had a history of LCIS. Subjects were randomized to receive either placebo or 20 mg/d of tamoxifen. The study was stopped early after a median follow-up of 48 months, when an interim analysis showed that the benefit of tamoxifen had already reached statistical significance, decreasing the risk of invasive breast cancer in the total study population by 49% (P < .00001).

While tamoxifen was beneficial in all age groups, older women appeared to gain the most benefit[14]; the relative risk (RR) was 0.56 (95% confidence interval [CI] = 0.37–0.85) for women under age 50, 0.49 (95% CI = 0.29–0.81) for women between the ages of 50 and 59, and 0.45 (95% CI = 0.27–0.74) for women 60 years of age and older. The decrease in breast cancer incidence was accounted for entirely by a decrease in ER-positive tumors, with no significant change in the occurrence of ER-negative tumors. Overall, there was also a 21% reduction in the incidence of fractures in women treated with tamoxifen.

The adverse events and toxicity with tamoxifen occurred predominantly in women over age 50 and included localized, nonfatal endometrial cancer (RR = 4.01; 95% CI = 1.20–10.90); increased rates of stroke, pulmonary embolism, and deep-vein thrombosis (DVT); and a 14% increase in the development of cataracts. Participants in the tamoxifen group experienced more vasomotor symptoms compared with the placebo group, as well as vaginal discharge.[16] Small (< 4.0%) but consistent differences were present among women on tamoxifen reporting definite or serious problems in at least three specific domains of sexual functioning, sexual interest, arousal, and orgasm. The investigators found no increase in depressive symptoms or prolongation of depressive episodes associated with tamoxifen.[17]

After 7 years of follow-up in the BCPT,[18] the cumulative rate of invasive breast cancer was reduced from 42.5 per 1,000 women in the placebo group to 24.8 per 1,000 women in the tamoxifen group (RR = 0.57; 95% CI = 0.46–0.70) and the cumulative rate of noninvasive breast cancer was reduced from 15.8 per 1,000 women in the placebo group to 10.2 per 1,000 women in the tamoxifen group (RR = 0.63; 95% CI = 0.45–0.89). Risks of pulmonary embolism were approximately 11% lower than in the original report, and risks of endometrial cancer were about 29% higher, but these differences were not statistically significant.

The net benefit achieved with tamoxifen varied according to age, race, and level of breast cancer risk. Despite the potential bias caused by the unblinding of the P-1 trial and subsequent crossover between the treatment groups, the magnitudes of all beneficial and undesirable treatment effects of tamoxifen were similar to those initially reported, with notable reductions in breast cancer and increased risks of thromboembolic events and endometrial cancer. The incidence of all osteoporotic fractures was reduced by 19% among women taking tamoxifen, and a 45% reduction in hip fractures missed reaching statistical significance because of the small number of events reported.

International Breast Intervention Study-I
Comencing in 1992, the International Breast Intervention Study-I (IBIS-I) was a randomized placebo-controlled study with a design similar to that of the BCPT.[19] Its goal was to determine whether tamoxifen would prevent breast cancer in women at increased risk. Women between the ages of 35 and 70 were eligible, and participants included 7,152 women aged 45 to 70 with a twofold relative risk, women aged 40 to 44 with a fourfold relative risk, and women aged 35 to 39 with a tenfold relative risk of developing breast cancer.

Unlike the BCPT, participants were permitted to use hormone-replacement therapy during the study. Approximately one-third of the participants had undergone hysterectomy, and 60% had two or more first-degree relatives with breast cancer. Few women had LCIS or atypical hyperplasia. Women were at moderately increased risk, based on a published model of breast cancer risk assessment.[20] Participants received either tamoxifen at 20 mg/d for 5 years or placebo. The primary outcome measure was the frequency of both invasive and in situ breast cancer.

After a median follow-up of 50 months, 69 breast cancers were diagnosed in 3,578 women in the tamoxifen group and 101 in 3,566 in the placebo group (risk reduction = 32%; 95% CI = 8%–50%; P = .013). Endometrial cancer was nonsignificantly increased, although the study may have been underpowered to show this risk. Overall, women in the tamoxifen group had a 2.5-fold increased risk
of venous thromboembolism, and among women older than 50 years of age, there were 26 events in the tamoxifen group vs 13 in the placebo group. The endometrial cancer was seen predominantly in participants aged 50 years or older, and all cases in the tamoxifen group were early-stage disease.

Results from IBIS-I were updated after a median follow-up of 96 months[21]: 142 breast cancers were diagnosed in the 3,579 women in the tamoxifen group and 195 in the 3,575 women in the placebo group (4.97 vs 6.82 per 1,000 woman-years, respectively; RR = 0.73; 95% CI = 0.58–0.91; P = .004). The risk-reducing effect of tamoxifen was fairly constant for the entire follow-up period, and no lessening of benefit was observed for up to 10 years after randomization. Side effects in the tamoxifen group were much lower, however, after completion of the active treatment period than during treatment.

Summary of Outcomes
An analysis of the large, prospective breast cancer risk-reduction trials that used tamoxifen was published in 2003.[22] These results are summarized in Table 1 (the individual results of the Italian prevention studies have not been presented here). Overall, the trials demonstrated that tamoxifen decreased breast cancer incidence by 38% (95% CI = 28%–46%; P < .0001), and estrogen receptor–positive tumors by 48% (95% CI: 36%–58%; P < .0001). The risk of side effects attributable to tamoxifen was reduced by the concomitant use of low-dose aspirin, as well as by careful selection of women to exclude those with risk factors for thromboembolism (eg, obesity and age) and endometrial cancer (postmenopausal women).

Table 1
Major Outcome Events in Clinical Trials Using Tamoxifen for Reduction of Breast Cancer Risk

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Placebo</td>
<td>Tamoxifen</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number Randomized</td>
<td>6,681</td>
<td>6,707</td>
<td>2,790</td>
</tr>
<tr>
<td>Women-Years of Follow-Up (&lt; 10 yrs)</td>
<td>124</td>
<td>124</td>
<td>454</td>
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<tr>
<td>Age &lt; 50 yr</td>
<td>10.3</td>
<td>10.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Age &gt; 50 yr</td>
<td>15.9</td>
<td>15.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Breast Cancers</td>
<td>Total</td>
<td>69</td>
<td>101</td>
</tr>
<tr>
<td>Invasive</td>
<td>80</td>
<td>175</td>
<td>28</td>
</tr>
<tr>
<td>ER Status (invasive)</td>
<td>Positive</td>
<td>41</td>
<td>130</td>
</tr>
<tr>
<td>Negative</td>
<td>38</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Breast Cancer Age &lt; 50 yr</td>
<td>38</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>Age &gt; 50 yr</td>
<td>51</td>
<td>107</td>
<td>27</td>
</tr>
<tr>
<td>Odds Ratio for Risk Reduction (95% CI)</td>
<td>0.61</td>
<td>0.76</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CI = confidence interval; ER = estrogen receptor; IBIS = International Breast Intervention Study; NSABP = National Surgical Adjuvant Breast and Bowel Project.

Adapted from Goldin et al[20]

Click for Larger Image

Raloxifene

Raloxifene hydrochloride (Evista) is a benzothiophene SERM with characteristics similar to but distinct from the triphenlyethylene SERMs such as tamoxifen.[25] A number of clinical trials have been conducted to assess the benefit of raloxifene on osteoporosis and fracture. These are listed in Table 2. After the publication of the results of the BCPT, these osteoporosis trials (ie, Multiple Outcomes of Raloxifene Evaluation [MORE] and Continuing Outcomes Relevant to Evista [CORE]) reported data related to the incidence of invasive breast cancer among women taking raloxifene compared to those taking placebo.
STAR Trial

To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes, the NSABP conducted the Study of Tamoxifen and Raloxifene (STAR), a prospective, double-blind, randomized clinical trial that began July 1, 1999, in nearly 200 clinical centers throughout North America. The study enrolled 19,747 postmenopausal women with a mean age of 58.5 years and an increased 5-year breast cancer risk (mean risk = 4.0% in 5 years), as estimated by the Gail model. Participants were randomly assigned to receive either tamoxifen at a dose of 20 mg/d or raloxifene at 60 mg/d over 5 years. Outcomes of interest were the incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events. The trial was designed to assess statistical equivalence of the two therapies and was powered to report data when 327 cases of invasive breast cancer occurred.

After a median of 3.2 years of therapy in the STAR trial, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence = 4.30 per 1,000 vs 4.41 per 1,000; RR = 1.02; 95% CI = 0.82–1.28). The cumulative incidence through 72 months for the two treatment groups was 25.1 and 24.8 per 1,000 for the tamoxifen and raloxifene groups, respectively (P = .83). When the treatment groups were compared by baseline categories of age, history of LCIS, history of atypical hyperplasia, Gail model 5-year predicted risk of breast cancer, and the number of relatives with a history of breast cancer, the pattern of no differential effect by treatment assignment remained consistent. There were no differences between the treatment groups in regard to distributions by tumor size, nodal status, or estrogen-receptor level.

There were 57 cases of noninvasive breast cancer in the tamoxifen group compared with 80 cases in the raloxifene group (incidence = 1.51 vs 2.11 per 1,000; RR = 1.40; 95% CI = 0.98–2.00). Cumulative incidence through 6 years was 8.1 per 1,000 in the tamoxifen group and 11.6 per 1,000 in the raloxifene group. About 36% of the cases were LCIS and 54% were ductal carcinoma in situ (DCIS), with the balance being mixed types. The pattern of fewer cases among the tamoxifen group was evident for both LCIS and DCIS.

In the STAR trial, patient-reported symptoms were collected from all participants using a 36-item symptom checklist. Quality of life was measured using multiple, validated instruments in a substudy of 1,983 participants with a median follow-up of 5.4 years (range = 4.6–6.0 years). Questionnaires were administered before treatment, every 6 months for 60 months and at 72 months. Primary quality-of-life endpoints were physical and mental component summaries. Among women in the quality-of-life analysis in STAR, mean scores worsened modestly throughout the study with no significant difference between the tamoxifen and raloxifene groups. Sexual function was slightly better for participants assigned to tamoxifen.

- Adverse Events—There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR
= 0.62; 95% CI = 0.35–1.08). No differences were found for other invasive cancer sites, for ischemic heart disease events, or for stroke. Thromboembolic events (i.e., pulmonary embolism and DVT) occurred less often in the raloxifene group (RR = 0.70; 95% CI = 0.54–0.91). The absolute rate of venous thromboembolism was significantly lower among women assigned to raloxifene (2.6 per 1,000) than among those assigned to tamoxifen (3.7 per 1,000). The cumulative incidence of serious clotting events at 6 years was 21.0 per 1,000 for the raloxifene group and 16.0 per 1,000 for the raloxifene group. Pulmonary embolism and DVT occurred in 54 vs 35 women (RR = 0.64; 95% CI = 0.41–1.00) and in 87 vs 65 women (RR = 0.74; 95% CI = 0.53–1.03) assigned to tamoxifen and raloxifene, respectively.

Although there was no significant difference in the rates of death from any cause or total stroke according to group assignment in the STAR trial, raloxifene was associated with an increased risk of fatal stroke (59 vs 39 events; HR = 1.49; 95% CI = 1.00–2.24; absolute risk increase = 0.7 per 1,000 woman-years). The number of osteoporotic fractures in the groups was similar. There were fewer cataracts (RR = 0.79; 95% CI = 0.68–0.92) and cataract surgeries (RR = 0.82; 95% CI = 0.68–0.99) among women taking raloxifene. There was no difference in the total number of deaths or in causes of death.

**Risk-Benefit Considerations**

Guidelines for the use of SERMs for breast cancer risk reduction are listed in Table 3. Of the more than 65 million women aged 35 to 79 years without reported breast cancer in the United States in 2000, more than 10 million women would be eligible for tamoxifen chemoprevention using widely accepted definitions of increased risk.[31] The percentage of eligible women varies by race, with 19% of white women, 6% of black women, and 3% of Hispanic women being eligible. Of the more than 50 million white women in the United States aged 35 to 79 years, nearly 2.5 million would have a positive benefit-risk index for tamoxifen chemoprevention.

**Table 3**

Use of Selective Estrogen-Receptor Modulators for the Reduction of Breast Cancer Risk

**Women Who May Consider the Use of Tamoxifen for Risk Reduction**
- History of lobular carcinoma in situ
- History of ductal carcinoma in situ
- History of atypical ductal or lobular hyperplasia
- Premenopausal, with mutations in either the BRCA1 or BRCA2 genes or other predisposing genetic mutations
- Age ≥ 35 yr with Gail model 5-yr probability of breast cancer ≥1.66%

**Women in Whom Caution Should Be Used When Considering Tamoxifen Use**
- History of stroke, transient ischemic attack, deep-vein thrombosis, or pulmonary embolus
- History of cataracts or cataract surgery
- Current use of hormone-replacement therapy

Chemoprevention with tamoxifen is particularly beneficial to women with atypical hyperplasia, a 5-year Gail et al model risk of more than 5%, LCIS, or two or more first-degree relatives with breast cancer.[32] Conservative cost modeling predicts that tamoxifen prolongs the average survival of
women initiating use before age 60 years[33-36] and prolongs quality-adjusted survival most for those with either atypical hyperplasia or LCIS.

Aromatase Inhibitors

Aromatase inhibitors have yet to be approved by the US Food and Drug Administration for the chemoprevention of breast cancer, but data from the adjuvant setting have provided the rationale for study of their potential use as chemopreventive agents.[37] Ongoing, randomized, placebo-controlled trials investigating the use of third-generation aromatase inhibitors in the chemoprevention of breast cancer in postmenopausal women include the National Cancer Institute of Canada Clinical Trials Group’s MAP.3 (ExCel) trial (Exemestane in Preventing Cancer in Postmenopausal Breast Cancer Patients at Increased Risk of Developing Breast Cancer), and the International Breast Cancer Intervention Study (IBIS-II) trial.[38] The North American MAP.3 study randomizes patients to exemestane or placebo in patients who refuse treatment with a SERM, and the international IBIS-II trial compares anastrozole for 5 years vs placebo for chemoprevention in patients at increased risk. Until these trials are completed, it is not appropriate to use aromatase inhibitors to reduce the risk of breast cancer in postmenopausal women. Aromatase inhibitors have no role in treating or preventing breast cancer in premenopausal women.

Summary

A list of clinical maxims related to the use of SERMs to reduce breast cancer risk is shown in Table 4. No single risk number should be used to decide whether a woman should take a preventive intervention like tamoxifen. The risks and benefits of tamoxifen therapy depend on age as well as a woman’s specific risk factors for breast cancer.[37,38] The absolute risks from tamoxifen for endometrial cancer, stroke, pulmonary embolism, and DVT increase with age, as does the protective effect of tamoxifen on fractures.[32]

For example, a 40-year-old woman with a 5-year Gail risk of 2.0% might be advised to take tamoxifen because she has very small risks of adverse effects such as stroke, pulmonary emboli, or endometrial cancer, whereas a 60-year-old woman with the same 2.0% risk would probably not be advised to take tamoxifen because the risks from adverse events outweigh the benefits. Raloxifene is a safer option than tamoxifen for postmenopausal women because of the 30% lower risk of
clotting seen in the STAR trial.

Tamoxifen has its greatest clinical benefit with less severe side effects in women who do not have a uterus and in women at higher risk of breast cancer. Published tables are available to describe the risks and benefits of tamoxifen and to identify classes of women for whom the benefits outweigh the risks.[32] Compared to placebo in postmenopausal women at average risk of breast cancer in the published osteoporosis trials, raloxifene reduces the risk of invasive breast cancer by 44% to 76%, as summarized in Table 2.[25] Among younger postmenopausal women who are at increased risk of breast cancer, raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer. Raloxifene appears to be less effective than tamoxifen in reducing the risk of in situ breast cancer, although the results in the STAR trial were not statistically significant. Across all placebo-controlled trials with raloxifene, however, in situ cancers occurred more often with raloxifene than with placebo or tamoxifen. In high-risk, younger postmenopausal women, raloxifene appears to offer a net benefit when balancing reduction of the risk of breast cancer and the prevention of fractures against the risk of stroke, venous thromboembolic events, uterine events, and symptomatic side effects.

Other agents such as the aromatase inhibitors are in development for breast cancer risk reduction in the postmenopausal population, and preliminary results from ongoing prevention trials are expected in the next few years.

**Future Directions**

Primary prevention trials with breast cancer incidence as the endpoint are large and expensive, but they remain the standard for the approval of drugs seeking primary risk reduction indications. An alternative design would be to grant approval for primary risk reduction to agents such as tamoxifen and the aromatase inhibitors that show reduction in the incidence of contralateral, second breast primary tumors in adjuvant therapy trials of women with primary breast cancer. Such trials afford both the demonstration of efficacy and safety in populations of women who are at increased risk of breast cancer due to their initial diagnosis, and who are representative of women at increased risk of breast cancer who are potential candidates for primary risk reduction. Using these designs would significantly reduce the cost of demonstrating efficacy in the primary risk reduction setting and would bring effective agents to clinical practice in a more timely manner than the current approval standard.

This article is reviewed here:

Addressing Concerns About Breast Cancer Prevention
The Search for Antiestrogens
In Memoriam

Dr. Martin Abeloff was my teacher and my friend. In the early 1980s, when I was a medical oncology fellow at Johns Hopkins, there were very few academic physicians talking in a meaningful way about cancer prevention. The Johns Hopkins School of Hygiene and Public Health (now the Bloomberg School of Public Health) had always studied and promoted prevention as both a lofty ideal and a clinical and public necessity. When I was a fellow at the hospital learning the tenets of clinical oncology under Marty’s watchful tutelage, the School of Public Health pioneered a program, with the support of the Andrew W. Mellon Foundation, in clinical epidemiology. It sought to train clinicians in the rigors of epidemiology and biostatistics to prepare us for careers in clinical research. It was with some fear and apprehension that I approached Marty and told him that I wanted to pursue the training as the first Mellon fellow from medical oncology (several others would soon follow with Marty’s encouragement), and that my real passion was to study the etiology and prevention of breast cancer. Marty said without any hesitation or reluctance that I could attend classes at the school in the morning and make consult rounds or go to the clinic in the afternoon.

As I slowly learned over the next 2 decades, I should not have been surprised that Marty was not only supportive of my intentions, but also that he was wildly enthusiastic about my personal and professional goals. He invited me back to Hopkins several times, and on each visit I sensed his pride in both my interests and my modest accomplishments. As he neared the end of his career, he was
even more committed to clinical and translational prevention research. Along with our entire profession, I mourn our untimely loss of his compassion, imagination, and leadership. I owe a debt of enormous personal gratitude to him that I can never completely nor adequately repay. Thank you, Marty. We miss you dearly, and we promise to build upon the legacy of your guidance and vision.

—Victor G. Vogel, MD, MHS, FACP

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