Chemoprevention of breast cancer and the trials of the National Surgical Adjuvant Breast and Bowel Project and others

R E Smith and B C Good

National Surgical Adjuvant Breast and Bowel Project, Four Allegheny Center, 5th Floor, Pittsburgh, Pennsylvania 15212, USA

Abstract

The idea of breast cancer prevention by hormonal means stemmed from the results of treatment trials, many of them carried out by the National Surgical Adjuvant Breast and Bowel Project (NSABP). Over the years, a number of NSABP treatment studies demonstrated that breast cancer recurrence was reduced in women with the disease who were given tamoxifen, a selective estrogen receptor (ER) modulator (SERM). Five subsequent tamoxifen prevention trials with this agent have shown a 48% reduction in ER-positive cancers, but no effect for ER-negative cancers, and an increase in endometrial cancer and thromboembolic events. The drug raloxifene, another SERM, originally examined as an osteoporosis agent, has also shown promise for the prevention of breast cancer, although, as with tamoxifen, the drug carries a risk for thromboembolic events. There is recent evidence in a large treatment trial that the aromastase inhibitor anastrazole, a 'pure anti-estrogen', holds promise as a breast cancer preventive agent. Longer follow-up and the testing of additional agents is required before these drugs can be used widely for prevention. In addition, future research should focus on the identification of at-risk women who can perhaps be targeted for specific prevention agents.

Introduction

Medical options for women at high risk of breast cancer, some of whom are in the high-risk category because of the BRCA1 or BRCA2 mutation, until recently included prophylactic mastectomy and frequent monitoring including mammography. The possibility of an effective chemohormonal agent for the prevention of breast cancer was given new impetus with the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP)'s prevention study (P-1), in which tamoxifen was shown to reduce the risk of recurrence and the risk of dying from breast cancer (Fisher et al. 1998a). To the present time, tamoxifen remains the endocrine treatment of choice for the prevention of estrogen receptor (ER)-positive breast cancer. However, tamoxifen has a number of toxicities and unpleasant side-effects, including and most prominently hot flashes, and thus the pursuit of more effective agents that are less toxic continues.

When the 3- and 4-year results from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial were published in 1999 and 2001 (Cummings et al. 1999, Cauley et al. 2001), the drug raloxifene also demonstrated usefulness in reducing the risk of breast cancer in women with osteoporosis, as its authors concluded, 'through prevention of new cancers or suppression of subclinical tumors, or both'. In addition, the selective non-steroidal aromatase inhibitors, including aromatase, have become established as second-line endocrine therapy in advanced postmenopausal breast cancer and are now being looked at as possible preventive agents.

In this article we discuss some of the studies that led to the chemoprevention trials that have been and are being conducted in the search for an agent that will prevent the development of breast cancer in otherwise healthy women, the major chemoprevention trials themselves, and a number of the hormonal/chemotherapeutic agents that may be studied in the future.

The role of ER blockers in breast cancer

Hormone receptor blockade and downregulation are important components in the treatment of both early and advanced hormone receptor-positive breast cancer. Results from the treatment studies of the NSABP and other cancer trials
groups led to this conclusion, and as a result of these efforts, a number of ER blockers are currently available or are in preclinical development. It is widely anticipated that, as knowledge of specific molecular therapeutic targets and their mechanisms of signal transduction expands, more options will become available for the modulation of hormone receptor activity. It is obvious that a complex relationship exists among the family of epidermal growth factor receptors, vascular endothelial growth factor receptors, and hormone receptors that permits significant molecular cross-communication that may be of value in the application of targeted therapies (Adams et al. 2000, Ellis et al. 2001, Knoop et al. 2001, Kurokawa & Arteaga 2001, McNamara et al. 2001).

Recently ER blockers (also known as anti-estrogens) have come to be referred to as SERMs (selective ER modulators). This change in terminology is largely due to the differing effects (estrogen agonistic vs estrogen antagonistic) specific agents might have at different tissue sites and to the recognition that the mechanisms of their anti-estrogenic activity is diverse. For example, tamoxifen and toremifene, the SERMs for which the longest clinical experience is available, act as estrogen antagonists in breast tissue and as estrogen agonists in bone and endometrium (Hayes et al. 1995, Tomas et al. 1995). On the other hand, raloxifene, an agent currently used to prevent osteoporosis, behaves as an estrogen antagonist in both breast and endometrium (Black et al. 1983, Fuchs-Young et al. 1995). These differences in the activity of SERMs appear to be related to differences in their molecular structures (e.g. tamoxifen and toremifene are both triphenylethylenes; raloxifene is a benzothiophene; and faslodex is a steroidal estradiol analogue). The triphenylethylenes and benzothiophenes are partial estrogen analogues, in that a communication that may be of value in the application of preclinical development. It is widely anticipated that, as knowledge of specific molecular therapeutic targets and their mechanisms of signal transduction expands, more options will become available for the modulation of hormone receptor activity. It is obvious that a complex relationship exists among the family of epidermal growth factor receptors, vascular endothelial growth factor receptors, and hormone receptors that permits significant molecular cross-communication that may be of value in the application of targeted therapies (Adams et al. 2000, Ellis et al. 2001, Knoop et al. 2001, Kurokawa & Arteaga 2001, McNamara et al. 2001).

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**NSABP adjuvant trials with tamoxifen**

The NSABP is interested in the application of hormonal manipulation in the adjuvant therapy of breast cancer and its role as a risk-reducing modality in patients at risk for the development of breast cancer. As a result of the work of the NSABP and other cooperative groups, over the last 20 years tamoxifen has become an important part of the treatment armamentarium for patients with hormone receptor-positive breast cancer and an agent for the prevention of the development of breast cancer.

A number of the NSABP’s treatment trials can be looked at as stepping stones to the group’s chemoprevention studies. In NSABP treatment trials B-09, B-14, B-21, B-23, B-24 and P-1, more than 17 000 women have been randomized to receive either tamoxifen or placebo (Table 1). The duration of treatment was 2 years in trial B-09 and 5 years in the other trials. In Protocol B-14, patients who completed 5 years of tamoxifen had the option of being randomly assigned to receive either up to an additional 5 years of tamoxifen or placebo. In Protocols B-09 and B-23, patients were randomized to receive chemotherapy with or without tamoxifen.

**NSABP Protocol B-09**

Patients included in the B-09 trial had node-positive breast cancer and were 49 years of age or younger with both estrogen and progesterone receptor levels of 10 femtamoles per milligram of background protein (fmol/mg protein) or more; 50–59 years of age, with progesterone receptor levels greater than 10 fmol/mg protein or more; or 60–69 years of age. All patients in the B-09 trial received the same chemotherapy (melphalan and fluorouracil) regimen for the first 2 years and patients in the B-09 trial received the same chemotherapy (melphalan and fluorouracil) regimen for the first 2 years and were randomly assigned to either tamoxifen or no tamoxifen for 2 years. After the completion of that trial, a cohort of patients was offered continued tamoxifen for an additional third year. A comparison of women who received chemotherapy plus tamoxifen for 2 years vs women who received the same treatment plus an additional year of tamoxifen demonstrated that those in the latter group had a better disease-free survival (DFS) rate (odds ratio (OR) 1.54; 95% confidence interval (CI) 1.02–2.37; P = 0.04) through their fifth postoperative year. Women 50 years of age or older benefitted, but those 49 years or younger did not (Fisher et al. 1981, 1987). Because the benefit achieved beyond the third year was obtained when tamoxifen was given without...
chemotherapy, the question remained whether the use of chemotherapy with tamoxifen was better than treatment with tamoxifen alone. The results of this trial and the derivative question led to the development of NSABP Protocol B-16.

**NSABP Protocol B-16**

NSABP B-16 was performed in attempt to answer this question in terms of improving DFS, distant DFS (DDFS), and survival in node-positive, tamoxifen-responsive patients aged ≥ 50 years. Women were randomized among three treatment groups: (i) tamoxifen alone; (ii) Adriamycin (doxorubicin), cyclophosphamide and tamoxifen (ACT); or (iii) melphalan (L-PAM), fluorouracil (5-FU), and tamoxifen (PFT). The PFT arm was later modified so that new patients also received Adriamycin (PAFT). Findings from 1124 eligible patients through 3 years of follow-up indicated a significantly better DFS for ACT-treated patients than for those who received tamoxifen alone (84 vs 67%; \(P = 0.0004\)). An advantage in DDFS and survival was also observed after ACT therapy (83 vs 73% \((P = 0.04)\) in the former) and 93 vs 85% \((P = 0.04)\) in the latter). Both the DFS and DDFS of PAFT-treated patients were better than in those treated by tamoxifen alone (83 vs 66%, \(P = 0.0002\) and 85 vs 73%, \(P = 0.003\)). Patients who received PTF also fared better in DFS and DDFS than did patients taking tamoxifen (81 vs 72%, \(P = 0.07\) and 85 vs 74%, \(P = 0.02\)). The major conclusion from this study was that node-positive breast cancer patients aged ≥ 50 years demonstrated better outcome with the use of postoperative, prolonged tamoxifen and short-course doxorubicin/cyclophosphamide (AC) therapy (completed in 63 days) than with prolonged tamoxifen therapy alone.

**NSABP Protocol B-23**

In contrast to the B-09 trial, the B-23 trial compared chemotherapy (AC with cyclophosphamide/methotrexate/fluorouracil (CMF)) with or without tamoxifen or placebo in women with clinically node-negative and ER-negative breast cancer. Through 5 years of follow-up, there was no difference in either DFS \((P = 0.52)\) or survival \((P = 0.89)\) between patients who received tamoxifen and those who received placebo \((Fisher et al. 2001a)\).

**NSABP Protocol B-21**

NSABP trial B-21 was designed to evaluate the role of radiotherapy and tamoxifen in the management of women with node-negative breast cancer whose primary tumor was less than 1 cm in diameter. Patients were assigned to post-lumpectomy in-breast irradiation alone, tamoxifen alone, or in-breast irradiation plus tamoxifen. Although through 60 months of follow-up there was no difference in overall survival among the three groups \((P = 0.9)\), there was a significant difference in the cumulative incidence of both ipsilateral breast tumor recurrence (IBTR) and contralateral breast tumor (CBT) among the three groups. The cumulative incidence of IBTR was significantly reduced by tamoxifen with or without radiation (tamoxifen alone vs radiation therapy (RT) alone vs RT plus tamoxifen: cumulative incidence, 4.8, 2.0, 10.7% respectively, \(P < 0.00001\); RT alone vs tamoxifen alone, \(P = 0.01\); RT alone vs RT plus tamoxifen, \(P = 0.007\); RT plus tamoxifen vs tamoxifen alone, \(P = 0.0000002\), as was the cumulative incidence of CBT (RT alone vs tamoxifen with or without RT, 3.0 vs 0.6%, \(P = 0.04\) \((Wolmark et al. 2000)\).

**NSABP Protocols B-06 and B-17**

NSABP B-06 was a randomized trial that demonstrated that lumpectomy followed by radiation therapy was as effective as modified radical mastectomy in the treatment of patients with invasive breast cancer. What followed was that many patients with invasive disease were treated with conservation surgery, while those with non-invasive malignancies were still treated with the more aggressive mastectomy \((Fisher et al. 1995, Katz et al. 2001)\). The uncertainty in the medical community of how to approach patients with small, non-invasive tumors or ductal carcinoma in situ (DCIS) stimulated the NSABP to implement Protocol B-17 to compare conservative surgery (i.e. lumpectomy) alone or the combination of lumpectomy followed by radiation therapy for the treatment of these patients. After 12 years of follow-up, lumpectomy and postoperative in-breast irradiation were shown to be more appropriate than lumpectomy alone for the prevention of both ipsilateral invasive (cumulative incidence, 7.7 vs 16.8%; relative risk (RR) 0.38; 95% CI 0.25–0.59; \(P = 0.00001\)) and ipsilateral non-invasive (cumulative incidence, 8.0 vs 15.7%; RR 0.49; 95% CI 0.32–0.76; \(P = 0.001\) disease, but not for contralateral invasive (RR 1.05; 95% CI 0.53–2.08; \(P = 1.00\)) or contralateral non-invasive (RR 3.49; 95% CI 0.99–12.38; \(P = 0.06\) disease \((Fisher et al. 1998b, 2001b)\). Despite these promising results, it became obvious that there exists a population of women either (i) with mammographically detected, scattered, diffuse microcalcifications thought to be indicative of unremoved DCIS or (ii) who had disease in which margins free of DCIS could not be attained. It was already known that tamoxifen had both anti-initiator and anti-promoter properties, reduced the incidence of IBTR, and prevented secondary CBTs \((Jordan et al. 1990, Osborne et al. 1985, ‘Nolvadex’ Adjuvant Trial Organisation 1985, Breast Cancer Trials Committee 1987, CRC Adjuvant Breast Trial Working Party 1988, Baum et al. 1991, Rutqvist et al. 1991)\).

**NSABP Protocol B-24**

Because of the encouraging results from B-17 and the concerns noted above, NSABP Protocol B-24 was initiated.
This was a double-blinded, randomized controlled trial that tested the hypothesis that, in patients with DCIS, treatment with lumpectomy followed by in-breast irradiation and tamoxifen would be more effective than lumpectomy followed by in-breast irradiation alone in preventing invasive and non-invasive cancers in both the ipsilateral and contralateral breast. At 7 years of follow-up, a comparison of the cumulative incidence of ipsilateral invasive (2.6 vs 5.3%; RR 0.53; 95% CI 0.32–0.86; \( P = 0.01 \)) and ipsilateral non-invasive (5.0 vs 5.8%; RR 0.85; 95% CI 0.56–1.29; \( P = 0.48 \)) cancer was in favor of those patients who received tamoxifen, as was the cumulative incidence of contralateral disease (invasive 1.8 vs 3.2%; RR 0.64; 95% CI 0.35–1.17; \( P = 0.16 \); non-invasive RR 0.32; 95% CI 0.09–0.93; \( P = 0.03 \)) (Fisher et al. 2001b).

It is important to emphasize that although the proportion of patients assigned to the two arms of this study was balanced for tumor size, tumor margin status, the presence of comedonecrosis, age and ethnicity, ER status was not a prerequisite for enrollment. Of 1804 total patients with DCIS enrolled in the study, results from ER analysis were available from 676 patients (344 patients assigned to receive placebo; 332 patients assigned to receive tamoxifen). ER status was determined for 450 of these patients in a ‘central’ reference laboratory using a standardized immunohistochemical method, and the ER status of the remaining 226 was performed at other ‘outside’ laboratories using various immunohistochemical methods.

The distribution of ER status between the subset that received placebo and the tamoxifen-treated subsets was remarkably similar (ER-negative: placebo 25%, tamoxifen 20%; ER-positive: placebo 75%, tamoxifen 80%) and not statistically significantly different. In addition to ER status, there were no statistically significant imbalances between the placebo- and tamoxifen-treated subsets in the distribution of several other variables that might influence clinical outcome including tumor size, the status of surgical margins, the presence or absence of comedonecrosis, and patient age.

### Table 2 Sites and frequency of first breast cancer events by ER status and treatment in NSABP study B-24 (median follow-up = 8.7 years)

<table>
<thead>
<tr>
<th>Site of Event</th>
<th>ER status</th>
<th>Placebo (n = 84)</th>
<th>TAM (n = 82)</th>
<th>Placebo (n = 243)</th>
<th>TAM (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>ER-negative</td>
<td>22 (26%)</td>
<td>14 (23%)</td>
<td>56 (23%)</td>
<td>24 (10%)</td>
</tr>
<tr>
<td></td>
<td>ER-positive</td>
<td>15 (18%)</td>
<td>11 (17%)</td>
<td>32 (13%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Is ipsilateral</td>
<td>ER-negative</td>
<td>5 (6%)</td>
<td>3 (5%)</td>
<td>20 (8%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td></td>
<td>ER-positive</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Contra lateral</td>
<td>ER-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>ER-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER-positive</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

TAM, tamoxifen.

As indicated in Table 2, with a median follow-up of 8.7 years, about two-thirds of all events in the B-24 study were local recurrences in the ipsilateral breast. Almost all the remaining events were in the contralateral breast, although there were a few recurrences at other locations. In patients with ER-negative DCIS, the proportions of events were similar in the placebo- and tamoxifen-treated subsets. Among patients with ER-positive DCIS, there was a 50% reduction in the proportion of first-time breast cancer events in the tamoxifen-treated subset compared with the subset assigned to receive placebo.

The value of tamoxifen treatment is emphasized in Fig. 1, which shows the Kaplan–Meier curves for time to the first breast cancer event among the ER-positive and ER-negative subsets. As shown in this figure, 90% of the tamoxifen-treated patients with ER-positive DCIS were disease-free at 9 years; among patients in the other groups, the proportion of those free of breast cancer events at 9 years was 70–80%.

The RR of subsequent breast cancer among patients with ER-positive DCIS was 0.41 among tamoxifen-treated patients (a 59% reduction, \( P = 0.0002 \)) compared with patients with ER-positive DCIS assigned to receive placebo. Unexpectedly, the risk among tamoxifen-treated patients with ER-negative DCIS was 0.8 (a 20% reduction, \( P = 0.5 \)) when compared with patients with ER-negative DCIS who received placebo.

The explanation for this trend toward a benefit for tamoxifen among patients with ER-negative DCIS, however, appears to be due to a disjunction in the interpretation of ER status between the ‘central’ reference laboratory, which used a standardized immunohistochemical technique and other ‘outside’ laboratories, which carried out their interpretations using various methods. When the frequency of breast cancer events among patients with ER-negative DCIS was compared by treatment and type of laboratory performing the ER analysis, the RR reduction was 57% among patients whose ER status was analyzed at the ‘outside’ laboratories, but the RR reduction was only 1% when the analysis was performed by a central laboratory using a standardized method. It is likely, therefore, that the group of patients defined by the outside laboratories that used various methods to determine the ER status as having ER-negative DCIS had an unacceptable high frequency of false-negative results, leading to the impression of response to tamoxifen.

**NSABP Protocols B-13 and B-14**

In September 1985, the National Institutes of Health Consensus Development Conference on Adjuvant Chemotherapy and Endocrine Therapy for Breast Cancer concluded that there was sufficient information to make recommendations about the treatment of patients with primary breast cancer and positive axillary nodes, but the panel offered no recommendations about systemic therapy for patients with node-negative dis-
ease. Because few data were available at that time from clinical trials specifically conducted to evaluate systemic therapy in such patients, the NSABP mounted two parallel clinical trials. NSABP Protocol B-13 assessed the effectiveness of sequential methotrexate and fluorouracil in women who had ER-negative tumors (< 10 fmol/mg protein) and a high risk for recurrence (Fisher & Redmond 1992). Protocol B-14 was carried out to determine the effectiveness of tamoxifen in patients with ER-positive breast cancer (≥10 fmol/mg protein) who were regarded as having a good prognosis. In this trial, women were randomized to receive either postoperative tamoxifen (10 mg twice daily) or placebo for 5 years. Later, the protocol was modified to allow patients who had completed 5 years of tamoxifen and remained disease-free to be randomized again to receive either an additional 5 years of tamoxifen or placebo. After the study began, other patients who met the same eligibility criteria for the study as the randomized patients were registered on study and assigned to receive 5 years of tamoxifen. As with the original group of randomized patients assigned to receive tamoxifen, if the registered patients remained disease-free for 5 years, they were offered the opportunity to be randomized to tamoxifen or placebo for an additional 5 year period.

Through 10 years of follow-up, a significant advantage in DFS (69 vs 57%; RR 0.66; 95% CI 0.58–0.74; P < 0.0001), DDFS (76 vs 67%; RR 0.70; 95% CI 0.61–0.81; P < 0.0001), and survival (80 vs 76%; RR 0.84; 95% CI 0.71–0.99; P = 0.02) was found for patients in the group first assigned to receive tamoxifen. In addition, tamoxifen therapy was associated with a 37% reduction in the incidence of CBT (P = 0.007). Interestingly, through 4 years after the reassignment of tamoxifen-treated patients to either further tamoxifen or placebo, advantages in DFS (93 vs 86%, P = 0.003), and DDFS (96 vs 90%, P = 0.01) and survival (96 vs 94%; P = 0.08) were found for those who discontinued the tamoxifen treatment (Fisher et al. 1987, 1989, Fisher & Redmond 1992). With 15 years of follow-up, significant differences in DFS (P < 0.0001), DDFS (P < 0.0001) and survival (P = 0.0004) in favor of tamoxifen remain. Of interest is that although the DFS and DDFS benefits were obvious early in follow-up, the survival advantages did not become apparent until 7 years of follow-up (Fisher et al. 2002).

The reduction in the incidence of CBT is further supported by the overview of randomized trials investigating the use of tamoxifen for early breast cancer performed by the Early Breast Cancer Trialists’ Collaborative Group (1998). The data submitted to the trialists for this study were from 37,000 women participating in 55 randomized trials including women participating in NSABP B-14. The overview found that in the trials of 1, 2 or about 5 years of tamoxifen, the proportional reductions in the incidence rate of CBT among women allocated to tamoxifen were respectively, 13% (s.d. 13; NS), 26% (s.d. 9; two-sided P = 0.004), and 47% (s.d. 9; two-sided P < 0.00001). These results are consistent with those reported from the B-14 trial.

**NSABP Protocol B-20**

In NSABP B-20, 2363 ER-positive, node-negative patients whose tumors had been resected were assigned to either tamoxifen alone (788 patients) or CMF plus tamoxifen (789 patients). With 11.8 years of median follow-up, in patients either ≤ 49 years of age or reported to be premenopausal, the use of CMF plus tamoxifen resulted in highly significant benefit in DFS (≤ 49 years, P = 0.01; pre-, P = 0.0001), relapse-free survival (≤ 49 years, P = 0.005; pre-, P = 0.001),

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**Figure 1** Time to first breast cancer event among ER-positive and ER-negative patients in the NSABP B-24 trial, by agent.
DDFS (≤ 49 years, \( P = 0.003 \); pre-, \( P = 0.0008 \)), and survival (≤ 49 years, \( P = 0.01 \); pre-, \( P = 0.002 \)). In patients 50–59 years of age, the use of CMF plus tamoxifen resulted in a benefit in DFS (\( P = 0.01 \)), relapse-free survival (\( P = 0.003 \)), DDFS (\( P = 0.06 \)), and survival (\( P = 0.04 \)) similar to or better than that seen in patients 49 years of age or less. In patients ≥ 60 years of age, the use of CMF plus tamoxifen failed to enhance the benefit from tamoxifen in regard to DFS (\( P = 0.15 \)), relapse-free survival (≥ 60 years, \( P = 0.9 \); post-, \( P = 0.04 \)), DDFS (≥ 60 years, \( P = 0.5 \); post-, \( P = 0.16 \)), and survival (≥ 60 years, \( P = 0.5 \); post-, \( P = 0.46 \)) (Fisher et al. 2002).

The next step

The striking reduction in the incidence of tumor recurrence and CBT among patients with ER-positive breast tumors who received tamoxifen for either an invasive or a non-invasive malignancy while participating in NSABP Protocols B-21, B-24, and B-14, along with similar observations by other investigators, led to the speculation that tamoxifen might serve as preventive intervention among patients at high risk for the development of breast malignancies (Fisher & Redmond 1991). A record of good compliance and an acceptable adverse event profile associated with prolonged tamoxifen use were also compelling reasons to undertake a prevention study.

The NSABP Breast Cancer Prevention Trial (P-1)

The NSABP initiated the Breast Cancer Prevention Trial (P-1) in 1992 (Fisher et al. 1998a). A total of 13 388 women at increased risk for developing breast cancer because they (i) were 60 years of age or older; (ii) were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%; or (iii) had a history of lobular carcinoma in situ (LCIS), were randomly assigned to receive either tamoxifen (20 mg/day) or placebo for 5 years. In this study, the algorithm used for determining breast cancer risk was based upon the multivariate logistic regression model developed by Gail et al. (1989) in which combinations of risk factors were used to estimate the probability of occurrence of breast cancer over time. The variables included in this model are age, number of first degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathological diagnosis of atypical hyperplasia, and age of menarche. The results from this study were striking, and by March 1997 enough data had been gathered and assessed to convince the independent data-monitoring committee overseeing the conduct of the trial to recommend early disclosure of the results.

The P-1 trial demonstrated that tamoxifen for 5 years reduced the risk of invasive breast cancer by 49% (two-sided \( P < 0.0001 \)), with a cumulative rate of invasive disease through 69 months of follow-up of 43.4 vs 22.0 per 1000 women in the placebo and tamoxifen groups respectively. The decreased risk occurred in women 49 years of age or younger (44%), 50–59 years (51%), and 60 years or older (55%). The risk of developing breast cancer was also reduced in women with a history of LCIS (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of non-invasive breast cancer by 50% (two-sided \( P < 0.002 \)) and the occurrence (event/1000 women) of ER-positive tumors by 69% (41 vs 130), but there was no difference in the occurrence (event/1000 women) of ER-negative tumors (38 vs 31) or of tumors that were receptor unknown (10 vs 14). This contrasts with other data about the effect of tamoxifen on the occurrence of ER-negative tumors (Li et al. 2001).

Using data from a population-based tumor registry, investigators from the Fred Hutchinson Cancer Research Center (Seattle, WA) retrospectively classified 4654 women as having received adjuvant tamoxifen therapy and 4327 women as having not received adjuvant tamoxifen. Eighty-nine tamoxifen users and 100 tamoxifen non-users were identified with CBTs; of all of these, 112 had ER-positive tumors, 20 had ER-negative tumors, and 57 had tumors that were considered either ER unknown or undetermined by acceptable methods. Using the Cox regression model, the risk of ER-positive and ER-negative CBTs among tamoxifen users was estimated as 0.8 (95% CI 0.5–1.1) and 4.9 (95% CI 1.4–17.4) times that of the non-tamoxifen users, respectively. This difference in risk by ER status is significant (\( P < 0.0001 \)).

In the P-1 trial, tamoxifen did not alter the average annual rate of ischemic heart disease, but it did reduce the number of hip (RR 0.55; 95% CI 0.25–1.15), radius (RR 0.54; 95% CI 0.24–1.23), and spine fractures (RR 0.74; 95% CI 0.41–1.32) in those who received it compared with those who did not. The rate of endometrial carcinoma was increased among tamoxifen users relative to non-users (RR 2.53; 95% CI 1.35–4.97), primarily among women aged 50 or older whose tumors were classified low grade and stage 1. Because there is a small increased risk for the development of uterine sarcomas among patients receiving tamoxifen in P-1, the rate of occurrence of endometrial cancer or uterine sarcoma was evaluated longitudinally and across protocols (B-09, B-14, B-21, B-23 and B-24). Among patients assigned tamoxifen, the rate (per 1000 patient years) of adenocarcinoma of the uterus was 1.26 and the rate of uterine sarcoma 0.17. Among patients not assigned tamoxifen, the rate of adenocarcinoma of the uterus was 0.58; no uterine sarcomas were reported in this group. No deaths from either endometrial cancer or uterine sarcoma were reported. The risks of stroke (RR 1.59; 95% CI 0.93–2.77), pulmonary embolism (RR 3.01; 95% CI 1.15–9.27), and deep-
vein thrombosis (RR 1.60; 95% CI 0.91–2.86) were elevated in the tamoxifen users compared with those assigned placebo. As with the rate of endometrial carcinoma, these events were more frequent among women who were 50 years or older. The only symptomatic differences between the tamoxifen users and the non-users were the frequency of hot flashes (81 vs 69%) and the frequency of vaginal discharge (55 vs 35%). (It is interesting to note that the non-compliance rate among patients assigned to tamoxifen in the P-1 trial was 23.7% and has been reported to be as high as 25% (Guerrieri-Gonzaga et al. 2001), and the refusal rate among women offered tamoxifen risk-reduction intervention was 94% in one study (Port et al. 2001).) The primary reason for withdrawal from tamoxifen administered for the purpose of risk reduction was the severity of hot flashes; patient refusals were also related to fear of side-effects such as endometrial carcinoma and thromboembolic events.

It is interesting that in a minority of ER-positive women, tamoxifen is ineffective. This fact has been attributed to an interaction between breast tumors that are HER-2/neu-positive and high levels of the ER coactivator SRC-3 (AIB1), which correlate with poor outcome in patients with ER-positive disease. It is possible that in both the treatment and the prevention of breast cancer, an aromatase inhibitor rather than a SERM such as tamoxifen could be effective (Jordan 2003, Osborne et al. 2003).

**Other SERM breast cancer prevention trials**

**European studies**

Both the risk-reduction effects and adverse event results reported in the P-1 trial have been supported by other studies in which SERMs were used in women at high risk of developing breast cancer (Table 3) (Powles et al. 1998, Cummings et al. 1999, Cuzick 2001, Veronesi et al. 2002). A meta-analysis of these four tamoxifen trials identified a 38% reduction in breast cancer with tamoxifen (95% CI 28–46). There was no effect for ER-negative breast cancers (ER hazard ratio 1.22 (95% CI 0.89 < 1.67); P = 0.21), while ER-positive tumors were decreased by 48% (95% CI 36–58, P < 0.0001) (Cuzick 2003). One of these trials, the multicenter, randomized, double-blinded MORE trial, examined whether 7705 postmenopausal women younger than 81 years (mean age 66.5 years) with osteoporosis who were assigned raloxifene (60 mg/day) had a lower risk of invasive breast cancer than did a similar group of women assigned to placebo (Cummings et al. 1999). Thirteen cases of breast cancer were reported among the 5129 women assigned to raloxifene and 27 among the 2576 women assigned to placebo (RR 0.24; 95% CI 0.13–0.44; P < 0.001). In contrast to the 49% reduction in invasive breast cancer seen in the P-1 trial, raloxifene decreased the risk of ER-positive breast cancer by 90% (RR 0.10; 95% CI 0.04–0.24). As in the P-1 trial, there was no significant reduction in ER-negative invasive breast cancer (RR 0.88; 95% CI 0.26–3.0). The risk of thromboembolic disease among patients assigned to raloxifene was reported to be increased relative to that in women assigned placebo (RR 3.1; 95% CI 1.5–6.2). This was consistent with the increased risk for thromboembolic disease seen in the P-1 trial for tamoxifen. However, unlike in P-1, the risk of endometrial cancer was not increased among patients assigned raloxifene compared with those assigned placebo (RR 0.8; 95% CI 0.2–2.7).

**The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial**

The apparent increased efficacy of raloxifene as a risk-reducing agent relative to tamoxifen and the apparent absence of estrogen-agonistic activity in the breast and endometrium has made raloxifene attractive as a potential preventive agent. With this in mind, the NSABP initiated the STAR trial (Vogel et al. 2002) in June 1999. This trial will recruit 19 000 postmenopausal women and is powered to demonstrate superior efficacy of either agent or equivalence of the two agents in reducing the incidence of primary breast cancer in high-risk women. Risk eligibility is determined by the Gail model (Gail et al. 1989), as in NSABP Protocol P-1. Participants are randomly assigned to receive either tamoxifen (20 mg/day/5 years) or raloxifene (60 mg/day/5 years). As of May 2002, 13 345 women were randomized; the mean age is 58 years, and the mean 5-year risk of breast cancer is 4.0%. The Gail model risk was an average 3.0% in 5 years. The risk of endometrial cancer was not increased among patients assigned raloxifene compared with those assigned placebo (RR 0.8; 95% CI 0.2–2.7).

**Table 3 Randomized prospective trials of SERMs for primary breast cancer risk reduction**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients randomized</th>
<th>OR/RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-1</td>
<td>13 387</td>
<td>0.51</td>
<td>0.39–0.66</td>
</tr>
<tr>
<td>IBIS 1</td>
<td>7410</td>
<td>0.67</td>
<td>0.49–0.91</td>
</tr>
<tr>
<td>Royal Marsden 3</td>
<td>2494</td>
<td>0.83</td>
<td>0.58–1.16</td>
</tr>
<tr>
<td>Italian 4</td>
<td>5408</td>
<td>0.76</td>
<td>0.47–1.60</td>
</tr>
<tr>
<td>MORE 5</td>
<td>7705</td>
<td>0.24 (RR)</td>
<td>0.13–0.44</td>
</tr>
</tbody>
</table>

OR, odds ratio; RR, response rate; CI, confidence interval; IBIS, International Breast Cancer Prevention Study; P-1, Breast Cancer Prevention Trial; MORE, Multiple Outcomes of Raloxifene Evaluations.

1Fisher et al. (1998).
3Powles et al. (1998).
4Veronesi et al. (2002).
5Cummings et al. (1999).
will achieve its accrual goal within 5 years of activation. The primary analysis is planned to occur when 327 invasive cancers have been observed; it is anticipated that this will be approximately 1.5 years after accrual is terminated. The endpoints of this study include invasive and non-invasive (LCIS or DCIS) breast cancer and atypical hyperplasia, cardiovascular death, and various non-fatal cardiovascular events (myocardial infarction, stroke, pulmonary embolism, deep-vein thrombosis, etc), osteoporosis, cancers other than breast cancer, and death from any cause.

The Raloxifene for Use in the Heart (RUTH) trial

The RUTH trial is a randomized, placebo-controlled, double-blinded study comparing raloxifene (60 mg/day/5 years) with placebo (5 years) in patients with an increased risk of cardiac events and breast cancer (Mosca et al. 2001). Recruitment is now completed, with 10,011 postmenopausal women having been randomized. The primary endpoint of this study is the occurrence of cardiac disease, and the added secondary endpoint is the occurrence of breast cancer. Data about breast cancer reduction rates in this trial are not expected until 2005.

The future of breast cancer prevention trials

No randomized trials evaluating aromatase inhibitors as risk-reducing agents for primary breast cancer have yet been performed. However, aromatase inhibitors hold great promise because increased estrogen levels correlate with increased breast cancer risk in postmenopausal women and because aromatase inhibitors markedly reduce estrogen activity in both plasma and breast tissue in these women. Furthermore, aromatase inhibitors and inactivators have emerged as rational treatment options for patients with advanced hormone receptor-positive breast cancer (Goss & Strasser 2001). The Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial (ATAC 2002) randomized 9366 patients with early-stage breast cancer to three treatment arms: tamoxifen (20 mg/day), anastrozole (1 mg/day), or the combination for 5 years. Primary study endpoints included DFS and safety/tolerability; new (contralateral) breast cancer primary tumors were a secondary endpoint. Anastrozole, but not the combination therapy, was shown to be superior to tamoxifen in these postmenopausal women in DFS after a median follow-up of 33.3 months. Anastrozole use was also associated with a 58% reduction in new primary CBTs (RR 0.42; 95% CI 0.22–0.79 for anastrozole compared with tamoxifen groups; P < 0.0068). The absolute reduction in risk of developing a new CBT associated with anastrozole compared with tamoxifen was less than 1%. Women on the anastrozole arm had significantly fewer vascular and endometrial events but more musculoskeletal events and fractures compared with those on the tamoxifen arm. The effects of aromatase inhibitors (e.g. anastrozole, letrozole) and inactivators (e.g. exemestane) in advanced breast cancer and the reported risk-reducing properties of anastrozole on CBT support further evaluation of aromatase inhibitors and inactivators for breast cancer risk reduction (Winer et al. 2002).

Raloxifene is widely used in clinical practice as an anti-osteoporotic agent. The promising results of the MORE trial on reduction in the risk of developing breast cancer makes raloxifene an appealing intervention for physicians currently caring for women with osteoporosis who are felt to be at high risk for developing breast cancer. The putative favorable adverse event profile of raloxifene relative to that reported for tamoxifen also makes raloxifene a reasonable alternative from the patient perspective. Likewise, the reduction in CBTs observed among women in the ATAC trial who received anastrozole alone also makes anastrozole therapy appealing to both the practicing physician and the patient. It is important, however, to emphasize that at present the only risk-reducing agent for high-risk patients recommended by both the American Society of Clinical Oncology Risk Reduction Update Working Group and the Prevention Services Task Force consensus panels remains tamoxifen (Chlebowski et al. 2002, US Preventive Services Task Force 2002). There is currently insufficient evidence to justify the use of either raloxifene or an aromatase inhibitor or inactivator in prevention.

As new therapeutic modalities (e.g. newer SERMs (faslodex, arzoxifene), aromatase inhibitors and inactivators, selective peroxisome proliferator-activated receptor gamma modulators, luteinizing hormone-releasing hormone analogues, demethylating agents (5'-aza-2'-deoxycytidine), cyclooxygenase-2 inhibitors, etc.) with acceptable adverse event profiles are shown to be useful for the treatment of patients with advanced disease, they will routinely be considered as possible risk-reducing interventions (Sporn & Suh 2002). Future breast cancer prevention trials will likely require new types of designs. It is uncertain whether another prevention trial of the magnitude of the currently accruing STAR trial is practical. If, as expected, the margin in clinical benefit ascertained from comparisons of various newer risk-reducing agents narrows, prevention trials may require larger accrual targets to achieve a power appropriate to determine whether endpoint differences are significant. This alone will make trials with more than three arms or factorial designs difficult to complete and will require greater selectivity of trial design by investigators and innovative methods during the conduct of such trials to maximize patient accrual and compliance. It is likely that future prevention trials will require international participation. Since the populations for these trials are also event-driven (i.e. the rate of development of invasive or non-invasive breast cancer), as new techniques become available to better identify and quantify patients’ risks for the development of breast cancer, the population selected for these trials may be refined to include only those
in extraordinarily high-risk categories. It also seems appropriate to consider whether randomized trials of potential risk-reducing agents among patients with so-called ‘non-invasive premalignant processes’ (e.g. DCIS, LCIS or atypical hyperplasia) may be used as surrogate designs for prevention trials that may have accrual targets difficult to achieve.

Risk reducers currently being examined in clinical trials are targeted primarily toward postmenopausal women. It will be important in future clinical trial designs to include women who are premenopausal and to evaluate agents that have a high likelihood of interfering with the development of tumors that are not hormone-dependent.

Conclusions

Since the introduction of tamoxifen as an anti-estrogen for the treatment of hormone receptor-positive breast cancer, evidence has developed for its use as a risk-reducing agent in populations of women thought to have a high risk for the development of the disease. This is supported by the results of the NSABP P-1 trial as well as by European tamoxifen trials (which did not evaluate only high-risk women). Whether tamoxifen use is associated with emergence of a disproportionate frequency of the ER-negative tumors at the time of recurrence is controversial. The results of the prospective NSABP P-1 trial indicate that there was no significant increase in the incidence of ER-negative recurrences among women assigned to receive tamoxifen. In contrast, Li et al. (2001) retrospectively analyzed tumor registry-derived data and found that women reported to have taken tamoxifen had a higher frequency of ER-negative CBTs than women who were reported not to have been treated with tamoxifen. These results are difficult to reconcile. The number of breast cancer events was relatively modest in the P-1 trial and many subjects are still at risk for disease recurrence. On the other hand, the Li et al. (2001) study was retrospective, reported only CBTs, and was based on data not confirmed by source documentation.

Recent developing evidence implies strongly that raloxifene and anastrozole may also be useful as risk reducers, although at the present time the strength of this evidence is too weak to support any conclusions. NSABP Protocol P-2, which is currently accruing participants, and the RUTH trial, which is awaiting endpoint analysis, will further establish if raloxifene can be used to reduce the risk of breast cancer among high-risk, postmenopausal women. The P-2 trial is designed to compare both the efficacy and adverse event profiles of tamoxifen and raloxifene and should determine whether differences in the two drugs are important. It is possible that aromatase inhibitors and inactivators, as well as other novel agents currently being developed in the advanced disease and adjuvant settings, may have a place as risk reducers. This is especially true for the aromatase inhibitor anastrozole.

Future research into the prevention of breast cancer must involve the identification of women at high risk who are most likely to benefit from various types of hormonal therapy as well as the development of additional SERMs and aromatase inhibitors that can be effective as well as non-toxic.

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