Tamoxifen Prevention of Breast Cancer: an Instance of the Fingerpost

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Tamoxifen as a chemopreventive agent has produced a fundamental change in the outlook for controlling breast cancer. Tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Breast Cancer Prevention Trial (BCPT) achieved a striking 49% reduction in the incidence of invasive breast disease in women at increased risk of breast cancer (1). With this finding, the Food and Drug Administration (FDA) approved tamoxifen for risk reduction in this setting, marking the historic first FDA approval of any agent for cancer risk reduction. The BCPT finding and FDA approval have created a paradigm shift toward pharmacologic preventive approaches (i.e., chemoprevention) for controlling breast cancer.

A major portion of this commentary is devoted to highlights and related issues of the course of tamoxifen’s recent history in breast cancer prevention research, which has been remarkable. In April 1998, the National Cancer Institute (NCI) and NSABP unblinded the BCPT and released the compelling positive interim-analysis data responsible for this decision. In May 1998, the Early Breast Cancer Trialists’ Cooperative Group (EBCTCG) published their updated worldwide overview of adjuvant trial results showing the preventive effects of tamoxifen on the incidence of contralateral breast cancer (2). In July 1998, negative related data from two ongoing European tamoxifen trials were published (3,4). In September 1998, the NSABP published the full primary report of the BCPT (1). In October 1998, the FDA released its approval for tamoxifen in the setting of primary or contralateral breast cancer risk reduction. In December 1998, the NSABP reported positive preliminary results (5) of the B-24 trial of tamoxifen in ductal carcinoma in situ (DCIS) (subsequently published in full in June 1999) (6). In May 1999, the NSABP and NCI announced the opening of the Study of Tamoxifen and Raloxifene (STAR) (randomization began in July 1999). The STAR is the first chemoprevention trial to employ a pharmacologic standard-of-care (tamoxifen) control arm (7).

The BCPT has achieved an extraordinary advance for the control of breast cancer and has provided the proof of principle of the chemoprevention approach. It is now established that human cancer can be prevented with a pharmacologic intervention. Why did the BCPT succeed, whereas many other phase III trials, particularly those involving β-carotene (7–11), have not achieved positive results? The answer seems to relate largely to strength of rationale, which for the BCPT involved tamoxifen’s therapeutic efficacy, secondary phase III clinical findings (involving contralateral breast cancer), and mechanistic/molecular-targeting study. These issues will be discussed later, along with the implications they and other issues of the BCPT have for future directions of chemoprevention. We will assess the BCPT, the crowning achievement of positive studies of tamoxifen prevention, as an instance of the fingerpost for resolving the intense debate on the future direction of chemoprevention research.

**Literature Search Methods**

Our search methods for selecting studies to include in this commentary were based on published guidelines for review papers (12). The literature search included references on tamoxifen, breast cancer, and chemoprevention published in English from 1990 through September 1999. Primary sources for our search were the computerized databases MEDLINE® and Current Contents and reference lists from recent reviews published in either book chapters or medical journals.

**Clinical Trials**

**Overview**

Involving more than 50 000 women, studies of tamoxifen have produced prevention/risk reduction results in the narrow range of from 43% to 49% in the three distinct invasive breast cancer risk settings of 1) patients with early-stage breast cancer (reduction of contralateral breast cancer risk) (2), 2) healthy high-risk women (1), and 3) patients with DCIS (6) (see Table 1). These preventive effects of tamoxifen highlight the remarkable consistency of this agent in settings of high breast cancer risk.

Many disparate effects of tamoxifen in different tissues produce a complex mix of benefits and risks requiring highly individualized assessments of the overall benefit for every woman considering its use. This important characteristic of tamoxifen shows what may be developing into a common theme of chemoprevention (7). Many other promising chemopreventive agents in development (e.g., raloxifene and retinoids) also appear to have a complex mix of benefits and risks.

**Adjuvant Trials—Contralateral Breast Cancer Risk Reduction**

The scale and results of adjuvant tamoxifen trials provided powerful data for the rationale of the BCPT. Fifty-five trials involving more than 36 000 patients with early-stage breast cancer (who were randomly assigned either to adjuvant tamoxifen or to nontamoxifen study arms and among whom 854 contralateral breast cancers were diagnosed) were included in the world-
Table 1. Consistent tamoxifen risk prevention results*

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<thead>
<tr>
<th>Trial/setting</th>
<th>No.</th>
<th>Risk</th>
<th>Reduction†</th>
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<tr>
<td>Adjuvant trials (EBCTCG) (2)</td>
<td>&gt;36000</td>
<td>CBC†</td>
<td>47% (P&lt;.00001)</td>
</tr>
<tr>
<td>BCPT (healthy/high-risk women) (1)</td>
<td>13388</td>
<td>IBC‡</td>
<td>49% (P&lt;.00001)</td>
</tr>
<tr>
<td>NSABP B-24 (DCIS) (6)</td>
<td>1804</td>
<td>IBC</td>
<td>43% (P = .004)</td>
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<tr>
<td></td>
<td></td>
<td>All BC</td>
<td>37% (P = .0009)</td>
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*BC = breast cancer; BCPT = Breast Cancer Prevention Trial; CBC = contralateral breast cancer; DCIS = ductal carcinoma in situ; EBCTCG = Early Breast Cancer Trialists’ Cooperative Group; IBC = invasive breast cancer; NIBC = noninvasive breast cancer; NSABP = National Surgical Adjuvant Breast and Bowel Project; FDA = the Food and Drug Administration.
†P values are two-sided.
‡FDA-approved risk-reduction settings

wide overview (meta-analyses) of the EBCTCG (2). A subset analysis showed that about 5 years of adjuvant tamoxifen treatment achieved a 47% reduced incidence of contralateral breast cancer (two-sided P<.00001). Incidence reductions in contralateral breast cancer were 13% at 1 year (two-sided P = not significant) and 26% at 2 years (two-sided P = .004). The estrogen receptor (ER) selectivity of tamoxifen was shown: 5-year therapy with tamoxifen reduced recurrence of ER-positive and ER-negative tumors by 50% and 6%, respectively. (In contrast, cytotoxic agents appear to be more active in ER-negative than ER-positive tumors.) The ER status of primary tumors, however, did not affect the benefit of tamoxifen in reducing the incidence of contralateral breast cancer, which was similar in patients with ER-positive and ER-negative primary tumors. Therefore, the ER status of contralateral breast tumors appears to be independent of the primary tumor, since it is highly likely that tamoxifen prevented ER-positive contralateral tumors, whether secondary to an ER-positive or an ER-negative primary tumor. The clinical implications of these adjuvant findings are that tamoxifen can benefit women with ER-positive tumors (by reducing the rate of recurrence and contralateral breast tumors) as well as women with ER-negative tumors (by reducing the rate of contralateral tumors).

Adjuvant trial findings on overall breast cancer risk/reduction and ER specificity and other major secondary findings (e.g., regarding endometrial and other cancers) were very predictive of subsequent BCPT findings. Although secondary, the contralateral breast cancer findings were very strong because of their consistency throughout many large trials and tight biologic linkage to the primary (therapeutic) end point.

Breast Cancer Prevention Trial

The BCPT was designed to test 5 years of tamoxifen (20 mg/day) against placebo in preventing breast cancer in high-risk women (1). The major high-risk eligibility criteria were age 60 years or older, history of lobular carcinoma in situ (LCIS), or women from 35 to 59 years of age with a 5-year breast cancer risk of at least 1.66% (based on the Gail model, in which major risk factors are age, family breast cancer history, and history of atypical hyperplasia) (12). The actual baseline overall average 5-year breast cancer risk of women participating in the BCPT was 3.2%.

The BCPT was unblinded by the data-monitoring committee after a planned interim analysis found that tamoxifen had produced a dramatic 45% reduction in breast cancer risk (Breast Cancer Prevention Trial shows major benefit, some risk [joint press release]—NSABP, NCI; April 6, 1998). This figure subsequently was updated to a 49% reduction in breast cancer risk (two-sided P<.00001) (1). Participants receiving placebo were offered tamoxifen along with advice on its potential benefits (and risks). The primary BCPT report included analysis of 13,175 women (13,388 were randomized, beginning in mid-1992). At respective mean and median follow-up times of 48 and 55 months, respective invasive breast cancer figures for the tamoxifen and placebo groups were as follows: 89 cancers versus 175 cancers; average annual rates of 3.43 versus 6.76 per 1000 women; absolute 5-year risks of 1.3% versus 2.6%. The protective effect of tamoxifen was limited to ER-positive tumors (69% reduction), which is consistent with the therapy and molecular-targeting rationale supporting the BCPT. Tamoxifen was associated with a 50% reduction (35 versus 69 cases) in noninvasive (DCIS and LCIS) breast cancers. Tamoxifen reduced overall mortality by 19% and reduced breast cancer deaths (three on tamoxifen versus six on placebo); however, these reductions were not statistically significant.

Relative breast cancer risk reductions by tamoxifen were roughly similar (and statistically significant) for all age groups (although slightly greater for postmenopausal women). The picture is not so clear, however, with regard to risk. The greatest and only statistically significant effects occurred in the lowest (<=2.00% in 5 years) and highest (>5.01% in 5 years) risk groups. It is provocative that the highest risk subgroups (atypical hyperplasia, LCIS, and Gail model >5.01%) had among the highest relative risk reductions, which translate into striking absolute risk reductions. For example, subjects with a history of atypical hyperplasia had an 86% reduced relative risk, which translated into an absolute reduction from 10.11 breast cancers down to only 1.43 breast cancers (per 1000 women per year) (compared with overall BCPT relative and absolute risk reductions of 49% and from 6.76 down to 3.43, respectively). This pattern of preventive effects may relate to the complexity and timing of ER changes (discussed later) or to the chance findings of subset analyses.

A beneficial secondary finding was fewer fractures in the tamoxifen group (111 versus 137; risk ratio [RR] = 0.81; 95% confidence interval [CI] = 0.63–1.05). The lack of statistical significance of the fracture results may have been due to the relatively low fracture risk of the young trial population (nearly 40% were <50 years old) and the direct relationship between breast cancer risk and bone mineral density (14). The two major secondary adverse findings associated with tamoxifen were increased endometrial cancers (36 [all stage I] on tamoxifen versus 15 on placebo; RR = 2.53; 95% CI = 1.35–4.97) and vascular events (110 versus 77; statistically significant only for pulmonary embolism [RR = 3.01; 95% CI = 1.15–9.27]). These increased risks were statistically significant only in women 50 or more years old. Tamoxifen was associated with increased risk of cataracts, predominantly in the older age group (overall RR = 1.14; 95% CI = 1.01–1.29), but not with increased risk of self-reported macular degeneration. A recently published analysis (15) of age-related effects of tamoxifen on quality-of-life issues provided data on prevalences and relative risks of these side effects. Hot flashes and vaginal discharge were increased in the tamoxifen group in all age strata and at every follow-up evaluation. With respect to hot flashes in the tamoxifen group, the highest prevalence occurred in women 50–59 years old, and

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the greatest relative increase (compared with placebo) occurred in the youngest group (35–49 years old). With respect to vaginal discharge, this was the most consistent tamoxifen-associated side effect in all age strata, was most prevalent in the youngest group, and had the greatest relative tamoxifen-associated increase in the oldest group (≥60 years old). Tamoxifen was also associated with increased adverse sexual functioning symptoms. None of these quality-of-life-related effects was frequent or severe enough to prevent the vast majority of women receiving tamoxifen from coping with everyday life (15). Findings were neutral on the secondary end points of liver, colon, and other cancers (besides endometrial), coronary heart disease, depression, weight gain, and mental function (1,15).

The FDA approved tamoxifen for breast cancer risk reduction in high-risk women. The FDA recommendation is 20 mg/day for 5 years for high-risk women (defined in terms of risk required for BCPT eligibility) and warns of tamoxifen-associated risks. Somewhat surprisingly, the FDA also approved tamoxifen for reducing the incidence of contralateral breast cancers, based on consistent secondary adjuvant data (2,16). (See Table 2 for the complete list of FDA-approved uses of tamoxifen.) Risk reduction for patients with DCIS is not included in the current FDA approval for tamoxifen, although many investigators believe that it should be recommended under certain conditions (6,17,18) (see below). The positive results of the NSABP B-24 trial in DCIS patients were reported after the FDA approval of tamoxifen for risk reduction (5,6).

Multiple effects of tamoxifen on different tissues make this agent’s use a complex, highly individualized decision, complicated even further by patient fears and concerns. First, each woman must absorb her actual breast cancer risk profile, a complicated assessment (19) that is complicated even further when considering tamoxifen’s relative (49%) and absolute (1.3%) risk reductions. Then, a group of other age-related benefits/risks, including fracture, endometrial cancer, and vascular events, must be addressed, remembering that the effects of tamoxifen on these other risks are founded on secondary data with a lower level of evidence. This complexity is daunting (20). In very general terms, however, three rules of thumb point toward an improved tamoxifen risk-to-benefit ratio for high-risk women: 1) higher breast cancer risk (at any age), 2) lower age (at any breast cancer risk), and 3) hysterectomy (at any breast cancer risk of women ≥50 years old). With respect to item 1, the improved ratio is due to increased benefit or increased absolute breast cancer risk reduction. (A common chemoprevention theme is to target high-risk subjects, who have the most to gain, may tolerate greater toxicity, and allow smaller sample sizes due to greater anticipated event rates.) With respect to items 2 and 3, the improved ratios are due to reduced risk (non-breast cancer related). One notable caveat must be stated regarding potential increased benefit for BRCA1 or BRCA2 gene mutation carriers, who were not specifically evaluated. These women’s potential benefit for reasons of high risk and young age (items 1 and 2) would appear to favor their use of tamoxifen (discussed below). The only other current preventive options for these women are bilateral prophylactic mastectomy (21,22) and oophorectomy (23).

Two other important groups also were not addressed adequately by the BCPT, which bears on the issue of their tamoxifen risk reduction recommendation. First, minority women were inadequately assessed in the BCPT because of inadequate recruitment/accrual (discussed below under “Unresolved Tamoxifen Prevention Issues”). Second, low-to-average-risk women were excluded completely from both the BCPT (by design) and the FDA approval.

There is substantial public resistance to tamoxifen (as there was to mammography) in the setting of breast cancer prevention and control. A major contribution of tamoxifen may be in pioneering community-wide acceptance of approved cancer chemopreventive agents. The concept of pharmacologic “risk treatment” is well accepted in other medical arenas, such as adjuvant treatment of breast cancer and primary prevention/risk reduction of heart disease and osteoporosis, but it is new to the public health setting (although not to the research setting) of primary cancer prevention. Chemoprevention of cancer lags far behind that of cardiovascular disease (e.g., with lipid-lowering agents) with respect to surrogate end point development, effective agent combinations, and extrapolating positive findings in high-risk populations to the general population. This work in the cardiovascular setting has been under way for 5 decades and has achieved substantial reductions in cardiovascular mortality. As noted above in the “Overview” of this section, a common theme of the development of chemopreventive agents is the complex mix of benefits and risks involved with many of these agents. Although some agents have gained wide (non-FDA-approved) community acceptance for cancer chemoprevention, these either have not yet been definitively tested for both beneficial and harmful effects (e.g., raloxifene, selenium, and vitamin E) or have failed such testing (e.g., β-carotene) (7–11,24,25).

Many physicians still are not recommending tamoxifen to women/patients who may benefit, despite the approval of the FDA and American Society of Clinical Oncology (ASCO) of tamoxifen for breast cancer risk reduction (7,24,25). A major obstacle appears to be the fear that, while preventing one cancer (breast), tamoxifen may be causing another (endometrial). The BCPT tamoxifen results (announced in a NSABP/NCI press release) (25) and preliminary Multiple Outcomes of Raloxifene Evaluation (MORE) trial results (presented in an ASCO plenary session) (26) were made public at about the same time. The raloxifene story, however, apparently made more of a public impact. Large numbers of physicians and their patients currently are opting for raloxifene (discussed below) over tamoxifen. This probably is due to the belief that raloxifene can reduce breast cancer risk as well or better than tamoxifen can but with less endometrial cancer risk and greater fracture prevention (still to be established by the STAR). This is a major stumbling block to tamoxifen acceptance and ignores the distinction between established primary trial results (BCPT/tamoxifen) and provocative, but unconfirmed secondary analysis results (MORE/raloxifene) (7), which are discussed in more detail later. This issue has been

<table>
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<th>Table 2. FDA-approved uses of SERMs*</th>
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<td>SERM</td>
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<td>Tamoxifen</td>
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<td>Raloxifene</td>
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*SERMs = selective estrogen-receptor modulators; BC = breast cancer; FDA = the Food and Drug Administration; IBC = invasive breast cancer; CBC = contralateral breast cancer.
addressed conclusively by the FDA and ASCO (7,24); Tamoxifen is recommended for broad-based community use to reduce breast cancer risk; raloxifene currently is not.

**DCIS—NSABP B-24**

Although not eligible for the BCPT, women with a history of DCIS are at high risk for ipsilateral and contralateral breast cancers (17). The NSABP B-24 trial tested 5 years of tamoxifen (20 mg/day) versus placebo as adjuvant therapy after resection and radiation therapy in 1804 patients with DCIS (including that which was diffuse and/or margin positive) (6). At a median follow-up of 74 months, total (invasive plus noninvasive) breast cancer figures for the tamoxifen and placebo groups, respectively, were as follows: 84 (41 invasive) cancers versus 130 (70 invasive) cancers; annual rate of 18.33 versus 29.32 per 1000 women (37% reduction; RR = 0.63 [95% CI = 0.47–0.83]); 5-year cumulative incidences of 8.2% versus 13.4% (two-sided P = .0009). There were 43% fewer invasive breast cancers (two-sided P = .004) and 31% fewer noninvasive breast cancers (P = .08) in the tamoxifen group. Tamoxifen also achieved reductions in all ipsilateral (n = 150) and all contralateral (n = 64) cancers of 30% (two-sided P = .04) and 52% (two-sided P = .01), respectively. There was a 44% reduction in invasive ipsilateral cancers in the tamoxifen (versus placebo) group (two-sided P = .03). Since the majority of patients who developed ipsilateral (especially invasive) disease in either study arm had mastectomies, the number of mastectomies in the tamoxifen arm was substantially reduced.

**European Tamoxifen Breast Cancer Prevention Trials**

Two smaller European tamoxifen breast cancer prevention trials (one British and one Italian) were negative (3,4). Both trials had much lower statistical powers than did the BCPT. The BCPT had about twice the sample size (13 388) and three times the number of breast cancer events (368) as had both European trials combined. Each trial also had individual differences from the BCPT. The British Royal Marsden Hospital trial (3) was designed and initiated as a pilot feasibility trial prior to the International Breast Cancer Intervention Study, which is ongoing and remains blinded after accruing more than 4000 of 7000 planned subjects. Results of this pilot trial were derived from an interim analysis at 70 months’ median follow-up (RR = 1.06). The key differences of the Royal Marsden trial were younger age, stronger family history of breast cancer, and concurrent use of hormone replacement therapy (by 26% of subjects). It remains unclear why this study was negative. Possible reasons are the study’s small size (2471 women accrued from 1986 through 1996), low statistical power, and greater risk of BRCA1 gene mutations. The factors of younger age and stronger family history led Royal Marsden investigators to speculate that more of the British women were at greater risk for BRCA1 mutations and the development of ER-negative tumors not influenced by tamoxifen use. (BRCA1 and ER negativity are discussed in greater detail below.) Because BRCA1 gene mutation has a low attributable risk, even in British women with a family breast cancer history (27), this would not seem to be a major factor in this trial’s negative preliminary result. The key differences of the Italian trial were a relatively low-risk population (48% had had bilateral oophorectomies and only 41 breast cancers developed at a median follow-up of 46 months), poor compliance (26% dropped out, most in the first year), and premature closure to accrual (4). Because of the high dropout rate in the first year and the importance of tamoxifen duration (2,28), a subset of patients with at least 1 year of tamoxifen treatment was analyzed, showing a favorable trend in breast cancer incidence in this group (two-sided P = .16).

**Unresolved Tamoxifen Prevention Issues**

Unequivocally, the BCPT tested its primary hypothesis that tamoxifen would reduce breast cancer incidence. The BCPT, however, also has raised many new, key issues, including optimal tamoxifen dose and duration, generalizability to minority women and high-risk BRCA1 and BRCA2 gene mutation carriers, timing of ER-status changes, prevention versus treatment, and net tamoxifen benefit to the community (including effects on overall breast cancer and mortality).

It is uncertain what dose or duration of tamoxifen treatment will be optimal in protecting against the development of breast cancer. The issue of optimal dose is far less resolved than that of optimal duration. The choice of the dose of 20 mg/day of tamoxifen for the BCPT and European tamoxifen prevention trials was based on earlier therapy trial results. There are data suggesting that a lower dose may be effective in the prevention setting, where low toxicity is a preeminent concern. Although there is no dose–response breakdown from the adjuvant tamoxifen trials with respect to contralateral breast cancers, there is with respect to recurrence. Doses of 20–40 mg per day (2) seemed to produce similar reductions in recurrence and mortality. In a recent study (29), 10 mg every other day appeared to be as biologically active (e.g., in suppressing insulin-like growth factor I) as was 20 mg per day and was associated with an 80% reduction in tamoxifen blood level.

With respect to duration, animal data suggested that tamoxifen is cytostatic and loses its effect if stopped, suggesting the need for prolonged, continuous intervention (28). Clinical data on contralateral breast cancer incidence reduction from adjuvant tamoxifen trials clearly show that the reduction increases directly in relation to treatment duration from 1 to 5 years (2). The NSABP B-14 adjuvant study of stage I ER-positive tumors suggests that 5 and 10 years of tamoxifen therapy provide roughly the same protection against development of contralateral breast tumors, whereas risks of endometrial cancer and vascular events declined in association with the shorter therapy (16). Therefore, 5 years of treatment may improve tamoxifen’s risk-to-benefit ratio (compared with 10 years of treatment), as protective effects persist and associated risks (and costs) decline. Whether 5 years of tamoxifen treatment can sustain breast cancer risk reduction beyond 10 years remains unresolved.

Questions about the applicability, or generalizability, of the BCPT results to ethnic minorities have been raised by low representation of minorities in this trial involving predominantly white, well-educated, and middle-class women (15). Overall, there were 3.0% minority women, 1.7% African-American (1). Unfortunately, this problem is not uncommon in chemoprevention studies, but it has been emphasized in the case of the BCPT by tamoxifen’s striking positive clinical implications. NSABP adjuvant trials, with contralateral breast cancer reductions closely paralleling BCPT primary breast cancer reductions, suggest that positive and negative tamoxifen effects on women are relatively equivalent with respect to race (Wickerham DL: personal communication). The highly complex issue of baseline risks (e.g., lower breast cancer rates in Hispanic women) and
tamofoxifen effects on cancer and other risk evaluations for minority women is extensively reviewed elsewhere in this issue of the Journal (20).

The question of tamoxifen’s effects in women at highest genetic risk due to either BRCA1 or BRCA2 gene mutation was not evaluated in the BCPT. There are important biologic, pathologic, and clinical differences between BRCA1 and BRCA2 tumors and between these and non-BRCA tumors (30–39). Seventy percent to 80% of breast cancers that develop in BRCA1 mutation carriers are ER negative (compared with 30%–40% in non-BRCA1 mutation carriers) (30–37), and ER-negative tumors were not reduced by tamoxifen in the BCPT. The outlook is more promising, however, for BRCA2 mutation carriers because apparently a higher percentage of breast cancers developing in these women are ER positive (30,31). The timing of ER-negative tumor development bears on the issue of potential tamoxifen effects in BRCA1 mutation carriers, as discussed in the following paragraph. Also, since approximately 20%–30% of tumors developing in carriers of BRCA1 gene mutation are ER positive, this subset of BRCA1 carriers may benefit from tamoxifen’s protective effect.

Although the clinical importance of ER status in tamoxifen breast cancer therapy is well established, ER changes in breast carcinogenesis are very complex and poorly understood (18,38). The timing of ER changes has become a very important issue in light of tamoxifen’s effects in preventing breast cancer, including DCIS (in the BCPT) and invasive cancer in patients with DCIS (in NSABP B-24). If development of ER-negative tumors involves an ER-positive preinvasive phase, tamoxifen may be protective, depending partially on the timing of ER loss. It is possible, however, that breast carcinogenesis resulting in ER-negative tumors does not depend on an ER-positive precursor (38). For example, recent data indicate that DCIS in BRCA1 mutation carriers is predominantly ER negative (31,32), whereas DCIS is generally ER positive (6,18). Moreover, even if ER-negative malignancy has a developmental ER-positive stage, it is possible that tamoxifen resistance in this subgroup is due to other cellular or molecular events [e.g., loss of P53 expression or overexpression of c-erbB-2 (31,37)] associated with ultimate ER negativity (31,37–40). Nevertheless, tamoxifen has great biologic relevance for women under 50 years old and of low-average risk, because of the agent’s favorable toxicity profile in this group and its provocative potential to prevent early development of ER-negative tumors. The many tamoxifen–ER status issues should be further elucidated by continuing mechanistic/molecular study, including investigations of the interaction between ER and wild-type or mutant BRCA1 (41) (e.g., in the BCPT population), and long-term assessments of ER-negative tumor development in women of the BCPT tamoxifen arm.

The unresolved debate on whether tamoxifen treats or prevents breast cancer has been discussed in detail elsewhere (1,25). One consequence of this debate was the language of the FDA approval, which used “risk reduction” in lieu of “prevention,” based in part on the prevailing “treatment” view of the FDA Oncologic Drugs Advisory Committee in making its recommendation to the FDA (25). This language appears to be contributing to public resistance to the use of tamoxifen for prevention. All of the risk-reduction evidence taken together suggests that tamoxifen is both treating microscopic invasive disease and preventing development of invasive breast cancer, including suppressing late-stage preinvasive disease, which is within the mainstream of cancer chemoprevention (7). Fisher et al. (1) stated in the first paragraph of the BCPT primary report that the term “prevention,” as applied to the BCPT [and most other phase III cancer chemoprevention trials (7)], indicates a reduction in the incidence (risk) of invasive breast cancer over the period of the study. These investigators stated further (in the “Discussion” section) that tamoxifen fundamentally has achieved the goal of primary cancer prevention (1), which is to prevent the clinical expression of tumors in relatively healthy people.

We believe that the prevention-versus-treatment debate is fueled in large part by the reluctance of many physicians, including oncologists, to accept chemoprevention as a standard clinical practice. Wider acceptance of chemoprevention as a standard cancer control modality should enhance further development of this valuable and relatively new approach.

Assessing the net health benefit to society of tamoxifen breast cancer prevention is complex, given the agent’s mix of potential adverse/beneficial effects, public resistance to the agent in this setting, and insufficient data on tamoxifen’s effects on breast cancer mortality. According to a recent commentary by Fisher (25), there are approximately 29 million women in the United States who would have been potentially eligible for the BCPT. Tamoxifen potentially could prevent 700,000 invasive and noninvasive primary breast cancers in the United States in 5 years. Five-year absolute figures per 1000 of these women translate into 49 fewer breast cancers (including 33 invasive breast cancers) versus seven additional endometrial cancers (virtually all early stage) and seven additional vascular events. These figures demonstrate that tamoxifen prevention potentially could impart a substantial net benefit to the public health.

Another major factor of the net public health benefit will be tamoxifen’s effects on breast cancer and/or overall mortality (24). This issue was not resolved by the BCPT, primarily because mortality was a secondary end point, and secondarily because the median follow-up was only for 55 months. The BCPT trend in both mortality categories, however, favored tamoxifen: three breast cancer deaths on tamoxifen versus six on placebo and 19% fewer all-cause deaths in the tamoxifen arm. Fewer deaths from all cancers occurred with tamoxifen versus placebo (23 versus 42 deaths; two-sided P = .018) (1,42). As a secondary result, however, this figure is subject to type-I (false-positive) statistical error. Also, 5-years’ adjuvant treatment with tamoxifen in early-stage disease produced 40%–50% reductions in both recurrent (mainly in ER-positive tumors) and contralateral breast cancer and 20%–30% reductions in mortality at 10 years (2). The provocative (by no means certain) suggestion of the positive adjuvant data involving mainly ER-positive disease is that incidence reduction involving ER-positive tumors as achieved in the BCPT will result in subsequent mortality reduction. This suggestion would be even stronger if, as has been argued (and as discussed below), tamoxifen in the BCPT primarily “treated,” rather than “prevented,” microscopic/subclinical disease, which would more closely parallel the adjuvant setting. Long-term follow-up of the participants in the BCPT and European tamoxifen breast-cancer prevention trials may help clarify these issues in the future.

RALOXIFENE VERSUS TAMOXIFEN IN BREAST CANCER PREVENTION

The selective ER modulator (SERM) raloxifene is FDA approved in several breast cancer therapy and prevention settings.
The NSABP will conduct the next phase III large-scale trial in breast cancer prevention (as a follow-on to the BCPT), which is called the Study of Tamoxifen and Raloxifene (STAR, or P-2) and will test the SERM raloxifene. This agent received FDA approval for prevention of osteoporosis (in postmenopausal women) in December 1997 (Table 2).

STAR will be conducted in 22,000 postmenopausal women (in contrast to premenopausal and postmenopausal women in the BCPT). Postmenopausal women were selected because the preliminary raloxifene data are on this population (based on osteoporosis studies), and there is a lack of adequate long-term safety testing in premenopausal women (although raloxifene currently is being tested in premenopausal women, who may be included later in STAR). Besides menopause status, stricter vascular exclusions, and breast cancer risk calculations for women 60 years old or older, eligibility criteria, mainly involving increased breast cancer risks, are similar between STAR and its predecessor, the BCPT. Subjects will be randomly assigned to 5 years' treatment with either tamoxifen (20 mg/day) (control) or raloxifene (60 mg/day), which STAR hypothesizes will have a higher therapeutic index (mainly due to lower endometrial cancer risk) than does tamoxifen. Excluding endometrial cancer, the side effects of raloxifene (e.g., vascular events) and tamoxifen are similar. Therefore, raloxifene (like tamoxifen) potentially would have a higher therapeutic index in younger, premenopausal women. STAR’s use of a control of pharmacologic standard of care (rather than placebo) reflects tremendous progress in large-scale phase III chemoprevention study (7).

MORE trial secondary results involving breast cancer incidence (43) provided the main rationale, along with ER molecular-targeting data, supporting the study of raloxifene in the STAR. There were 7705 postmenopausal osteoporotic women in MORE, randomly assigned to 3 years of raloxifene (two arms; 60 or 120 mg/day) or placebo. The following results (assessed at 40 months’ median follow-up) were reported: 40 invasive breast cancers (13 on raloxifene, 27 on placebo; RR = 0.24; 95% CI = 0.13–0.44; two-sided P<.001); statistically significant risk reduction only for ER-positive tumors; no statistically significant difference in noninvasive breast cancer incidence (seven on raloxifene and five on placebo); 10 total endometrial cancers (the RR in the raloxifene group was 0.80; 95% CI = 0.2–2.7); statistically significantly increased endometrial thickness (determined by transvaginal ultrasound); and statistically significant increase in raloxifene-associated vascular events (RR = 3.1; 95% CI = 1.5–6.2). Publication of the primary end point results of reduction of fracture risk occurred 2 months after that of the secondary breast cancer results (44). There was no raloxifene dose–response relationship with risk of breast cancer (RR = 0.22 on the 60-mg arm, and RR = 0.26 on the 120-mg arm) (43), although there was a trend toward one with risk of vertebral fracture (RR = 0.7 on the 60-mg arm, and RR = 0.5 on the 120-mg arm) (44).

Further updates of the ongoing MORE and other related studies in osteoporosis will be informative for raloxifene effects on breast cancer incidence (24,26,43). Because raloxifene data regarding cancer outcomes are generated by secondary analyses, the benefit regarding breast cancer risk must be established in a definitive hypothesis-testing trial, such as the STAR. Whereas secondary analyses are appropriate for hypothesis generation, they are insufficient for definitive testing for several reasons that involve, for example, patient selection and stratification and the statistical issue of multiplicity (e.g., involving increased type I error rates) (7,45).

MORE’s low breast cancer risk population (relative to that of the BCPT) raises another interesting issue. Raloxifene’s 76% reduction in invasive tumors has been compared with tamoxifen’s 49% reduction to justify the view that raloxifene may be the better drug, even for breast cancer risk reduction. Tamoxifen’s definitive result, however, was achieved in high-risk women. It is entirely plausible to hypothesize that tamoxifen’s results would be far greater in lower risk women similar to those tested in the MORE. Women in the BCPT with the lowest risk (<2.0% in 5 years) had a statistically significant 63% risk reduction (1), which is a subset-analysis result to compare with the 76% secondary-analysis result of MORE. The issue of tamoxifen’s effects in lower risk women has been discussed earlier.

Raloxifene’s effect on breast cancer was minimal in the first 12 months of MORE, followed by a reduced incidence in ensuing months that became substantially more reduced almost immediately after year 2 (43). This pattern contrasts with tamoxifen’s preventive effect in the BCPT, which occurred early (33% reduction in year 1) and continued over time. Many researchers believe that tamoxifen’s early effects are due to treating microscopic invasive disease. Therefore, raloxifene, if truly delayed, may be a more purely preventive agent than is tamoxifen, an inference supported by raloxifene’s apparent failure (at doses of from 200 mg to 300 mg/day) as a breast cancer therapy drug in early trials (24). On the other hand, the effects of raloxifene in MORE only may have been detected late, since breast cancer ascertainment in the trial required mammography at the end of the second year, possibly resulting in more cancers being detected at that time point. This interpretation of the delayed effect is confounded, however, by the 48% mammography (or breast sonography) screening rate during year 1 and the trial’s provision for follow-up examinations every 6 months (43).

MECHANISTIC/MOLECULAR TARGETING PARADIGM: BREAST CANCER CHEMOPREVENTION

Tamoxifen/SERM Development

The strength of the BCPT rationale was based to a substantial degree on rational mechanistic drug development through molecular targeting studies. Preclinical and epidemiologic studies of the important roles of estrogen (and its receptors) in breast carcinogenesis and of related tamoxifen actions led to an endocrine hypothesis: Tamoxifen inhibits the action of estrogen on breast tissue at the level of the ER (40,46,47). This hypothesis underlies the mechanistic rationale for the BCPT.

The molecular target ER was identified in rats about 40 years ago (47). In vitro studies in ER-positive breast cancer cell lines, primarily MCF-7, led to understanding that ERs are ligand-activated nuclear transcription factors and to the discovery of the steroid receptor superfamily (47,48). Estrogen binds and activates cytoplasmic ERs, which translocate to the nucleus, dimerize, bind estrogen response elements (EREs), and activate transcription. EREs contain transcriptional activation factors (AF1 and AF2) and DNA-, ligand-, and cofactor-binding domains (also discussed below) (38,40,41,47,48). A mechanistic link between estrogen action/ERs and breast carcinogenesis was established through these and other studies.

Tamoxifen (the trans-isomer of a triphenylethylene derivative) was formulated in the latter half of the 1960s, after its
related predecessor, ethamoxytriphetol, failed in clinical breast cancer therapy trials (47). Tamoxifen has become the best studied agent to date in breast cancer prevention, with more than two decades of translational research. In 1976, Jordan (49) showed that tamoxifen prevented mammary cancer in rats. This finding coincided with the 1976 coming (in the context of oncology) of the term “chemoprevention” (50) and the 1977 FDA approval of tamoxifen for breast cancer therapy, which has been reviewed elsewhere (40). Tissue-specific and cytostatic effects of tamoxifen, including its increased efficacy over longer administration (up to 5 years, as confirmed clinically in adjuvant trials (2,16)), also were described (28,40,47).

Tamoxifen’s clinical trial record covers more than 10 million patient-years and tens of thousands of women. In the breast, tamoxifen is a nonsteroidal antiestrogen that competitively inhibits the binding of estrogen to ERs, thus affecting expression of estrogen-regulated genes that influence G1 growth arrest and apoptosis (40,47,48,51–54).

ERs are present in several sites, including normal tissue of the breast and 60%–70% of breast cancers. Tamoxifen and related nonsteroidal agents, such as toremifene, raloxifene, droloxifene, idoxifene, LY353381, and EM-800 (7,40,47,48,51–56), are called SERMs because these agents can have ER-agonistic, ER-partial agonistic, or ER-antagonistic effects, depending on the species, tissue, and gene. The molecular basis of these SERM activities remains unclear and under active investigation (discussed below) (40,51–54). Raloxifene, a benzothiophene analogue, is the second-best-studied SERM in breast carcinogenesis. In animal models, raloxifene (also called keoxifene) appeared to be less active against mammary carcinogenesis and less causative of uterine carcinogenesis compared with tamoxifen (47,51,55,56). There are ER-targeting agents with purely antiestrogenic effects, such as the steroidal agent faslodex (ICI 182,780) (47,56).

The therapeutic beginnings of tamoxifen’s development for prevention bear on the future development of cancer chemoprevention agents. Tamoxifen therapeutic and preventive effects involve the same molecular target (the ERs), and the toxicity profile of tamoxifen therapy suggested possible use in prevention. These therapy/prevention inter-relationships now are being addressed with respect to many new molecular-targeting agent classes, such as inhibitors of tyrosine kinases or matrix metalloproteinases (7).

**ER-Dependent and ER-Independent New Agent Development**

Intensive study of the highly complex structure and function of ERs has led to developing new SERMs, pure antiestrogens, and novel approaches to regulate ER transcriptional activity and to identifying many new targets and levels of regulation (7,38,40,41,47,48,51–54,56–59). ER activation requires ligand and cofactor recruitment, transcriptional machinery assembly at target gene promoters, and chromatin remodeling by histone acetylation (47,48,51,53,59,60). Subtle differences in ligand-receptor conformation is associated with major differences in tissue-specific SERM pharmacology (47,48,51–54,59).

This complexity of ER targeting and SERM pharmacology became even greater when ERβ, the second ER, was identified recently, leading to intensive efforts to develop ER-subtype-specific agonists and antagonists. Although much about ERs and their interactions with SERMs remains to be discovered, we do know that the two ERs (α and β) are genetically distinct and can differ with respect to their distributions in neoplastic and normal tissues [e.g., the α:β ratio is higher and different ERβ isoform patterns occur in breast cancer compared with adjacent normal tissue (60)], response-element binding (57), transcriptional activity [e.g., ERα activates and ERβ inhibits AP-1 (52,57,58)], and estrogen and SERM interactions/effects [e.g., tamoxifen has a higher relative affinity for and greater estrogen antagonist activity through ERβ than ERα; such relationships of raloxifene are higher for ERα than ERβ (58)]. Functional studies of ERα and ERβ (monomers, dimers, and isoforms), ER/ER-related receptors, and ER/progesterone receptor-targeting interactions are uncovering more levels of receptor complexity (47,48,51–53,57–60). Other molecular targets in the estrogen signaling pathway are downstream ER-regulated genes. A major focus of future studies will be on developing agents/combos that will antagonize the effects of estrogen on the breast and uterus and will have estrogenic effects on bone, liver, and brain.

Results of both the BCPT (1) and MORE trial (43) demonstrate that the breast antiestrogenic agents tamoxifen and raloxifene do not decrease the incidence of ER-negative tumors. In addition tamoxifen resistance in ER-negative tumors, 31% of ER-positive tumors were tamoxifen resistant in the BCPT. The well-described resistance to tamoxifen that develops in ER-positive breast cancers (40) has been addressed in a recently reported study of peptide antagonists of ERα to combat possible tamoxifen partial agonist effects due to conformational ER changes after tamoxifen binding (48,51,53,59). Tamoxifen resistance is largely responsible for renewed efforts, including molecular targeting studies, to identify additional breast cancer chemopreventive agents (both single and combined). ER-negative DCIS may be a good model for studying ER-independent agents (18).

Classes of promising molecular-targeting agents for breast cancer prevention that may act independently of ERs include vitamin D analogues, polyamine biosynthesis inhibitors, arachidonic acid metabolizing enzyme (cyclooxygenase and lipooxygenase) inhibitors, telomerase inhibitors, cyclin-dependent kinase inhibitors, and retinoids (7,61–63). Gene therapy [e.g., targeting BRCA1 (41)] is a promising molecular chemopreventive approach. Supporting gene therapy in this setting, studies in human breast cancer cells (41) indicate that wild-type BRCA1 can suppress estrogen-dependent proliferation by inhibiting ERα signaling and that BRCA1 loss/mutation may contribute to carcinogenesis. These molecular findings are supported by pathologic data (e.g., high mitotic index) in BRCA1-associated breast cancer (39).

Retinoids are one of the most promising and best studied classes of non-SERMs. The nuclear retinoid receptors—retinoic acid receptors (RARs) and retinoid X receptors (RXRs)—and ERs are nuclear transcription factors within the same intracellular receptor family. The most promising retinoids for breast cancer prevention include RAR-subtype-selective, RXX-selective, anti-AP-1, and potent apoptosis-inducing retinoids (e.g., retinamides and retroretinoids, which have nuclear retinoid receptor-independent activity that is mediated in part by induction of reactive oxygen species) (7,64–70). The retinamide fenretinide, which has receptor-dependent and receptor-independent activities (64–66), is the most extensively studied retinoid in breast cancer prevention, with activity in ER-positive and ER-negative breast cancer cells and a high therapeutic index (and
Several studies suggest the potential of anti-AP-1 retinoids for preventing breast cancer, including that which is tamoxifen resistant. AP-1 transcription factors are important transducers of mitogenic signals in normal and malignant breast cells (52, 81, 83–87). RAR-selective receptor antagonists have been shown to transrepress AP-1 signaling (88–91), and tamoxifen resistance of certain breast cancer cells has been shown in vitro and in vivo to be associated with increased AP-1 activity (92, 93). Schiff R, Reddy P, Coronado-Heinsohn E, Grim M, Hilsenbeck SG, Herrera R, et al.: manuscript submitted for publication). Anti-AP-1 retinoids (e.g., BMS453) have been shown to inhibit the growth of malignant breast cancer cells, which have increased AP-1 activity (94). It is possible that anti-AP-1 retinoids will be active alone or in combination with SERMs, such as tamoxifen, in preventing breast cancer.

As with SERMs, retinoids appear to have a complex mix of benefits and risks (7, 75, 79, 95–98).

New preclinical (95) and clinical models for breast cancer prevention are being developed. New translational models include the high-risk groups of atypical hyperplasia, LCIS, DCIS, and BRCA1 and BRCA2 mutation carriers. Two intriguing new models are 1) patients with resected/early-stage (adjuvant) breast cancer (for testing new agents in preventing primary and contralateral disease) and 2) ER-negative DCIS (discussed earlier).

**CONCLUSION**

Implications of the positive outcomes of the BCPT and other tamoxifen breast cancer prevention studies are profound, not only for women at increased risk of breast cancer but for the entire field of chemoprevention as well (7, 96). According to many experts in the field, chemoprevention sits at a crossroads leading toward two promising, potentially competitive avenues of research: 1) relatively small phase II trials designed to assess translational end points (with a recent focus on molecular targets) (97) and 2) large-scale phase III trials, such as the BCPT. Although not necessarily mutually exclusive, these two avenues are tending to polarize cancer chemoprevention investigators into adherents of one or the other.

Arguments supporting smaller scale translational/mechanistic research include the claim that, since most large-scale phase III trials have been negative, their tremendous expense is not a wise choice for limited research dollars. Smaller laboratory-related investigations could provide better biologic bases for large trials. The smaller trials also are crucial for developing surrogate end point biomarkers, which, like high blood pressure or high cholesterol level for heart disease, may provide economic end points for definitively testing chemoprevention agents (7, 96, 99).

On the other hand, supporters of large-scale phase III study argue that the BCPT proved the value of this type of research. Even the negative large trials provided great public benefit, e.g., warning smokers of potential lung cancer risk with b-carotene (7, 9, 100–103). Positive phase III secondary findings on cancers other than the primary end point generate the strongest hypotheses for new trials, e.g., secondary adjuvant tamoxifen trial findings leading to the BCPT and secondary MORE raloxifene findings leading to the STAR. These trials are the most powerful and valid means of testing preventive agents with respect to both primary and secondary effects. Even if valid intermediate end points become available, it would take a stag-
gering advance in molecular/cellular and statistical modeling techniques to allow surrogate end point biomarker/phase II trials to adequately assess multiple secondary outcomes.

Another powerful argument for large phase III studies is that they (and not only phase II trials) provide the opportunity for translational study. Biorepositories are an invaluable resource of the large trials, facilitating innumerable studies of correlative molecular/cellular biomarkers. For example, planned studies of the molecular risk markers BRCA1 and BRCA2 in BCPT participants will benefit from that trial’s large population. Also, these trials can validate surrogate end point biomarkers, i.e., establish a statistically significant correlation between cancer outcome and changes in these biomarkers (99).

The BCPT illustrates the importance of multiple outcomes assessments and their application to clinical care. Preliminary data had suggested that tamoxifen would have potential secondary negative effects, e.g., increased endometrial, liver, and colon cancers, and potential secondary beneficial effects, e.g., preventing heart disease and bone fractures. As it turned out, in the BCPT, liver and colon cancers were not increased, and heart disease was not prevented. Hard secondary BCPT data such as these give clinicians the chance to provide solid recommendations in counseling patients on the spectrum of risks and benefits associated with tamoxifen use (1,15,20,24,25).

Proposed by Sir Francis Bacon (104) in 1620, an early axiom of the scientific method states that instances of the fingerpost can illuminate the way to resolving scientific questions that have eluded ready answers. Is the BCPT an instance of the fingerpost, deciding possibly once and for all whether goest chemoprevention? We believe it is. But, perhaps unexpectedly, we believe that the BCPT clearly points chemoprevention down both of the highly productive research avenues being debated, not just one or the other.

The BCPT was the first completed phase III chemoprevention trial to have its rationale founded on both mechanistic, molecular-targeting studies and on secondary analyses of large clinical trials. This strength of rationale may well explain the spectacular positive results of the BCPT, distinguishing it from the vast majority of other definitive phase III cancer end point prevention trials (7). Chemoprevention should pursue both phase III and phase II objectives. Choosing one path over the other would entail the loss of many benefits offered by the path not taken.

Potential type I and II statistical errors and other factors confound the ability of phase III secondary findings to definitively answer clinical questions. Countless molecular/cellular and technical factors confound the ability of translational biomarker studies to predict clinical outcome. Taken together, however, the secondary analyses and mechanistic data provide powerful hypotheses and rationales for new trials.

In the intense discussions sparked by the BCPT, the two tamoxifen issues of substantial associated risks and proof of the chemoprevention principle tend to be pitted against each other. We believe that the two issues should be separated. Yes, there are substantial associated risks. And yes, tamoxifen has provided the proof of principle of chemoprevention. Tamoxifen in the BCPT and in trials in several other breast cancer prevention settings has illuminated more than just the future direction of chemoprevention research. Tamoxifen studies cumulatively are an instance of the fingerpost for the entire field of chemoprevention. They have validated this avenue of cancer control research, proving once and for all the principle that chemoprevention can control the incidence of cancer in humans. This proof of principle stands, regardless of whatever final clinical recommendations for tamoxifen come to pass.

References


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NOTES

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