Two Good Choices to Prevent Breast Cancer: Great Taste, Less Filling

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Abstract

An important report in this issue of the journal by Vogel et al. (beginning on p. 696) discloses long-term follow-up data of the Study of Tamoxifen and Raloxifene (STAR) showing persisting strong effects of both drugs in preventing invasive and noninvasive breast cancer after drugs were stopped in 2006. In addition, safety improved with longer follow-up (median of 81 months versus 47 months for the initial report). For 12 years, the public has avoided Food and Drug Administration–approved tamoxifen or raloxifene for breast cancer risk reduction; it is time to reemphasize the great preventive benefit of these agents to the public.

Perspective on Vogel et al., p. 696

Phase III breast cancer prevention trials and contralateral breast cancer studies in phase III adjuvant breast cancer treatment trials have conclusively shown that the selective estrogen-receptor modulators (SERM) tamoxifen and raloxifene effectively prevent a large number of breast cancers in high-risk women. These results led the U.S. Food and Drug Administration (FDA) to approve both SERMs for breast cancer risk reduction. These seminal results and the FDA approvals, however, have not influenced the use of these agents for breast cancer prevention among at-risk women. This disconnect perplexes many experts in the field. Breast cancer is a life-threatening disease, and one would think the chance to avoid it would be appealing. However, concerns over the side effects of the SERMs, limited education about the benefits and risks of SERM therapy, and a general dissatisfaction with taking medications to prevent cancer have led to the very poor use of these effective cancer-preventive drugs. Now, with the report by Vogel et al. on the long-term follow-up analyses of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR; beginning on p. 696 in this issue of the journal; ref. 1), there is new hope that these agents will be reevaluated by the medical community and the public for improving women’s health.

The results of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (BCPT; ref. 2) showed that tamoxifen cuts the risk of breast cancer in half. The initial results of STAR (first reported in 2006; ref. 3), which primarily compared tamoxifen (20 mg/d) with raloxifene (60 mg/d; each taken for 5 years) for preventing invasive breast cancer, confirmed the efficacy of tamoxifen and showed that raloxifene was equivalent in preventing invasive breast cancer but less effective in preventing noninvasive disease. STAR also showed that raloxifene had a better safety profile (fewer cases of hot flushes, blood clots, and uterine cancers). A massive body of evidence from these and several other phase III cancer prevention trials now show that both SERMs reduce the incidence of breast cancer regardless of the estimated baseline risk. A recent meta-analysis indicated that the relative risk for estrogen receptor (ER)–positive invasive breast cancer is 0.55 for tamoxifen and 0.43 for raloxifene, representing a 45% and a 57% reduction in risk of ER-positive breast cancer, respectively (4). Important data from long-term follow-up of the International Breast Cancer Intervention Study I (IBIS-I; ref. 5) and other placebo-controlled tamoxifen prevention trials showed that this risk reduction persists for at least 5 to 10 years beyond the 5- to 8-year course of tamoxifen (6). This carryover preventive effect is reminiscent of the persistent, greater-than-15-year benefit of a 5-year course of tamoxifen in the adjuvant setting (7) and is a major advantage of SERM therapy. Furthermore, the adjuvant data indicated that an overall survival benefit of 5-year tamoxifen was not seen until ~10 years of follow-up. The persistent cancer-preventive effect is accompanied by reduced side effects (after SERM therapy is stopped), resulting in an improved risk/benefit ratio compared with the first 5 years during active drug therapy.

Vogel and his coinvestigators deserve congratulations for their simple and elegant new, long-term analyses of STAR, which provide mature results that inform our selection of the best agents for the prevention of breast cancer. Furthermore, the biomaterials collected during STAR will facilitate a better understanding of the biological effects of these two drugs and the identification of risk markers and intermediate and predictive biomarkers of clinical...
SERM effects; these biomaterials also will provide critical information for designing future breast cancer prevention trials (8).

Salient findings of the new analyses begin with the extended median follow-up of 81 months (n = 19,490 women) versus 47 months (n = 19,747 women) in the initial report in 2006 (3). The mean 5-year breast cancer risk of women in this analysis was 4.03%. The major risk ratios (RR) of raloxifene to tamoxifen were as follows: 1.24 [95% confidence interval (CI), 1.05–1.47] for invasive breast cancer, 1.22 [95% CI, 0.95–1.59] for noninvasive breast cancer, 0.55 [95% CI, 0.36–0.83; P = 0.003] for endometrial cancer, 0.19 [95% CI, 0.12–0.29] for uterine hyperplasia, and 0.75 (95% CI, 0.60–0.93) for thromboembolic events. As these long-term data indicate, raloxifene was 76% as effective as tamoxifen in preventing invasive breast cancer (a reduction from initial STAR results). Raloxifene also was 78% as effective as tamoxifen in preventing noninvasive breast cancer (reflecting an improvement in the cancer preventive activity of raloxifene since the initial report). Raloxifene also had far less toxicity in the long term, with no increase in uterine cancers and significantly fewer thromboembolic events, cataracts, and hot flushes.

The long-term STAR results show the durability of the therapeutic benefit of both agents and clarify the differences and similarities between them. The challenge facing us today is to successfully communicate these results to the public to enhance the use of SERMs and further reduce the burden of breast cancer.

The important new information from the long-term analyses includes the findings that tamoxifen retained its therapeutic effect and that the effect of raloxifene decreased modestly in preventing invasive breast cancer, compared with the initial, 2006 STAR results. The more mature results and a larger number of events also show that the initial differences in preventing noninvasive breast cancer have become clearly nonsignificant. With the RRs for invasive and noninvasive cancers now being nearly identical, the long-term follow-up results show a clear and more understandable effect of raloxifene on both invasive and noninvasive breast cancer development. These new results bring a better perspective to the results of previous raloxifene trials [such as the first report of STAR and the Raloxifene Use for the Heart (RUTH), Multiple Outcomes of Raloxifene Evaluation (MORE), and Continuing Outcomes Relevant to Evista (CORE) studies] that showed no reduction of the incidence of noninvasive breast cancer (9, 10). These previous results were based on very few events. The longer STAR follow-up data correct the previously confusing apparent differential in the effect of raloxifene on invasive and noninvasive disease. Also based on more events, the nonsignificant trend of a reduced incidence of endometrial cancer with raloxifene reported in 2006 is now highly significant, compared with tamoxifen.

How can the different durations of effect of these two SERMs be explained? Despite having a similar mechanism of action, the two drugs are clearly different. For example, as the work of Jordan and others (11–13) has shown, raloxifene has poor bioavailability and a short half-life due to rapid excretion (measured in hours), whereas tamoxifen has a long half-life that is measured in weeks. Furthermore, tamoxifen is largely metabolized to endoxifen, an antiestrogen with a high affinity for the ER, whereas raloxifene is not. These pharmacokinetic differences suggest that issues of compliance, schedule, and duration of treatment could have a major effect on the efficacy of raloxifene, but less so for tamoxifen.

For example, modest noncompliance (that might occur after taking the medication for several years) would be more detrimental to the ability of raloxifene to prevent breast cancer. This possibility is compatible with the data in Fig. 1 of the STAR update report (1) showing similar cancer-preventive effects of tamoxifen and raloxifene for the first 30 months, followed by a gradual divergence of the incidence curves after 30 months. The impact of treatment duration on raloxifene effects is supported by data from the CORE trial in women with osteoporosis. The continuation of daily raloxifene for 8 years resulted in a persistent reduction in breast cancer risk without any apparent loss of therapeutic effect, in contrast to the updated invasive breast cancer results of STAR, in which raloxifene was stopped in most women after a little more than 3 years of usage (signifying that most women were off raloxifene for 2–3 years before the current analysis).

Despite the compelling results of the BCPT and STAR, there has been minimal use of these two SERMs by women at risk for breast cancer (14). Studies monitoring SERM sales have shown that only 5% to 20% of women who matched the eligibility criteria of the breast cancer prevention trials opted for SERM therapy for breast cancer risk reduction. More recent reports suggest that use has decreased, with only 6% of women offered a SERM agreeing to take this medication. Furthermore, only a small proportion of these women filled the SERM prescription that they had verbally agreed to take.

Tamoxifen had already been used for many years at a fairly consistent level before 1998 as treatment for breast cancer. In 1998, results of BCPT (the first National Surgical Adjuvant Breast and Bowel Project breast cancer prevention trial) were reported and led to the FDA approval of tamoxifen for breast cancer risk reduction. After 1998, however, there was no appreciable increase in the use of tamoxifen, and several factors have contributed to the virtually absent uptake of tamoxifen for prevention. Preliminary reports of 1998 had indicated that tamoxifen was ineffective in two smaller European trials, the Royal Marsden and Italian trials (15–17), although they had very different designs and were underpowered. Tamoxifen was portrayed as a potentially toxic cancer drug and was rarely prescribed by nononcologists, who were unfamiliar with it. Many women and physicians feared the rare adverse effects such as endometrial cancer and thromboembolic complications. Although none of the tamoxifen prevention trials was powered to assess a survival benefit, there was strong criticism that such a survival advantage was not shown. Last but not least, women and their primary care physicians have
had difficulty in assessing the complex risk/benefit ratio of tamoxifen and raloxifene when making the decision to prescribe or take these cancer-preventive medications.

From its FDA approval and introduction to the market in 1997 for osteoporosis prevention (18), raloxifene use gradually increased and was enhanced in 1999 by its approval for osteoporosis treatment based on the MORE trial (19) and by secondary findings of MORE showing reduced breast cancer risk (20). After the publication of the Women’s Health Initiative (WHI) results showing adverse effects of hormone replacement therapy (21), the use of SERMs decreased, perhaps because SERMs and hormones were painted with the same brush in the public eye. Decreased use continued despite the positive results of STAR. This pattern reflects, in part, the fear of serious adverse effects, such as thromboembolic complications. Another contributor to declining raloxifene use was the bisphosphonates, which have been increasingly used and have become the preferred agent for osteoporosis treatment. The gradual, steady reduction in raloxifene usage was unaffected by the 2006 publication of STAR results showing the great efficacy of raloxifene in preventing invasive disease—unaffected despite the FDA approval of raloxifene for reducing breast cancer risk based on these results.

Other factors that also may have contributed to the less-than-vigorous translation of the results of BCPT and STAR into clinical practice include misinformation, limited high-risk predictor(s), a lack of a marker or condition to help monitor cancer risk reduction effects, cost, insufficient public and professional information, and unmet expectations. The adverse effects of SERMs have been largely exaggerated in the public eye by the media and others who do not fully understand the magnitude of risk reduction with these agents. There is concern in some quarters about the accuracy of our risk prediction models for individuals, which can lead to doubt about an individual’s benefit when taking a SERM for cancer prevention. There has been insufficient education of the medical profession and the public at large about the magnitude of the benefits and risks of SERM prevention. The randomized trials were largely done by oncologists, but the application of SERM prevention falls largely into the hands of the primary care community, who see the healthy women at risk for breast cancer. Last, raloxifene was initially anticipated to be beneficial to cardiovascular health and to be more effective than tamoxifen for breast cancer prevention. The Raloxifene Use for the Heart (RUTH) trial and STAR, however, did not show these benefits. These unmet expectations may have disappointed women and primary care specialists and, thus, may have diminished enthusiasm for raloxifene. Subjective and quality-of-life factors for the low uptake of SERMs for breast cancer prevention are discussed elsewhere in this issue of the journal (14).

Regarding the risk-benefit profiles of the two SERMs tested in STAR, the number of women who experience serious adverse effects (risk) is far smaller than the number of women who will avoid breast cancer (the major benefit) because of these drugs. The new long-term results indicate that tamoxifen is slightly more effective in reducing breast cancer risk and that raloxifene retains most of its cancer-preventive benefit while having a safer side effect profile, including no association with endometrial cancer and only a modest effect on thromboembolic complications. Other long-term analyses show that the substantial carryover benefit of tamoxifen now exceeds 15 years (5, 6).

The following data in this paragraph may help to visualize the benefits and risks of SERMs. Tamoxifen will prevent 20 invasive and 20 noninvasive breast cancers [based on the long-term data at an 81-months median follow-up (∼7 years)] in 1,000 women at the elevated 5-year risk of 4% (the average risk in STAR) versus causing 2.25 endometrial cancers (in women with an intact uterus at study entry) and 3.3 thromboembolic events in the same group of women over 7 years. Raloxifene will prevent 15 invasive and 16 noninvasive breast cancers over 7 years in 1,000 women at an elevated risk (4%) versus causing 2.47 thromboembolic events and no endometrial cancers in the same group over 7 years. For these major effects, tamoxifen causes 40 beneficial versus 5.53 adverse effects (benefit/risk ratio of ∼7:1) and raloxifene causes 31 beneficial versus 2.47 adverse effects (benefit/risk ratio of ∼13:1) over 7 years. These ratios indicate a rather extraordinary net gain for women at a 4% 5-year risk of breast cancer and would improve substantially for women at a 4% or higher risk, who number ∼600,000 in the United States. These figures also suggest that women at considerably lower risks (between 1.67% and 4%) would still have a positive benefit/risk ratio with these drugs.

Why should eligible, at-risk women use these agents today for breast cancer prevention? First, because their magnitude of risk reduction is large, exceeding the effect of most other medical preventive interventions (such as aspirin to prevent stroke or statins to prevent heart attacks). Furthermore, the only breast cancer preventive intervention more effective than SERM therapy is bilateral prophylactic mastectomy, a very drastic and potentially traumatic intervention. Second, the safety profiles of both SERMs are excellent. Millions of women have taken tamoxifen over three decades or raloxifene over the past 12 years, with only a modest number of serious side effects. Furthermore, preventing breast cancer spares women the emotional and physical trauma of the diagnosis and treatment of breast cancer. Most important, preventing breast cancer eliminates the possibility of dying from this life-threatening disease.

There are no perfect drugs. Other drugs used for preventing other diseases, however, enjoy greater acceptance and tolerance of adverse effects, including, for example, hypertension drugs (used for the prevention of heart attacks and stroke) and cholesterol-lowering drugs (also used to prevent heart attacks and stroke). The incidence

3 Personal communication, Barry Graubard, April 23, 2010.
of serious side effects of these agents exceeds that of the SERMs. The serious and other side effects (a) of hypertension drugs include hypotension, bradycardia, worsening heart failure, allergic reactions, electrolyte imbalance, fatigue, diarrhea, dizziness, confusion, depression, drowsiness, impotence, headache, chronic cough, and edema; and (b) of cholesterol drugs include myopathy (weakness, muscle pain), rhabdomyolysis (may be fatal), renal failure, liver failure, headache, nausea, vomiting, constipation, diarrhea, rash, and drug interactions. Despite these effects, millions of men and women take antihypertensive and cholesterol-lowering drugs daily, often for life. It has been postulated that a major factor in the greater acceptance of drugs causing these side effects (versus SERMs) is that risk biomarkers (e.g., cholesterol level and blood pressure) for monitoring the activity of these drugs provide ongoing evidence of benefit and thus peace of mind for individuals taking these drugs.

These issues illustrate what can be called a “silo effect.” Different branches of medicine have widely different perceptions of risk and benefit, and of an acceptable therapeutic ratio. For a practicing medical oncologist, the adverse effects of SERMs pale in comparison with the complications of, and disability caused by, breast cancer. The discomfort and suffering from the side effects of SERMs is considered to be greatly outweighed by the potential benefit to the hundreds of thousands of women who die each year around the world as a result of advanced breast cancer.

In summary, tamoxifen appears better in 2010 after the long-term analysis of STAR (1) than it did in 1998 after BCPT (3) and in 2006 after the initial STAR report (2) and, thus, is an excellent choice for breast cancer risk reduction in premenopausal women and in postmenopausal women without a uterus. This long-term analysis also shows that raloxifene has extended its safety advantage over tamoxifen, while retaining 76% of its breast cancer–preventive effect. Therefore, raloxifene is a good option for women with osteoporosis and for postmenopausal women with an intact uterus. Future research is needed to optimize the schedule and duration of raloxifene.

The long-term outcome of the STAR shows that tamoxifen and raloxifene are both effective in preventing ER-positive breast cancer and are well tolerated, albeit with somewhat different therapeutic profiles. Although these agents are currently the best options for breast cancer–preventive therapy, potentially more-effective agents for preventing both ER-positive breast cancer (e.g., aromatase inhibitors and new-generation SERMs; ref. 22) and ER-negative breast cancer (e.g., epidermal growth factor receptor/HER2 tyrosine kinase inhibitors) are being investigated. Until such agents are shown to be effective and safe for breast cancer prevention, however, it is critical to inform the general public and our colleagues in the primary care specialties of the major preventive effects of the two FDA-approved SERMs for breast cancer prevention. The 50% reduction of invasive breast cancer seen with tamoxifen exceeds by far the modest risk reductions observed for other preventive agents commonly used to prevent heart attacks, stroke, osteoporosis, and the effects of diabetes. These data and conclusions are reminiscent of the popular beer commercial that pitted “Great taste” against “Less filling.” The clear message? The choice of drugs for breast cancer prevention should not be either tamoxifen (the great taste of enhanced efficacy) or raloxifene (less filling because of fewer adverse events) but is instead tamoxifen and raloxifene—two good choices, depending on individual risk factors and preferences, for the 10-million-plus U.S. women eligible to take them (per FDA approval; ref. 23).

**Disclosure of Potential Conflicts of Interest**

P.H. Brown is on the Scientific Advisory Board of the Susan G. Komen for the Cure organization. G.N. Hortobagyi disclosed no potential conflicts of interest.

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**References**


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