Tipping the Balance for the Primary Prevention of Breast Cancer

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There are millions of postmenopausal women in the United States who are at risk for both osteoporosis and breast cancer, and both diseases cause thousands of deaths each year (1). Clearly, a preventive strategy is more attractive than treating progressive or advanced disease, but neither the primary care community nor medical oncologists have embraced chemoprevention of breast cancer as their own responsibility, despite the fact that professional organizations have endorsed primary prevention as a standard of care (2,3).

In this issue of the Journal, LaCroix et al. (4) describe the effect of lasofoxifene in reducing the incidence of breast cancer in postmenopausal women with osteoporosis. Lasofoxifene appears to represent an advance in the progression of pharmacological agents at our disposal, which can reduce both the risk of fractures in women with osteoporosis and the risk of breast cancer in postmenopausal women (5–7), possibly because it binds with high affinity to both estrogen receptors (ER)-α and ER-β. A previously reported 42% reduction in the risk of vertebral fractures (13.5 vs 23.0 per 1000 person-years) at 3 years attributable to lasofoxifene is similar to that observed with raloxifene, estrogen therapy, oral bisphosphonates, and tibolone (8). The decreased risk of nonvertebral fractures is also similar to that reported in association with other antiresorptive therapies in women with osteoporosis.

In contrast to lasofoxifene, however, raloxifene—the selective estrogen receptor modulator (SERM) currently approved by the US Food and Drug Administration for treatment of osteoporosis—does not reduce the risk of nonvertebral fractures, perhaps because lasofoxifene decreases markers of bone turnover and improves spine bone mineral density more than does raloxifene at a dose of 60 mg, although the two agents have similar effects on total hip bone mineral density (8,9).

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

Multiple studies have shown that tamoxifen reduces the risk in women at increased risk of breast cancer (10,11). In addition, we now have several strategies to identify women at increased risk: quantitative risk models (12–14), increased mammographic density (15–17), circulating estrogen levels (18–20), and the presence of high-risk benign breast disease such as atypical hyperplasia and lobular carcinoma in situ (21,22). We now also have several agents that have been studied prospectively in randomized controlled trials that have examined benefits, life-threatening side effects, and quality-of-life outcomes. We have estimates of the population benefit of using SERMs for breast cancer risk reduction (1), and we have estimates of the cost per year of life saved (23,24). Yet, despite the fact that the number of women needed to treat to prevent a case of breast cancer is acceptable with both of the SERMs, tamoxifen and raloxifene, neither drug has been able to tip the clinical utility scale to broad usage within the high-risk population for breast cancer risk reduction (25).

The Study of Tamoxifen and Raloxifene (STAR) Trial compared the first-generation SERM, tamoxifen, with the second-generation drug, raloxifene, in high-risk postmenopausal women. Raloxifene caused half as many uterine malignancies, 20% fewer pulmonary emboli, and 28% fewer deep vein thrombi. There were few strokes, and raloxifene was nearly as effective in preventing invasive breast cancer (Table 1), yet utilization did not rise (26). It is a clinical reality that drug toxicities and benefits must be balanced. Accordingly, available data show that tamoxifen will prevent 20 invasive and 20 noninvasive breast cancers in 1000 women at the elevated 5-year risk of 4% while causing 2.2 endometrial cancers and 3.3 thromboembolic events in the same group of women over 7 years (27). Similarly, raloxifene will prevent 15 invasive and 16 noninvasive breast cancers over 7 years in 1000 women at an elevated risk (4%) vs causing 2.5 thromboembolic events and no endometrial cancers in the same group over 7 years. For these major effects, tamoxifen causes 40 beneficial vs 5.6 adverse effects, and raloxifene causes 31 beneficial vs 2.5 adverse effects over 7 years.

There were differences among the participants in the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) trial and trials such as STAR. Women in PEARL were, on average, about 9 years older than STAR trial participants at entry (mean age, 67 years vs 58.5 years), and 91% of STAR trial participants were younger than 70 years at entry. Women in PEARL were also at lower risk of breast cancer with average Gail scores of 1.7% risk of breast cancer in 5 years compared with average Gail scores of 4.03% in STAR trial. Rates of venous thromboembolism were lower with raloxifene in STAR than with lasofoxifene at the 0.5 mg dose in PEARL (1.38 vs 2.9 events per 1000 woman-years), possibly reflecting the older age of the PEARL participants (Table 1). Nevertheless, the rate of invasive breast cancer in PEARL was more than six times higher than the stroke event rate in the placebo group; breast cancer incidence was decreased by 79% with lasofoxifene, while the stroke event rate...
also fell by 36% with lasofoxifene compared with placebo. It remains to be seen if this benefit translates into acceptance of the drug by patients and their physicians, but it is a very promising observation.

It is true that the PEARL trial was handicapped by a small number of both subjects and adverse events, yet the breast cancer risk reduction compared with placebo was dramatic at nearly 80%. It is also true that thromboembolic events were doubled, but the absolute event rates were very low. Net benefits will be greatest in younger postmenopausal women who are at greater risk of breast cancer.

A number of reasons have been put forth to explain why patients may not be willing to adopt a SERM for breast cancer risk reduction (25). Hormone replacement therapy is still widely used by postmenopausal women, even following the results of the Women’s Health Initiative (28), but it is contraindicated with concurrent SERM therapy. Patients erroneously perceive the risks of SERM therapy to be greater than its benefits, and they perceive the risks of therapy-related side effects to be greater than their risk of breast cancer. This problem is confounded by the fact that they (and perhaps their physicians) are confused by the concept of probabilistic risk. Finally, they fear endometrial cancer out of proportion to its true tamoxifen-related risk and do not understand that there is no increased risk of uterine malignancy associated with lasofoxifene; we must hope that lasofoxifene does not soon suffer the same fate of misinformation.

Despite strong evidence that it is efficacious, chemoprevention has been underused in eligible women. Additional reasons not to adopt and initiate strategies to reduce the risk of breast cancer include the fear of adverse effects, medication costs (29–31), lack of reasonably accurate and feasible methods for assessing personal individual risk (32), and lack of established risk thresholds that maximize benefit and minimize harms.

The American Society of Clinical Oncology (ASCO) has said that, “Five years of tamoxifen (20 mg/d) may be offered to women at increased risk of breast cancer to reduce their risk of estrogen receptor (ER)–positive invasive breast cancers for up to 10 years. Eligible women include those with a 5-year projected breast cancer risk ≥1.66%, or women with LCIS. The greatest clinical benefit and the fewest side effects were derived from the use of tamoxifen in younger (premenopausal) women 35 to 50 years of age who are unlikely to experience thromboembolic sequelae or uterine cancer, women without a uterus, and women at high risk of breast cancer.” (2)

ASCO also says that for postmenopausal women at increased risk for breast cancer, raloxifene (60 mg/day) for 5 years may be offered as another option to reduce the risk of ER-positive invasive breast cancer (2). No data regarding lasofoxifene were available at the time this recommendation was written.

We need more complete information about the long-term effects of lasofoxifene on both beneficial and unfavorable outcomes, but the early data regarding its risks and benefits are encouraging. In his thoughtful book, Gladwell (33) noted that little changes in perception can have big effects on the behavior of a population. When small numbers of people start acting differently, behavior can ripple outward until a critical mass or “tipping point” is reached, changing the world. We have been waiting for a tipping point in breast cancer chemoprevention for more than a decade. Perhaps with lasofoxifene, the time has arrived.

References