POINT/COUNTERPOINT

Should high-risk women take tamoxifen for breast cancer prevention?

Make chemoprevention an option now.

Breast cancer is still the No. 1 cancer among women. For patients who carry a gene that predisposes them to breast cancer, the weight of that possibility is ever present on their minds.

What do we have to offer women with such risk? Prevention strategies focused on estrogen metabolism have been shown to decrease second breast cancers as well as to prevent primary cancers in women at risk. Our options include the selective estrogen-receptor modulators tamoxifen and raloxifene and the newer aromatase inhibitors, but the choice among them is not clear-cut.

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The National Surgical Adjuvant Breast and Bowel Project's (NSABP) P-1 study reported tamoxifen prevented 50% of estrogen receptor–positive breast cancers in high-risk women on tamoxifen therapy for 5 years (J. Natl. Cancer Inst. 2005;97:1652-62). This large trial showed no prevention of estrogen receptor–negative breast cancers, however, and increases in thromboembolic events, cerebral vascular accidents, and endometrial cancers offset any benefit in some age and health risk groups.

Raloxifene did as well as tamoxifen, although in a smaller overall study group, with a lower endometrial cancer risk, in the subsequent NSABP P-2 investigation, the Study of Tamoxifen and Raloxifene (STAR) trial (JAMA 2006;295:2727-41). Raloxifene also had thromboembolic complications, however, and similar quality of life issues with hot flashes and symptoms of menopause. It did have bone-sparing effects but did not provide the kind of advance over tamoxifen on prevention side effects that would make it the first choice, particularly with the advent of aromatase inhibitors.

Aromatase inhibitors have a different side-effect profile, which makes them attractive for prevention trials (J. Clin. Oncol. 2005;23:1636-43). So far, trials have concentrated on women at risk of recurrence after successful treatment of early-stage breast cancer. In these studies aromatase inhibitors have been more effective than tamoxifen for disease-free survival and for prevention of contralateral cancers with a 58% reduction. Hot flash rates were similar to the experience in women on tamoxifen. Aromatase inhibitors significantly reduced gynecologic symptoms, cerebral vascular accidents, and deep vein thrombosis, but arthralgias, arthritis, bone loss, and possibly some cardiovascular events increased on these medications.

Surgery is another option. Bilateral mastectomy decreases risk by 90%, and it will affect both estrogen receptor–positive and estrogen receptor–negative breast cancers. Many women are not ready for this step, however. Oophorectomy substantially decreases risk as well—by 50%—but primarily for estrogen receptor–positive tumors. It has the side effect of menopause symptomatology as well as bone loss effects and it forces a loss of fertility—a consequence some women also will not accept.

While we do not yet have a chemoprevention strategy that directly targets the estrogen receptor–negative tumors of importance to high-risk patients, a reduction in estrogen receptor–positive tumors still is of value to this group. We should discuss prevention trials and options with every woman at high risk for breast cancer and provide each patient with a clear assessment of the best choice for her individual health risks.

Future development of strategies for estrogen receptor–negative tumor prevention—possibly through retinoids, selective cyclooxygenase (COX) inhibitors, and tyrosine kinase inhibitors—may give us a combined and even more highly effective strategy as an alternative to surgical risk reduction (Exp. Opin. Invest. Drugs 2006;15:1583-600). Our patients need to know what is available to them today. ■

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Its prophylactic benefits are open to question.

Based on data indicating that 5 years of tamoxifen therapy after primary treatment for breast cancer could improve the disease-free interval, the National Surgical Adjuvant Breast and Bowel Project began its P-1 study in 1992. This study used three indicators to identify women at high risk for breast cancer: age 60 or older, younger age with a predicted risk of 1.66% (using the Gail model), or a history of lobular carcinoma in situ or atypical hyperplasia.

More than 13,000 women were randomized to tamoxifen or placebo. After 5 years of tamoxifen use, the study reported reductions in invasive and noninvasive breast cancer (J. Natl. Cancer Inst. 1998;90:1371-88). An update noted similar findings at 7 years of follow-up (J. Natl. Cancer Inst. 2005;97:1652-62).

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Although the reduction was highly significant statistically, the incidence of invasive breast cancer decreased by only 0.27%. The reduction in noninvasive breast cancer was even less: 0.09%. Estrogen receptor–positive tumors essentially accounted for the entire decline.

Investigators reported a significant decrease in fractures among women on tamoxifen. This group had a significant increase, however, in endometrial cancer, thromboembolic events, and cataracts. As more than a third had hysterectomies, the incidence of endometrial cancer could be even higher.

The tamoxifen group also had more strokes, but the increase was not statistically significant.

Excluding breast and endometrial cancers, there were 155 other cancers in the placebo arm, compared with 178 in the tamoxifen group. Tamoxifen appeared to have no effect on heart disease. The incidence of overall deaths per 1,000 was 2.8 for the placebo vs. 3.08 for tamoxifen (relative risk 1.10).

Although the update suggests that breast cancer protection continued for the 2 years after tamoxifen was stopped, the reduction in events decreased considerably in years 6 and 7 to 29% and 14%, respectively, from about a 50% reduction during years 2-5. Previous studies in breast cancer patients reported more recurrences with 10 years of tamoxifen use than with placebo.

As health care providers, we make every decision, hopefully, based upon the benefit-risk ratio, as noted in peer-reviewed studies. Although the NSABP study and several others suggest tamoxifen conveys at least a short-term protection against breast cancer, multiple questions remain. The update did not tell us whether the women were compliant in taking the drug. All similar studies show considerable noncompliance. How this affects the result is unknown.

The 7-year data represent only 69% of patients entered into the study. Presumably, the others were lost to follow-up. Could this affect the results?

More than one-third of the participants were 35-45 years of age. When do you put "high-risk women" on tamoxifen? How long do you give the drug? According to this study, all women over age 60 are at risk and would benefit from tamoxifen. This is highly questionable (less than one-third of the women studied were 60 years of age or older).

There were more deaths in the tamoxifen group, compared with placebo. What benefits did women obtain overall, not just in breast cancer—and at what price?

It appears from practice patterns that the general public as well as health care providers overall have been reluctant to accept a benefit from prophylactic tamoxifen even in "high-risk women." As the diminutive Clara Peller asked in the '80s, "Where's the beef?" That question appears appropriate for this discussion. ■

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Assay Predicts Relapse Risk in Node-Positive Breast Ca Patients

CHICAGO — The Oncotype DX, a 21-gene assay that has been shown to be useful in predicting relapse risk in breast cancer patients with no lymph node involvement, can also predict risk of relapse in patients who have up to three positive lymph nodes, according to a poster presented at the annual meeting of the American Society of Clinical Oncology.

"The results of this analysis, aided by ongoing studies, may tell us which patients with early-stage, node-positive breast cancer actually need chemotherapy," Dr. Lori J. Goldstein, director of the Breast Evaluation Center and leader of the Breast Cancer Research Program at Fox Chase Cancer Center, Philadelphia, said in an interview.

She and her coinvestigators tested the predictive value of the Oncotype DX Recurrence Score (Genomic Health Inc.) in 465 patients who were part of Intergroup Trial E2197, an Eastern Cooperative Oncology Group study of women with early breast cancer treated with standard chemotherapy. Of these patients, 203 had one to three positive lymph nodes, and 262 had no lymph node involvement.

Patients were treated with doxorubicin plus cyclophosphamide if they were hormone-receptor negative, and with docetaxel and hormonal therapy if hormone-receptor positive. The median follow-up was 76 months, and there was no difference in disease-free survival between treatment arms.

Recurrence scores were divided into three categories: low (less than 18), intermediate (18-30), and high (31 or above). The Oncotype DX Recurrence Score was a significant predictor of recurrence in patients with zero to three positive lymph nodes despite treatment with standard chemotherapy. Those whose risk score was less than 18 had excellent outcomes, with less than a 5% risk of recurrence at 5 years; those who had intermediate and high risk scores had a recurrence risk that was two and three times greater, respectively, Dr. Goldstein said.

"These data show the assay can be used to stratify patients at residual risk after being treated with chemotherapy," said Dr. Soonmyung Paik, director of pathology for the National Surgical Adjuvant Breast and Bowel Project, who was instrumental in developing the assay. "Perhaps patients [with] a high oncotype assay result should be treated with something in addition to chemotherapy. This is an important study," he said in an interview.

—Fran Lowry