Prophylactic Tamoxifen Cuts Breast Cancer Risk by 45% in High-Risk Patients

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PITTSBURGH--Five years of prophylactic tamoxifen (Nolvadex) cut the risk of breast cancer almost in half in women at high risk for the disease. D. Lawrence Wickerham, MD, associate chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP), gave the first formal presentation of the results of the Breast Cancer Prevention Trial (BCPT) at the ASCO plenary session.

The trial was stopped last March when an interim analysis showed that the primary endpoint had been reached.

The study enrolled 13,388 women who were otherwise healthy but at high risk for developing breast cancer (see box below). The most common risk factor was family history of breast cancer (about 70% of patients had one or more relatives with the disease). Six percent of subjects had prior history of LCIS.

**Risk Factors for Inclusion in the BCPT**

- Age greater than 60 years

*In women less than age 60, at least one of the following:*

- First-degree relative(s) with breast cancer
- Nulliparity or older age at first live birth
- History of benign breast biopsies
- Younger age at first menstrual period
- History of lobular carcinoma in situ (LCIS) treated by excision alone

Patients were randomized to receive two 10-mg tablets of tamoxifen daily or two placebo tablets daily for 5 years. More than 57% of the patients in this study have been followed for more than 4 years, and median follow-up is 3.6 years.

Treatment with tamoxifen reduced the development of invasive breast cancer--154 cases in the placebo group vs 85 cases in the tamoxifen group (risk ratio 0.55, P < .00001). The benefit was seen in all age groups (*Table*). The greatest benefit was seen in women over age 60. Tamoxifen also reduced the rate of noninvasive breast cancers, with 59 cases seen in the placebo arm vs 31 in the tamoxifen group (risk ratio 0.52, P = .002).

Dr. Wickerham said the tamoxifen group had a significant reduction in estrogen-receptor-positive (ER-positive) tumors (38 vs 112 in the placebo arm), while no significant differences were seen in the number of ER-negative cancers. Tamoxifen reduced the number of breast cancers in women with a history of LCIS (7 vs 16) and in women with prior atypical hyperplasia (1 vs 18).

The tamoxifen group also had a significant decrease in risk of fractures but no change in risk of is-chemic heart disease events.

The risk of invasive endometrial cancer was increased about 2.5-fold among those treated with
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Tamoxifen (33 cases vs 14 cases for placebo), but the excess number was limited to women over age 50 at time of entry (26 vs 6 cases).

"The excess risk of endometrial cancer was not evident among those who were less than 49 years of age at entry," Dr. Wickerham said. He also noted that all cases of endometrial cancer in the tamoxifen-treated group were stage I at diagnosis. There was no increased risk of stroke in the tamoxifen arm. The risk of pulmonary embolism and deep-vein thrombosis increased significantly from 25 with placebo to 47 with tamoxifen, and this increase was concentrated in those over 50 years of age at entry. "There is no increased risk of serious side effects in women under the age of 50," he commented.

Questions Remain
Dr. Wickerham said that two questions remain in the wake of the BCPT: Is 5 years of tamoxifen enough to get the optimum effect, and is this effect due to true prevention of breast cancer or merely to delaying its appearance?

Some clues as to optimal duration of treatment can be gleaned from another NSABP protocol, B-14, in which breast cancer patients treated with adjuvant tamoxifen for 5 years could elect to stop at that point or to continue.

"During the first 5 years there was a 50% reduction in contralateral breast cancer. Those who stopped after 5 years did not then have a dramatic acceleration of contralateral breast cancer, and continuing beyond 5 years does not appear to provide significant additional protection," he said. As to the second question, the discussant C. Kent Osborne, MD, of the University of Texas Health Science Center, San Antonio, said that he believes the early results in this study and in the raloxifene (Evista) trial "are due primarily to the known treatment effect of the antiestrogens on ER-positive established breast cancer." It may be that the agents are having an early treatment effect on subclinical cancers present in some patients at the time of trial entry.

"This would explain tamoxifen’s failure to reduce the number of ER-negative tumors that became clinical and the somewhat greater effect of these drugs on older patients who would be expected to have a higher incidence of ER-positive subclinical cancer," he said. "We don’t know yet whether these drugs block progression at earlier stages, which might be considered a true prevention effect."

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