About Benefits and Costs

Edited by Leon Gordis **Prevention of Breast Cancer**

Since its introduction in 1971 as adjuvant therapy for primary breast cancer, tamoxifen has been taken by millions of women. Toxicity is low, and compliance is high. In randomized trials, two years of tamoxifen therapy reduced annual rates of recurrence by 25% and of death by 17%.

A suggestion that tamoxifen might be useful in prevention arose when a Swedish group looked at occurrence of new primary cancers in 1800 postmenopausal women. After an average follow-up of $4^1/_2$ years, second breast cancers occurred significantly less often (18 vs. 32) and endometrial cancer significantly more often (13 vs. 2) in treated patients than in controls.

Tamoxifen is a synthetic hormone with complex actions. In animal studies, tumors are suppressed by tamoxifen and resume growth when the drug is stopped, suggesting that its effect is cytostatic rather than cytocidal. If so, long-term, perhaps life-long, administration is necessary. But there is little information about long-term effects.

Tamoxifen is generally considered to be anti-estrogenic, but some of its actions are agonistic to estrogen, and estrogen is associated with the development of breast, endometrial, and liver cancer. In postmenopausal women, the decrease in contralateral breast cancer and the increase in endometrial cancer can reasonably be ascribed to tamoxifen. In premenopausal women, however, the outcome is confounded by long-term increased estrogen levels induced by tamoxifen.

Initiation of a prevention trial by the National Surgical Adjuvant Breast and Bowel Project generated a controversy over benefits and costs. NSABP, in Protocol B-14, had previously randomized 2800 women to five years of adjuvant tamoxifen therapy or placebo. There was a significant improvement in disease-free survival on tamoxifen (83% vs. 77% at four years), which was greater in patients under 50. These were low-risk patients, with negative nodes and with receptor-positive tumors.

The former director and the principal statistician of the NSABP argued editorially that the published findings supported the idea of a prevention trial. Their own review of more recent data showed 55 contralateral breast cancers in the untreated group and 28 in tamoxifen-treated patients after an average follow-up of 53 months. "More important," they wrote, "a reduction in the incidence of second cancers was observed in women younger than 50 as well as in those 50 or older."

The plan was to enroll 16,000 women at high risk for primary breast cancer and give half of them tamoxifen for five years. Because only about one third of breast cancers are associated with defined risk factors, the NCI opened enrollment to all women over 60, in whom the risk of primary breast cancer is about 1.7% over five years, and to women over 35 in whom an equivalent risk could be calculated. Adjuvant tamoxifen reduces contralateral breast cancer by at least 30%, so patients randomized to tamoxifen should show a decrease in risk to about 1.2%. There should be a difference in the number of primary breast cancers between about 135 in controls and about 95 in the treated population, or at least one less case per 1000 women per year.

The cost of giving tamoxifen to healthy women is the sum of the adverse side-effects. These are well established for postmenopausal women on adjuvant tamoxifen: a substantial increase in the relative risk of endometrial cancer (detectable and treatable, and risk is low to begin with); an excess of about one case of pulmonary embolism per 1000 women per year of therapy (possibly due to hematologic changes previously induced by the cancer); and ophthalmologic changes, particularly macular edema (reversible upon stopping treatment). Data on side-effects in premenopausal women are limited; but more than 40% of the first 6000 women enrolled in the prevention study are premenopausal.

Moreover, if tamoxifen principally suppresses tumor growth rather than prevents initiation, then the experience with adjuvant tamoxifen is not relevant to its use in women without breast cancer. Both breasts are subject to the same genetic, reproductive, hormonal, and environmental influences, and second breast cancers may have arisen synchronously with the initial tumors.

University of Wisconsin oncologist Richard R. Love has concluded that the prevention study involves "two significantly different populations" in which the projected benefits and costs "are different, both specifically and quantitatively, as well as in the degrees of confidence that characterize the projections. In these circumstances an analysis of mixed premenopausal and postmenopausal populations provides conclusions which are in fact applicable to neither."

Tommy Fornander et al., *Lancet* 1:117-120, January 21, 1989. [The Stockholm trial.]

Bernard Fisher et al., *New England Journal of Medicine* 320:479-484, February 23, 1989. [NSABP B-14.]

Bernard Fisher and Carol Redmond, *Journal of the National Cancer Institute* 83:1278-1280, September 18, 1991. [Supporting a preventive trial.]

Richard R. Love, *Cancer Epidemiology, Biomarkers & Prevention* 2:403-407, September-October 1993. [Opposing the inclusion of premenopausal women in the prevention trial.]