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Online Supplementary Material

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Supplemental Appendix. Additional Considerations for the Decision to Use Tamoxifen for Breast Cancer Prophylaxis

The central concerns regarding tamoxifen use are addressed by the following 2 questions: Is there sufficient evidence to declare tamoxifen effective in breast cancer chemoprevention? When does the benefit of breast cancer risk reduction outweigh the risk of adverse effects from tamoxifen use?

The first question arises because of the discrepancy between the published results from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (BCPT)[1] and those of the Italian trial by Veronesi et al[2] and the British trial by Powles et al[3] There are several explanations for the observed differences, which have been well outlined in the literature.[4-6] Both trials had much lower statistical power than the BCPT. The BCPT had twice the sample size and 3 times the number of baseline breast cancer events as had both European trials combined. In the case of the British Royal Marsden Hospital trial, younger participants and the concurrent use of hormone replacement therapy (26% of participants) are thought to contribute to the trial's negative result. The younger age of participants is important because the preventive effect in the BCPT was confined to estrogen-receptor-positive tumors, which are more common in older women.

The key differences in the Italian trial include a population of relatively low risk (baseline incidence of breast cancer in the placebo group was only one third of that in the BCPT) and poor compliance (26% drop out rate). In contrast, the BCPT findings are robust. The study had high statistical power, with 13,388 participants enrolled and 46,858 woman-years of follow-up. Only high-risk women were included as defined by the Gail model, which was validated for white women in previous studies.[7,8] The results were both clinically and statistically significant. Moreover, they were consistent with the results from the meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group showing a 47% reduction in new primary breast cancers in women treated with tamoxifen after a diagnosis of breast cancer.

After the completion of our study, the first results of the International Breast Cancer Intervention Study (IBIS) were published.[9] This study of 7,152 women at increased risk for breast cancer who were randomized to either placebo or tamoxifen for chemoprevention reported a 32% risk reduction. The same side effect profile observed in the BCPT was documented, with a nonsignificant increase in endometrial cancer and a significant increase in thromboembolic events. These early results add weight to the BCPT finding of a significant and clinically important risk reduction while simultaneously reinforcing concerns regarding the side effects of tamoxifen.

The issue of side effects leads to the second question concerning the risks associated with tamoxifen use. Several editorials have discussed the risks and benefits of tamoxifen, but the authors have drawn dissimilar conclusions.[5,10-13] There does exist general agreement that the risk-benefit ratio is more favorable for women who have a higher breast cancer risk, are younger, and have had a previous hysterectomy. If a subgroup of high-risk women could be defined for whom the benefits of tamoxifen clearly outweigh the risks, then family physicians might be more inclined to recommend it in this subgroup of women.

In 1999 a national conference of breast cancer experts developed a strategy to weigh risks and benefits of tamoxifen therapy for breast cancer risk reduction.[14] This review compared the baseline rates of endometrial cancer, pulmonary embolism and deep vein thrombosis, stroke, fractures, and cataracts from several large, population-based studies with the rates of each of these events in the treatment group of the BCPT, thereby generating a relative risk. These data were subdivided by age, 5-year projected risk of invasive breast cancer, and the presence or absence of a uterus. The algorithm summarizes the risks and benefits of tamoxifen in a single number. A favorable risk-benefit ratio is a positive number, and an

unfavorable ratio is a negative number. The risk-benefit ratio as calculated by this algorithm is summarized in Figure 2 in the main body of the article. The risk of adverse events from tamoxifen is sufficiently low in young women that high-risk women younger than 50 years will always benefit from tamoxifen. The opposite is true in that older women and high-risk women older than 70 years will not benefit. Women aged 50 to 70 years may benefit, but the benefit depends on the magnitude of the 5-year projected breast cancer risk and the presence or absence of a uterus. Of course the algorithm does not consider situations in which a specific factor exists that may alter the baseline risk of either pulmonary embolism and deep vein thrombosis, stroke, or endometrial cancer, such as a hypercoagulable state, obesity, or smoking. Contraindications include a history of pulmonary embolism or deep vein thrombosis, stroke or transient ischemic attack, uncontrolled diabetes, hypertension, or atrial fibrillation. Moreover, some women may be more fearful of having a stroke than developing invasive breast cancer—an important factor in their decisions.

Women with a BRCA mutation represent a distinct group of high-risk women. These women frequently have estrogen-receptor-negative tumors, whereas the BCPT showed the greatest effect in estrogen-receptor-positive tumors. Several studies have attempted to estimate the benefit of tamoxifen among this genetically susceptible group.[15,16] Overall, the results suggest a reduction in breast cancer incidence, with a more significant reduction among patients with BRCA2 mutations (27% to 62%) as compared to BRCA1 mutations (0% to 11%).

Raloxifene for breast cancer risk reduction has made a public impact after preliminary results of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial were published. This study found a 72% reduction in breast cancer incidence, as well as less endometrial cancer risk and greater fracture prevention, compared with tamoxifen among postmenopausal women with osteoporosis.[17,18] Physicians must bear in mind that breast cancer prevention was part of a secondary analysis and, as such, has an increased potential for type I error (false-positive finding).[19] Moreover, there was no stratification based on breast cancer risk, and the total number of events was small (61 breast cancers in all 3 arms). Although the results of the MORE trial are provocative, the Food and Drug Administration has not approved raloxifene for breast cancer risk reduction outside of a clinical trial. The ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP) study of Tamoxifen and Raloxifene (STAR) trial will provide valuable information on the relative efficacy and side effects of these 2 selective estrogen receptor modulators, but the results will not be published until 2006.

Counseling a woman on the use of tamoxifen for chemoprophylaxis requires an estimate of her 5-year projected risk of invasive breast cancer. The calculation of this number, based on the Gail model, is easily done online using computer software provided by the National Cancer Institute (http://bcra.nci.nih.gov/brc/questions.htm). It is equally important to determine a woman's perception of her own risk and the psychological factors that affect this perception. Once the 5-year risk is determined, women could be counseled on their individual risk-benefit analysis based on age, 5-year projected risk, and the presence or absence of a uterus (Figure 2). This effort should facilitate an individualized approach to decision making.

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