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Opinion statement
Several large, prospective trials have evaluated tamoxifen compared with placebo for breast cancer risk reduction in women at increased risk for breast cancer. The risk of developing breast cancer is the primary determinant of net benefit, with greater net benefits accruing to women with the highest risk of breast cancer. Both age and the presence of factors that increase the risk of toxicity have the greatest effect on the net benefit associated with tamoxifen. The greatest clinical benefit with least side effects is derived from the use of tamoxifen in younger, premenopausal women who are less likely to have thromboembolic complications and uterine cancer, in women without a uterus, and in women at higher breast cancer risk such as those with atypical hyperplasia or lobular carcinoma in situ. Tamoxifen may offer benefit to women who are carriers of \textit{BRCA2} mutations, although no prospective trials have been conducted. Compared to placebo in postmenopausal women at average risk of breast cancer in published trials of osteoporosis, raloxifene reduces the risk of invasive breast cancer. Among younger postmenopausal women who are at increased risk of breast cancer, raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer. Raloxifene appears to be less effective than tamoxifen in reducing the risk of in situ breast cancer. In high-risk, younger, postmenopausal women, raloxifene appears to offer net benefit when comparing reduction of the risk of breast cancer and the prevention of fractures with the risk of stroke, venous thromboembolic events, uterine events, as well as symptomatic side effects.

Introduction
Management of women at increased risk for breast cancer should be comprehensive of quantitative risk assessment, counseling appropriate to the individual’s risk, the opportunity for genetic testing where appropriate, and a specific management prescription \cite{1, 2}. The latter should include discussion of the risks and benefits of screening, prophylactic surgery where indicated, and risk reduction using approved chemopreventive agents. Clinicians who counsel women about selective estrogen receptor modulators (SERMs) in this context should strive to ensure that the patient makes a fully informed decision that incorporates her personal values and preferences. The counseling process should be interactive and sensitive to the patient’s educational level and cultural background. Women who are actively involved in decision-making are more satisfied with their decisions and more informed. Since an individual’s preferences and risk status can change substantially over time, it also is important that decisions about
chemoprevention not be regarded as either urgent or irreversible.

In this review, we describe the prospective evaluations of two SERMs, raloxifene and tamoxifen, in reducing the risk of breast cancer in women at increased risk for the disease. We compare the benefits with the risks of therapy and identify women who may be ideal candidates for breast cancer with reduction with SERMs.

The model developed by Gail et al. [3] is an accurate method of quantifying a woman’s risk of developing breast cancer. Only six factors need to be used as significant predictors of the lifetime risk of breast cancer:

1. Current age
2. Age at menarche
3. Number of breast biopsies
4. Age at first live birth (or nulliparity)
5. Family history of breast cancer in first-degree relatives
6. Race

A previous diagnosis of atypical lobular or ductal hyperplasia with atypia nearly doubles the estimated risk [4]. The model accurately estimates the 5-year probability of developing breast cancer but slightly overestimates the risk for women classified in the higher quintiles of predicted 5-year risk and underestimates the risk for those in the lower quintiles [5, 6].

**Selective estrogen receptor modulators**

- Tamoxifen, a triphenylethylene, was introduced into clinical use on the basis of its now well-recognized estrogen antagonist activity in the breast by inhibiting the binding of estrogen-to-estrogen receptors. In addition to its effects in the breast, tamoxifen has an estrogen agonist effect in bone, liver, and uterus that may explain the favorable effects on inhibiting bone loss, improving serum lipid concentrations, and the effect of increasing the incidence of uterine cancer. Tamoxifen was shown to induce regression of advanced breast malignancies. Serious, but rare, complications of tamoxifen therapy include endometrial cancer and thromboembolic events. More common side effects include hot flashes, fluid retention, vaginal discharge, vaginal bleeding, and altered menses [7].

- Several large, prospective trials have evaluated tamoxifen compared with placebo for breast cancer risk reduction in women at increased risk for breast cancer. These trials are described in Table 1, and their results are summarized in Table 2. Each will be reviewed briefly here.

**The Royal Marsden Hospital chemoprevention trial**

- The Royal Marsden Hospital Prevention Trial commenced in 1986 and was a pilot study for the subsequent IBIS-I trial described below. It was a randomized, placebo-controlled trial whose primary aim was to determine whether tamoxifen would prevent breast cancer in healthy women who, based on family history, were at increased risk of breast cancer [9]. Eligible women were between the ages of 30 and 70 years. Participants were required to have had at least one first-degree relative younger than 50 years of age with breast cancer, one first degree relative with bilateral breast cancer, or one affected first-degree relative of any age and another affected first-degree or second-degree relative. The study randomized 2494 women to receive either tamoxifen 20 mg per day or placebo for up to 8 years. Hormone replacement therapy (HRT) was permitted during the trial. It did not show a benefit of tamoxifen in reducing the risk of breast cancer, but it was not adequately powered to do so.