Does benefit always outweigh risk when a SERM is used to prevent primary breast cancer?

No This systematic review determined that use of tamoxifen or raloxifene raises the risk of venous thromboembolism by 4 to 7 cases in every 1,000 women (risk ratio [RR], 1.93 and 1.60, respectively), with raloxifene causing fewer adverse events than tamoxifen.

Compared with placebo, tamoxifen raises the risk of endometrial cancer by 4 cases in every 1,000 women (RR, 2.13). Women using tamoxifen also had a higher incidence of benign gynecologic conditions, surgical procedures (including hysterectomy), and uterine bleeding than women taking placebo did.

In one major trial, tamoxifen caused a higher incidence of cataracts than raloxifene did, although no difference was seen when data from all relevant trials were combined.

Nelson HD, Fu R, Griffin JC, Nygren P, Smith ME, Humphrey L. Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer. Ann Intern Med. 2009;110(50) [Epub ahead of print].

EXPERT COMMENTARY

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The selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene have been shown to reduce the risk of primary invasive breast cancer, as has the selective tissue estrogenic activity regulator tibolone. Tamoxifen and raloxifene are approved for use in high-risk women—although raloxifene is approved for this indication in postmenopausal women only. Tibolone is not available in the United States and is therefore not included in this discussion, although it was included in the review by Nelson and associates.

In the United States, tamoxifen is usually prescribed as adjuvant endocrine therapy after treatment of estrogen-receptor–positive breast cancer in both premenopausal and postmenopausal women. Raloxifene is most often prescribed for the prevention and treatment of osteoporosis in postmenopausal women. Use of these agents as chemoprophylaxis in women who have no history of breast cancer is less common, largely because of the risks and side effects of these drugs.

The increase in venous thromboembolism is of particular concern for women who have an elevated risk of this outcome, including overweight women and those of advanced age. The elevated risk of malignant and benign gynecologic disease associated with tamoxifen is of concern in all women who have an intact uterus.

Details of the review

Nelson and colleagues performed a systematic review, funded by the Agency for Health-

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clinicians who care for women at high risk of primary breast cancer should thoroughly counsel each candidate for chemoprophylaxis about the potential benefits and risks of these agents in her particular circumstances. It may be that the risks outweigh the benefits in some women—such as those who already have an elevated risk of venous thromboembolism.

In addition, because most of the participants in the studies included in this review were healthy and white, we cannot be certain how generalizable these findings are to other subpopulations.

›› ANDREW M. KAUNITZ, MD

FAST TRACK

Use of tamoxifen or raloxifene increased the risk of VTE by 4 to 7 cases in every 1,000 women. Use of tamoxifen raised the risk of endometrial cancer by 4 cases in every 1,000 women.

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care Research and Quality, that involved the aggregation of findings from seven placebo-controlled trials and one head-to-head, randomized, clinical trial involving women who had no history of preinvasive or invasive breast cancer. In the process, they focused on harms as well as benefits associated with use of these chemoprophylactic agents.

Tamoxifen and raloxifene reduced the risk of invasive breast cancer by 7 to 10 cases in every 1,000 women annually. These agents reduced the risk of estrogen-receptor–positive malignancy, but not estrogen-receptor–negative tumors, noninvasive cancer, or breast cancer–related mortality.

Tamoxifen and raloxifene were similarly effective in premenopausal and postmenopausal populations; both drugs also reduced the rate of osteoporotic fracture.

Most of the participants in the prevention trials were white and relatively healthy. Therefore, the relevance of these findings to women of other racial and ethnic groups and to women who have chronic disease or other morbidity is uncertain.

Aromatase inhibitors are being assessed for chemoprophylaxis, so we should have information on their risk-benefit ratio in the near future.

› For more on the use of tamoxifen and raloxifene to avert breast cancer, see "Chemoprevention of breast cancer"
BY STEVEN R. GOLDSTEIN, MD
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