Does raloxifene reduce postmenopausal women's risk of breast cancer?

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Research question

Does raloxifene reduce postmenopausal women's risk of invasive breast cancer?

Type of article and design

Multicentre, double-blind, randomized placebo-controlled trial.

Relevance to family physicians

Breast cancer is the most common malignancy seen in North American women: lifetime risk is estimated at one in 10.[1,2] Estrogen appears to play a role; prolonged exposure to estrogen (eg, nulliparity, age 24 years or older at birth of first child, higher body mass index), and high postmenopausal serum estradiol levels increase risk of breast cancer.[2] A recent meta-analysis of epidemiologic studies worldwide demonstrated that postmenopausal women taking hormone replacement therapy (HRT) for 5 years or longer increase their risk of breast cancer by 2% per year of use.[3] Despite the beneficial effects of HRT on heart disease and osteoporosis, women frequently cite "fear of cancer" as a reason for stopping or never starting HRT.[4,5]

Tamoxifen citrate has an antiestrogenic effect on breast tissue and has been shown to reduce the incidence of new contralateral breast cancer by one third in women who already have breast cancer.[6] Three recent clinical trials of tamoxifen for prevention of breast cancer in postmenopausal women without breast cancer have had conflicting results. The two smaller trials, one with postmenopausal women with a family history of breast cancer[7] and the other with women who have had hysterectomies,[8] showed no benefit over placebo. The largest trial, with 13 175 postmenopausal women at high risk of breast cancer, demonstrated a 50% reduction in incidence of breast cancer compared with those taking placebo during 4.5 years of follow up.[9] Tamoxifen is, however, associated with increased risk of endometrial cancer and thromboembolic disease.[9]

Raloxifene hydrochloride is a selective estrogen receptor modulator, or "designer estrogen," that acts as an estrogen receptor agonist on bone and lipid metabolism and an antagonist on breast and endometrium.[10,11] Hence, it could protect against osteoporosis, coronary artery disease, and breast and endometrial cancers and thus provide the benefits of estrogen without its risks. One clinical trial comparing raloxifene and placebo demonstrated that raloxifene improves bone mineral density and lowers low-density lipoprotein cholesterol with no effect on endometrial thickness.[12] Raloxifene has recently been approved in Canada for treatment of osteoporosis.

Does raloxifene reduce postmenopausal women's risk of breast cancer? How does raloxifene compare with tamoxifen in reducing risk of breast cancer? Should raloxifene be recommended to postmenopausal women at increased risk of breast cancer?

Overview of study and outcomes

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial, conducted at 180 clinical centres in the United States and Europe, was designed to determine whether raloxifene reduces risk of fracture in postmenopausal women with osteoporosis. The effect on breast cancer was a secondary end point of the trial.

The 7705 postmenopausal women with osteoporosis enrolled in the trial were at least 2 years postmenopausal, no older than 80 years, and had bone densities at least 2.5 standard deviations below the mean or a history of vertebral fractures. Exclusion criteria were a history of breast or endometrial cancer; stroke or venous thromboembolism in the past 10 years; any cancer in the

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previous 5 years; secondary causes of osteoporosis; use of systemic or frequent topical estrogen, progestins, androgens, or systemic corticosteroids in the past 6 months; or current alcohol intake of more than four drinks a day.

Patients were randomly assigned to placebo, 60 mg/d of raloxifene, or 120 mg/d of raloxifene. All patients received 500 mg of calcium and 400 to 600 IU of cholecalciferol a day.

Potential participants underwent breast examination and mammography before entering the study. Patients were followed up every 6 months. Mammograms were optional after 1 year, but mandatory after 2 years and after 3 years of treatment. Patients who declined mammography could have breast ultrasonography instead. Other end points included adverse effects, endometrial thickness, and venous thromboembolic disease.

Results

All 3 years of follow up were completed for 1924 (75%) of the 2576 women assigned to placebo and 3977 (78%) of the 5129 women assigned to raloxifene. During a median of 40 months of follow up, 27 cases (3.6 per 1000 woman-years) of invasive breast cancer were confirmed in the placebo group and 13 cases (0.9 per 1000 woman-years) in the raloxifene group—a 76% reduction in risk. This means that about 126 women would need to be treated for a median of 40 months to prevent one case of invasive breast cancer. The reduction in risk of invasive breast cancer was similar for those taking 60 mg/d and 120 mg/d of raloxifene. When stratified according to estrogen receptor status, raloxifene reduced the risk of invasive estrogen receptor–positive breast cancer by 90% but did not significantly reduce the risk of invasive estrogen-negative breast cancer.

Hot flashes, influenzalike symptoms, peripheral edema, and leg cramps were reported more frequently in the raloxifene group than the placebo group. Risk of venous thromboembolic disease was 3.1 times greater in the raloxifene group (1%) than in the placebo group (0.3%) by 40 months of follow up. There was no difference between groups in endometrial thickness or endometrial cancer. By patient report, more women in the raloxifene group than in the placebo group had new or worsening diabetes mellitus. There were, however, no objective differences in median changes in fasting blood glucose or hemoglobin A_{1c} and no differences in proportion of patients starting insulin or oral hypoglycemic agents. Finally, the groups were similar in all-mortality rates and cause of death.

Analysis of methodology

This was a large, well-designed study. The primary intent was to determine the effect of raloxifene on risk of fracture in postmenopausal women with osteoporosis, but the study had sufficient power to demonstrate a reduction in risk of invasive breast cancer. Drop-out rates were high; 22% of the raloxifene group and 25% of the placebo group were lost to follow up at 3 years. Reasons for drop-outs were not explained. Patients who declined mandatory mammography were given the option of breast ultrasonography instead, which might have affected diagnostic accuracy.

The short duration of the study prevents generalizations as to the long-term effects on risk of breast cancer and the safety of prolonged use of raloxifene. The subjects were selected from a population of women with osteoporosis who consumed no more than four alcoholic drinks per day. Because there is a positive association between alcohol intake and breast cancer,[13] this selection bias could have affected the results. Finally, interpretation of these findings is limited because raloxifene was not directly compared with tamoxifen.

Application to clinical practice

Raloxifene, a possible alternative to estrogen for postmenopausal women, appears to provide the benefits of estrogen for coronary artery disease and osteoporosis without the disadvantage of increased risk of breast or endometrial cancer. Results from this study demonstrate that, for postmenopausal women with osteoporosis, raloxifene reduces the risk of invasive breast cancer by 76% and invasive estrogen receptor–positive breast cancer by 90% after 40 months of treatment, compared with placebo. Further studies with longer follow up, however, are required to determine whether this benefit is sustained with longer use.

Adverse effects, such as hot flashes, leg cramps, and venous thromboembolic disease, were more frequently reported with raloxifene than with placebo. Only long-term studies can determine the safety of prolonged use of raloxifene.

How raloxifene compares with tamoxifen in reducing the risk of breast cancer is also unclear. Subjects in the ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP) trial on tamoxifen for prevention of breast cancer are premenopausal and postmenopausal women at increased risk of breast cancer, whereas subjects in the MORE trial were postmenopausal women with osteoporosis who were not necessarily at increased risk of breast cancer. Hence, how raloxifene compares with tamoxifen in reducing the risk of breast cancer cannot be determined by

comparing these two studies but rather by a head-to-head trial such as NSABP's current Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer.*

Bottom line

- Raloxifene reduces risk of invasive breast cancer by 76%, primarily through reducing risk of invasive estrogen receptor–positive breast cancer by 90%, after 40 months of treatment, compared with placebo. It is unclear, however, whether this benefit is sustained over time due to lack of long-term follow up. It also remains to be seen whether this finding in postmenopausal women with osteoporosis is generalizable to all women.
- Adverse effects, such as hot flashes, leg cramps, and venous thromboembolic disease, were reported more frequently with raloxifene than with placebo. The drop-out rate was high but similar between the two groups at 22% and 25%, respectively; reasons for drop-outs were not given. The safety of prolonged use of raloxifene is unknown, again due to lack of long-term follow up.
- Because raloxifene is currently accepted as an effective treatment for osteoporosis, postmenopausal women with osteoporosis and increased risk of breast cancer might consider raloxifene instead of estrogen as a first-line treatment option for their osteoporosis. They should be advised, however, that raloxifene is a relatively new drug that has been associated with increased hot flashes and a greater risk of thromboembolic disease.
- Currently, use of raloxifene to reduce risk of breast cancer in postmenopausal women at increased risk should be reserved until more studies demonstrate the drug's long-term efficacy and safety. We hope the NSABP's current Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer will provide more answers as to how raloxifene compares with tamoxifen in reducing the risk of breast cancer.

**To be eligible for this study, women must be ≥35 years old, postmenopausal, and at increased risk of developing breast cancer. Increased risk of breast cancer is determined by histologic diagnosis of lobular carcinoma in situ treated by local excision only or by a Breast Cancer Risk Assessment Profile generated by the NSABP Biostatistical Centre based on current age, number of first-degree female relatives with breast cancer, one or more previous breast biopsies, previous diagnosis of atypical hyperplasia of the breast, age at first live birth, nulliparity, race, and age at onset of menarche. For more information on the STAR project, call 1-888-STAR-990 in Ontario or contact the Canadian Cancer Society Information Services at 1-888-939-3333.*

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