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A new option for chemoprevention of invasive breast cancer

STAR trial studied a galaxy of SERM effects

CASE Should she start a SERM?

A 55-year-old postmenopausal woman who has not had a hysterectomy completes a breast cancer risk assessment form and discovers that her estimated 5-year risk of breast cancer is 4%.

Should she consider taking a selective estrogen receptor modulator such as raloxifene or tamoxifen for chemoprevention of breast cancer?

***FAST** TRACK*

In the STAR trial, both raloxifene and tamoxifen reduced the calculated breast cancer risk by about 50%

Preliminary results from the Study of Tamoxifen and Raloxifene (STAR) trial clearly demonstrate that the osteoporosis drug raloxifene is an effective option for preventing invasive breast cancer in postmenopausal women at increased risk for breast cancer. Initial analyses of the STAR trial were released by the National Institutes of Health, April 17, 2006.

The study participants were an average of 58 years of age, and their calculated 5-year risk of developing breast cancer was 4%, as assessed by the Gail model,[1] compared with the average population risk of 1.6% at age 58 years.

Equivalent results. Both raloxifene, 60 mg daily, and tamoxifen, 20 mg daily, were similarly effective in reducing the calculated breast cancer risk by about 50%. Both agents have been demonstrated to improve bone density.

Raloxifene was superior to tamoxifen on some important outcomes. For example, raloxifene was associated with 25% fewer deep venous thromboses, 35% fewer pulmonary emboli, and 36% fewer cases of endometrial cancer. Raloxifene may also cause fewer cataracts than tamoxifen.

Tamoxifen was superior to raloxifene in reducing the risk of 2 noninvasive forms of breast cancer. Tamoxifen, but not raloxifene, reduced the risk of developing ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).

On balance, the results from the STAR trial largely confirm and strengthen previously reported results[2–5] and indicate that both raloxifene and tamoxifen are effective agents for the chemoprevention of invasive breast cancer.

STAR: A productive collaboration

The STAR trial is an example of the high-quality, clinically important studies that can only be completed by the collaboration of the National Institutes of Health, hundreds of physician investigators, and the pharmaceutical industry. Almost 20,000 women were enrolled in the trial and followed for more than 4 years. Advances in medicine depend on large-scale trials that require the continuing collaboration of the government, the pharmaceutical industry, and practicing physicians.

Persistent questions

If we are to continue to develop breast cancer chemoprevention strategies, many challenges persist.

Is it prevention or treatment? One theoretical issue is: Are we really "chemopreventing" breast cancer, or are we actually treating subclinical, undiagnosed breast cancers? This question is difficult to answer with currently available diagnostic tools. Although of interest to the clinical

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Women who participated in the STAR trial were postmenopausal, at least 35 years old (average 58 years), and had an increased risk of breast cancer as determined by their age, family history of breast cancer, personal medical history, age at first menstrual period, and age at first live birth.

The initial analysis is based on 19,471 women (of 19,747 enrolled) for whom complete study information was available: 9,745 in the raloxifene group and 9,726 in the tamoxifen group.

- **Invasive breast cancer** rates were statistically equivalent: 167 women in the raloxifene group and 163 in the tamoxifen group.
- **Uterine cancers** (mainly endometrial). More than half of the women enrolled in STAR had had a hysterectomy. In women with a uterus, cancers developed in 36 of 4,732 women taking tamoxifen and in 23 of 4,712 women (36% fewer cases) taking raloxifene.
- **Deep vein thrombosis** (blood clot in a major vein) developed in 87 women taking tamoxifen and in 65 women (25% fewer cases) taking raloxifene.
- **Pulmonary embolisms** (blood clots in the lung) developed in 54 women taking tamoxifen and in 35 women (35% fewer cases) taking raloxifene.
- **Strokes** occurred in both groups at statistically equivalent rates: 53 women in the tamoxifen group and 51 in the raloxifene group had a stroke during the trial. Women at increased risk of stroke were excluded from the trial.
- **Noninvasive breast cancer**. While tamoxifen has been shown to reduce, by half, the incidence of lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS), raloxifene did not have an effect on these diagnoses. LCIS or DCIS developed in 57 women taking tamoxifen and in 81 women taking raloxifene. This result confirms data reported in the CORE Trial.[5]

investigator, the question is probably of little relevance to our patients.

What about aromatase inhibitors? Another important issue is whether aromatase inhibitors will prove superior to raloxifene and tamoxifen for chemoprevention of breast cancer in postmenopausal women.[6] Evidence suggests that aromatase inhibitors are superior to tamoxifen for the prevention of disease recurrence in postmenopausal women with invasive breast cancer. It is reasonable, therefore, to expect that aromatase inhibitors might also be more effective for the chemoprevention of breast cancer. Currently planned clinical trials will answer this important question.

Can we afford chemoprevention? A critical practical issue is whether we have sufficient resources to support a nationwide breast cancer chemoprevention program. Experts estimate that as many as 9 million menopausal women in the United States are at increased risk for breast cancer. Who will identify these women and counsel them concerning the chemoprevention option? Who will prescribe and supervise chemoprevention for these women?

Likely gynecologists, along with internists, family physicians, and oncologists will play a central role. ObGyns are experts in managing breast cancer screening using mammography. We also have experience prescribing raloxifene for osteoporosis. It would not stretch our current screening mammography practices to add the recommendation that patients perform a risk assessment using the Gail model,[1] and consider chemoprevention if they are at increased risk.

CASE Consider raloxifene when uterus is intact

In the case of a 55-year-old woman with a 5-year breast cancer risk of 4%, a consideration of the risks and benefits may well

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Helpful web sites for you and your patients

The STAR trial is coordinated by the National Surgical Adjuvant Breast and Bowel Project (NSABP), a network of cancer research professionals, and is sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health.

- **Tools to calculate breast cancer risk**
  http://cancer.gov/bcrisktool
  http://breastcancerprevention.com
- **STAR trial fact sheet**
  NCI's STAR home page at
  http://www.cancer.gov/star
  NSABP's Web sites at
  http://www.nsabp.pitt.edu
  or http://foundation.nsabp.org
- **Q&A on STAR results**
  http://www.cancer.gov/newscenter/pressreleases/STARresultsQandA

lead to a recommendation to initiate chemoprevention with raloxifene. For this woman, with an intact uterus, raloxifene is likely the superior choice because of the increased risk of endometrial cancer associated with tamoxifen use.

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