

# The STAR results: choosing between raloxifene and tamoxifen for preventing invasive breast cancer in postmenopausal women

*With the recently reported results from the Study of Tamoxifen and Raloxifene, clinicians and their patients will need these tools to sift through the data and make the best possible treatment choice.*

## What's new, what's important

Even though the US Food and Drug Administration long ago approved tamoxifen for breast cancer prevention in women with a high risk of developing the disease, the acceptance of this drug in the community has been limited by concerns about its side effects.

In comparing tamoxifen with raloxifene, the STAR study found that raloxifene is as effective as tamoxifen in decreasing the risk of invasive breast cancer in high-risk women. Reduction in fracture risk was also similar. But overall, raloxifene had fewer side effects, such as thromboembolic events, gynecologic problems, vasomotor symptoms, leg cramps, and cataracts, than tamoxifen. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar for both drugs. There was a higher, but not statistically significant, risk of *noninvasive* breast cancer in the raloxifene group. There were fewer cases of uterine cancer with raloxifene, but, again, no significant difference between the two treatment arms.

Because it is equally efficacious and has fewer side effects, raloxifene could be considered the preferred drug over tamoxifen, in the right clinical setting, for women with a high risk for breast cancer.

—Jame Abraham, MD  
Section Editor

**T**amoxifen has been approved for the reduction of breast cancer risk, and the second-generation selective estrogen receptor modulator raloxifene (Evista) has been shown to reduce the risk of breast cancer in older women with osteoporosis.

The recently reported Study of Tamoxifen and Raloxifene (STAR) trial<sup>1</sup> compared tamoxifen 20 mg/d (n = 9,726) with raloxifene 60 mg/d (n = 9,745) over 5 years in 19,747 postmenopausal women with an increased 5-year risk for breast cancer. The main outcome measures were rates of invasive breast cancer, non-invasive breast cancer, uterine cancer, bone fracture, and thromboembolic events (Table 1).

There was no significant difference in the incidence of invasive breast cancer in the two treatment groups, with rates of 4.30/1,000 patients noted in the tamoxifen arm versus 4.41/1,000 patients in the raloxifene arm. Although there were fewer cases of noninvasive breast cancer with tamoxifen, the difference between the groups was not statistically significant. There were fewer cases of uterine cancer with raloxifene, but no significant difference between the groups; raloxifene was associated with a significant 84% reduction in risk for uterine hyperplasia and a significant 56% reduction in risk for hysterectomy during follow-up. There were no differences between groups in the incidence of death (rates of 2.64 vs

2.49 per 1,000 in the tamoxifen vs raloxifene groups); in the causes of death (cancer in 46 vs 47; cardiovascular disease in 22 vs 20); and in the incidence of other invasive cancers, ischemic heart disease events, stroke, or osteoporotic fractures. However, raloxifene was associated with a significant 30% reduction in risk of all thromboembolic events. Raloxifene was also linked to a significant 21% reduction in risk for cataracts, as well as a significant 18% reduction in risk for cataract surgery.

A separate report<sup>2</sup> detailed find-

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**TABLE 1**

Main outcome measures in STAR

	Number of events		Rate per 1,000 patients		Risk ratio (95% CI): raloxifene vs tamoxifen
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	
Invasive breast cancer	163	168	4.30	4.41	1.02 (0.82–1.28)
Noninvasive breast cancer	57	80	1.51	2.11	1.40 (0.98–2.00)
Uterine cancer	36	23	2.00	1.25	0.62 (0.35–1.08)
Osteoporotic fracture	104	96	2.73	2.51	0.92 (0.69–1.22)
Thromboembolic events*	141	100	3.71	2.61	0.70 (0.54–0.91)

STAR = Study of Tamoxifen and Raloxifene; CI = confidence interval

\*Pulmonary embolism/deep vein thrombosis

Adapted from Vogel et al<sup>1</sup>

ings on patient-reported symptoms from all study patients via a 36-item checklist and a quality-of-life (QOL) study in a subpopulation (n = 1,983) via the Medical Outcomes Study Short-Form Health Survey (SF-36), Center for Epidemiologic Studies–Depression (CES-D) inventory, and Medical Outcomes Study Sexual Activity Questionnaire; the SF-36 physical component summary (PCS) and mental component summary (MCS)

were the primary QOL outcome measures.

Over 5 years, CES-D, PCS, and MCS scores worsened modestly over time for all patients, with no significant differences between the tamoxifen and raloxifene patients on any of these measures. Tamoxifen patients reported slightly but significantly better sexual function (age-adjusted repeated measure odds ratio, 1.22%; 95% confidence interval, 1.01%–

1.46%). With regard to symptoms, the raloxifene group reported significantly greater symptom severity scores (0–4; higher score = greater severity) for musculoskeletal problems (1.15 vs 1.10;  $P = 0.002$ ), dyspareunia (0.78 vs 0.68;  $P < 0.001$ ), and weight gain (0.82 vs 0.76;  $P < 0.001$ ). The tamoxifen group had significantly higher scores for gynecologic problems (0.29 vs 0.19;  $P < 0.001$ ), vasomotor symptoms (0.96 vs 0.85;  $P < 0.001$ ), leg cramps (1.10 vs 0.91;  $P < 0.001$ ), and bladder control symptoms (0.88 vs 0.73;  $P < 0.001$ ).

### References

1. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727–2741.
2. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2742–2751.

## From the Community Oncologist's Perspective

# Quality-of-life considerations in selecting raloxifene or tamoxifen

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**T**he Study of Tamoxifen and Raloxifene (STAR) trial data suggest that both tamoxifen and raloxifene (Evista) are equally effective in reducing the risk of developing invasive breast cancer in this at-risk population of healthy women.<sup>1</sup> Although media coverage of this study suggests a clear “winner” in raloxifene, the clinical data and patient symptoms suggest less clear conclusions. These treatments were not associated with dif-

ferences in mortality from any cause, other invasive cancer sites, ischemic heart disease, stroke, or osteoporotic fractures. Raloxifene was associated with slightly fewer thromboembolic events, hysterectomies, cataracts, and cataract surgeries, whereas tamoxifen was associated with slightly fewer cases of noninvasive breast cancer. The potential clinical consequences (ie, more surgery, more biopsies, invasive cancer) of this last observation are unknown. Although women

receiving raloxifene had significantly less uterine hyperplasia, there was not a statistically significant difference between the groups in the incidence of endometrial cancer.

The STAR symptom and quality-of-life (QOL) data revealed similarities between treatments in physical and mental health (ie, depression).<sup>2</sup> There were small differences between treatments with respect to sexuality, musculoskeletal

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# Helping women weigh the risks and benefits of raloxifene vs tamoxifen

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**T**he recent release of preliminary results of the Study of Tamoxifen and Raloxifene (STAR) trial has prompted women at increased risk for breast cancer to reconsider their use of chemoprevention. Many have been offered tamoxifen in the past but have declined due to the potential for developing adverse effects. As a nurse practitioner, I have had several patients ask recently about raloxifene—the “new drug that doesn’t have side effects”—and whether it would be appropriate for them. Their interpretation of the news sound bites

about raloxifene is that it’s a better drug than tamoxifen without associated toxicity.

Of course, the side-effect profile of raloxifene is actually similar to that of tamoxifen. And although the potential for developing some of the adverse effects is decreased, the risk still exists, but the number of women receiving either drug who develop any of these side effects is small.

The STAR trial showed that both drugs affect quality of life, although raloxifene causes slightly fewer side effects. On the other hand, women taking tamoxifen had fewer sexual

problems. According to the researchers, at nearly every assessment, a larger percentage of the patients in the tamoxifen group were sexually active. As a group, they were slightly more able to become sexually aroused and to enjoy sex.

## Questions to explore

To help postmenopausal women who are at risk for breast cancer more fully understand the differences and similarities between the two drugs, I suggest discussing with them the side-by-side comparisons in Tables 1 and 2 and asking them a list of

**TABLE 1**

STAR results: raloxifene versus tamoxifen

	<b>Raloxifene (number of women = 9,745)</b>	<b>Tamoxifen (number of women = 9,726)</b>
Ability to prevent invasive breast cancer	Equivalent to tamoxifen (4.4 women per 1,000 per year developed the disease)	Equivalent to raloxifene (4.3 women per 1,000 per year developed the disease)
Ability to prevent noninvasive breast cancer	Not as effective as tamoxifen (2.1 women per 1,000 per year developed the disease)	More effective than raloxifene, but not significantly (1.5 women per 1,000 per year)
Risk of uterine cancer	Slightly lower risk than with tamoxifen (1.3 women per 1,000 per year developed the disease)	Risk is higher, but still low overall (2.0 women per 1,000 per year developed the disease)
Risk of developing abnormal uterine cells (hyperplasia), a possible precursor to cancer	Risk is lower than with tamoxifen (0.8 women per 1,000 per year)	Risk is higher than with raloxifene (4.7 women per 1,000 per year)
Risk of blood clots	Risk is lower than with tamoxifen (2.6 women per 1,000 per year)	Risk is higher than with raloxifene (3.7 women per 1,000 per year)
Risk of cataracts	Risk is lower than with tamoxifen (9.7 women per 1,000 per year)	Risk is higher than with raloxifene (12.3 women per 1,000 per year)
Risk of heart disease (angina, heart attack, etc)	Slightly higher risk than with tamoxifen (3.3 women per 1,000 per year)	Risk is slightly lower than with raloxifene, but not significantly (3.0 women per 1,000 per year)
Risk of stroke	Equivalent to tamoxifen (1.3 women per 1,000 per year)	Equivalent to raloxifene (1.4 women per 1,000 per year)
Risk of bone fractures	Equivalent to tamoxifen (2.5 women per 1,000 per year)	Equivalent to raloxifene (2.7 women per 1,000 per year)

Source: Vogel VG, Costantino JP, Wickerly M, et al. Tamoxifen and Raloxifene in the Primary Prevention of Breast Cancer: Results From the National Surgical Adjuvant Breast and Bowel Project P-2 Trial. *JAMA* 2006;295:2727-2741.

**TABLE 2**

STAR results: frequency of moderate to severe side effects

	Raloxifene (number of women = 9,270)	Tamoxifen (number of women = 9,273)
Hot flashes, night sweats	23% of women under age 60 at least moderately bothered	32% of women under age 60 at least moderately bothered
Leg cramps	24% of women at least moderately bothered	32% of women at least moderately bothered
Bladder control problems (urinary incontinence)	14% of women at least moderately bothered	19% of women at least moderately bothered
Joint pain, muscle stiffness, general aches and pains	23% of women at least moderately bothered	21% of women at least moderately bothered
Gynecological problems, including painful intercourse	18% of women at least moderately bothered	16% of women at least moderately bothered
Weight gain	26% of women at least moderately bothered	23% of women at least moderately bothered
Forgetfulness	24% of women at least moderately bothered	24% of women at least moderately bothered

Source: Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2742-2751.

questions to develop an individual risk/benefit profile. Additional copies of these tables may be downloaded from [www.CommunityOncology.net/journal/0311.html](http://www.CommunityOncology.net/journal/0311.html).

Here's what to ask:

1. Do you smoke?
2. Do you have a personal or fam-

ily history of stroke or heart attack?

3. Do you have a personal or family history of uterine cancer, heavy or abnormal vaginal bleeding, or atypical Pap smears?

4. Do you have a personal or family history of breast cancer or atypical cells in the breasts?

5. Do you have a personal or family history of osteoporosis?

6. Do you have a history of cataracts?

7. Have you ever had a blood clot in your legs or lungs?

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## From the Administrator's Desk

# The economic concerns

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**T**he average wholesale price for raloxifene (Evista) is \$96.77; for tamoxifen, it is \$113.77. At retail pharmacies, patients can pay from \$86.99 to \$92.50 for 30 60-mg pills of raloxifene and from \$25.50 to \$37.99 for 30 20-mg pills of tamoxifen.

These costs can be significant for patients and for practices as well that cannot easily bill or collect expenses related to managing patient problems

via telephone triage. Up to 75% of inbound calls we receive in our practice are from patients who require a nurse's assistance. And given the potential for serious side effects caused by both tamoxifen and raloxifene, this demand on staff time could conceivably increase.

Because patients are prescribed these drugs for long-term use, adherence to treatment and follow-up are key issues with which staff members

must also deal. Understandably, patients may have economic reasons for wanting to obtain refills without another office visit so they don't have to incur the cost of that visit. This can create an ethical dilemma for caregivers who feel bound to prescribe medication, not by telephone, but in conjunction with a physical examination.

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## Quality-of-life considerations

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complaints, or vasomotor symptoms, but they were not clinically significant. Few women reported severe symptoms, and differences between the groups were small.

Assuming that raloxifene obtains US Food and Drug Administration approval for breast cancer prevention, the decision to choose one drug or the other should be based on women's medical and psychosocial histories. Sexually active women who value this aspect of their lives or those with arthritic symptoms may prefer tamoxi-

fen, whereas those who wish to avoid leg cramps, vaginal bleeding/discharge, vasomotor symptoms, or deep vein thrombosis might prefer raloxifene. Since the STAR Trial excluded those with a history of myocardial infarction or stroke, uncontrolled hypertension, or uncontrolled diabetes, women with these conditions should not receive raloxifene or tamoxifen. Moreover, raloxifene has not been adequately evaluated in premenopausal women at high risk for breast cancer; minority populations; and women who are *BRCA1* or *BRCA2* mutation carriers. Finally, since only 331 breast cancers occurred among the 19,747 women in the STAR trial, both patients and clinicians should be aware

that the probability of breast cancer treatment benefiting any given individual is low.

### References

1. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727-2741.
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