Raloxifene and tamoxifen had similar efficacy for preventing invasive breast cancer in women at increased risk

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;295:2727-41.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★☆☆ Oncology ★★★★★★☆

QUESTION

In postmenopausal women at increased risk, what is the comparative efficacy and safety of raloxifene and tamoxifen for preventing invasive breast cancer?

METHODS

Design: Randomized controlled trial.
Allocation: Concealed.*
Blinding: Blinded (clinicians, participants, and outcome assessors).*
Follow-up period: Mean 3.9 years.
Setting: Nearly 200 clinical centers in North America.
Participants: 19747 postmenopausal women ≥ 35 years of age (mean 59 y, 93% white) whose 5-year predicted breast cancer risk was ≥ 1.66% (mean 4.03%) based on the Gail model. Exclusion criteria included recent use of hormone therapy; history of stroke or venous thromboembolism (VTE); diagnosis of cancer in the previous 5 years; and uncontrolled atrial fibrillation, diabetes, or hypertension.
Intervention: Raloxifene, 60 mg/d (n = 9875), or tamoxifen, 20 mg/d (n = 9872), for a maximum 5 years.
Outcomes: Invasive breast cancer, noninvasive breast cancer, uterine cancer, uterine hyperplasia, ischemic heart disease, stroke, VTE, osteoporotic fractures, cataracts, and death.
Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Raloxifene and tamoxifen did not differ for invasive or noninvasive breast cancer, ischemic heart disease, uterine cancer, stroke, fractures, or death (Table). Raloxifene reduced risk for uterine hyperplasia, VTE, and cataracts compared with tamoxifen (Table).

CONCLUSIONS

In postmenopausal women at increased risk, raloxifene had similar efficacy to tamoxifen for preventing invasive breast cancer, with similar risk for ischemic heart disease. Raloxifene had lower risks for uterine hyperplasia, venous thromboembolism, and cataracts.

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*See Glossary.

Raloxifene vs tamoxifen for preventing invasive breast cancer in postmenopausal women at increased risk at mean 3.9 years†

Outcomes	Rate per 1000 woman-y		RRI (95% CI)	NNH
	Raloxifene	Tamoxifen		
Invasive breast cancer	4.4	4.3	2% (–18 to 28)	Not significant
Noninvasive breast cancer	2.1	1.5	40% (–2 to 100)	Not significant
Ischemic heart disease	3.3	3.0	10% (–15 to 43)	Not significant
			RRR (CI)	NNT (CI)
Uterine cancer	1.3	2.0	38% (–8 to 65)	Not significant
Uterine hyperplasia	0.8	4.7	84% (71 to 91)	254 (235 to 301)
Stroke	1.3	1.4	4% (–43 to 36)	Not significant
Venous thromboembolism	2.6	3.7	30% (9 to 46)	899 (586 to 2995)
Osteoporotic fractures	2.5	2.7	8% (–22 to 31)	Not significant
Cataracts	9.7	12.3	21% (8 to 32)	388 (255 to 1017)
Death	2.5	2.6	6% (–26 to 29)	Not significant

†Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from risk ratios in article.

COMMENTARY

An overview of first-generation clinical trials comparing tamoxifen with placebo showed that tamoxifen reduced the incidence of breast cancer by 38% in high-risk women (1). Raloxifene reduced breast cancer incidence by 44% to 76% in lower-risk women (2, 3). The Study of Tamoxifen and Raloxifene (STAR), designed to compare the relative effects of the 2 selective estrogen-receptor modulators (SERMs) on the incidence of invasive breast cancer and other diseases, showed that raloxifene and tamoxifen provided similar benefits with few differences in toxicity profiles.

Notably, about 50% of women screened for STAR did not meet entry criteria and 80% of eligible women declined participation. The median treatment duration was approximately 3 years, and the nonadherence rate was about 30%. Because the proportional reduction in new cases of breast cancer seems identical regardless of baseline risk, lower-risk women will have a smaller absolute risk reduction with treatment. In addition, primary prevention with SERMs has not been proven to improve overall survival; therefore, many lower-risk women may decline treatment. A substantial proportion of lower-risk women also may not complete the treatment, especially if they encounter side effects. Indeed, even in the adjuvant setting, where tamoxifen clearly reduces breast cancer recurrence and mortality, > 40% of women do not adhere to the regimen because of side effects (4).

The STAR results may help primary care providers to better counsel women about using tamoxifen and raloxifene. The estimated probabilities of SERM-associated benefits and risks can be weighed against a woman's risk for breast cancer as predicted by such tools as the Gail Model, thereby allowing women to make more informed treatment decisions. Although raloxifene is not yet approved by the U.S. Food and Drug Administration for breast cancer prevention, information from STAR may eventually allow primary care physicians, who are already comfortable prescribing raloxifene for bone health, to become equally comfortable prescribing SERMs for breast cancer prevention.

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References

1. **Cuzick J, Powles T, Veronesi U, et al.** Lancet. 2003;361:296-300.
2. **Cummings SR, Eckert S, Krueger KA, et al.** JAMA. 1999;281:2189-97.
3. **Barrett-Connor E, Mosca L, Collins P, et al.** N Engl J Med. 2006;355:125-37.
4. **Fallowfield L.** Breast. 2005;14:612-6.