The STAR Trial: Evidence for Raloxifene as a Breast Cancer Risk Reduction Agent for Postmenopausal Women

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Raloxifene, breast cancer, chemoprevention, risk reduction

Abstract
The 1998 approval of tamoxifen for breast cancer risk reduction opened the era of breast cancer chemoprevention. Women at increased risk for breast cancer now had an option other than healthy lifestyle and prophylactic surgery to reduce risk. However, women and their physicians were reluctant to use tamoxifen because of associated risks. Several trials investigating raloxifene suggested it may reduce breast cancer risk without having an apparent effect on the endometrium. The Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer trial opened in 1999 to directly compare raloxifene to tamoxifen for breast cancer risk reduction. Since the unblinding of the STAR trial in 2006, raloxifene has emerged as an option for reducing breast cancer risk for postmenopausal women at increased risk for the disease. (*JNCCN* 2007;5:817–822).

Since the 1998 approval of tamoxifen for breast cancer risk reduction, the field of breast cancer chemoprevention has exploded with numerous agents being identified as possible risk reduction agents. Because the identified risks of tamoxifen limited its use, the search for acceptable agents is ongoing. Raloxifene is approved by the U.S. Food and Drug Administration (FDA) for osteoporosis prevention and treatment. Several trials investigating raloxifene suggested a breast cancer risk reduction effect with fewer risks than tamoxifen. This article outlines the background trials leading to the definitive trial assessing raloxifene as a breast cancer risk reduction agent.

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Raloxifene

Raloxifene, a second-generation selective estrogen receptor modulator (SERM),[1] has been shown to reduce the incidence of breast cancer in preclinical models and several clinical trials evaluating it for the prevention of osteoporosis and heart disease.[2–8] Like tamoxifen, a first-generation SERM,[1] it has estrogen agonist and estrogen antagonist properties, with different effects in different body tissues. Raloxifene differs from tamoxifen principally by its lack of stimulation of the endometrium.[9]

Multiple Outcomes Raloxifene Evaluation Trial

The Multiple Outcomes Raloxifene Evaluation (MORE) study was designed to test whether raloxifene reduced the risk for fracture in postmenopausal women with osteoporosis.[4] From 1994 to 1998, 7705 postmenopausal women with osteoporosis were randomized to receive 60 mg raloxifene, 120 mg raloxifene, or placebo. At 36 months of follow-up in 6828 women, the risk for vertebral fracture was reduced 30% in women who received raloxifene. These women had an increased risk for venous thromboembolic events, both deep vein thrombosis and pulmonary embolus, compared with those assigned to placebo (relative risk [RR], 3.1; 95% confidence interval [CI], 1.5–6.2), but raloxifene did not increase vaginal bleeding.

A secondary end point of the MORE trial was invasive breast cancer. Women who participated in the MORE trial were not chosen for their breast cancer risk nor was risk calculated. If a woman had a history of breast cancer or was taking estrogen, she was not eligible. After 4 years of follow-up, a subset analysis of the MORE trial by

Cummings et al.[5] showed 22 cases among 5129 postmenopausal women randomized to receive raloxifene compared with 39 cases among 2576 postmenopausal women receiving placebo. The MORE trial concluded that, among older postmenopausal women with osteoporosis, the risk for estrogen receptor (ER)–positive invasive breast cancer decreased by 72% during 4 years of raloxifene treatment, with no apparent decrease in the incidence of ER-negative tumors.[6] Like tamoxifen, raloxifene increased the risk for thromboembolic disease but did not seem to increase the risk for endometrial cancer (RR, 0.8; 95% CI, 0.2–2.7); 4 endometrial cancers occurred in the placebo group and 6 in the combined raloxifene group.

Continuing Outcomes Relevant to Evista Trial

The Continuing Outcomes Relevant to Evista (CORE) trial examined the effect of an additional 4 years of raloxifene therapy on the incidence of invasive breast cancer in women in the MORE trial who agreed to continue therapy.[7] The primary end point was the incidence of invasive breast cancer; a secondary objective looked at the incidence of ER-positive invasive breast cancers. The study ran for 4 years beginning January 1, 1999. Of the 180 MORE sites, 130 participated in the CORE trial.

After 4 years of participation, with 5213 women participating in the CORE trial, the risk for invasive breast cancer was reduced by 69% (hazard ratio [HR], 0.41; 95% CI, 0.24–0.71) in the raloxifene group compared with the placebo group. During the 8 years of both the MORE and CORE trials, the incidence of invasive breast cancer and ER-positive invasive breast cancer was reduced by 66% (HR = 0.34, 95% CI, 0.22–0.50) and 76% (HR = 0.24, 95% CI, 0.15–0.40) in the raloxifene group compared with the placebo group, respectively. During the CORE trial, the RR for thromboembolism was 2.17 (95% CI, 0.83–5.70) in the raloxifene group compared with the placebo group. No increase in the risk for endometrial cancer was observed with raloxifene.

Raloxifene Use for The Heart Trial

The Raloxifene Use for The Heart (RUTH) trial evaluated the effect of raloxifene on cardiovascular events in 10,101 postmenopausal women with coronary heart disease, peripheral arterial disease, or multiple risk factors for coronary heart disease.[8] Primary outcomes were coronary events and invasive breast cancer. No significant difference was observed between the groups in the incidence of the primary outcome of death from coronary causes. A 44% decreased incidence of invasive breast cancers occurred in the raloxifene group (HR, 0.56; 95% CI, 0.38–0.83), mostly caused by the reduction in ER-positive invasive breast cancers, with a 55% decrease in the raloxifene group (HR, 0.45; 95% CI, 0.28–0.72). No significant difference was seen in ER-negative invasive breast cancers between the groups. Consistent with previous studies, an increase in venous thromboembolic events occurred in the raloxifene group compared with the placebo group. Although the overall number of strokes was not increased in the raloxifene group, a small increase in the mortality from stroke occurred.

Although some early evidence suggested potential cardiovascular benefits, this benefit was not shown in the RUTH trial. However, no unexpected harmful effects were found either, still making raloxifene an attractive preventive agent for osteoporosis and breast cancer.

The Study of Tamoxifen and Raloxifene Trial

Although raloxifene was suggested to reduce the incidence of breast cancer, the design of the trials limited the clinical application to women at increased risk for breast cancer. This, coupled with its lack of endometrial stimulation, led to the development and implementation of the Study of Tamoxifen and Raloxifene (STAR) trial (or P-2) in 1999 by the National Surgical Adjuvant Breast and Bowel Project.[10–12]

Design

The STAR trial was a prospective, double-blinded, randomized clinical trial that enrolled postmenopausal women who were at least 35 years old with increased risk for developing breast cancer. *Increased risk* is defined as a personal history of lobular carcinoma in situ (LCIS) treated by excision alone or a 5-year predicted breast cancer risk of 1.66% as determined by the Gail model.[13] Women could not have a prior history of a venous thromboembolic event, stroke, or risk factors for the development of blood clots, specifically, uncontrolled diabetes, uncontrolled hypertension, or atrial fibrillation.

The study was conducted at approximately 200 clinical centers throughout the United States, Canada, and Puerto Rico,[10–12] with 19,747 women randomized to either tamoxifen 20 mg/d or raloxifene 60 mg/d for 5 years. At randomization, the average age of

participants was 58.5 years. Because this trial enrolled only postmenopausal women, 9% of the participants were younger than 50 years, 49.8% were between 50 and 59 years, and 41.2% were 60 years or older (Table 1). Although significant efforts were made to enroll a diverse population, the trial was comprised predominately of Caucasian women (93%), with the remainder being African American (2.5%) and Hispanic (2.0%) women (Table 1). More than 70% of participants had a history of invasive breast cancer in a first-degree maternal relative (Table 1). Along with the Breast Cancer Prevention Trial (BCPT), the STAR trial is one of the largest prospective trials that enrolled women with proliferative breast lesions, with more than 9% having a personal history of LCIS and 22.7% having either atypical ductal or lobular hyperplasia on a previous breast biopsy (Table 1). The mean predicted 5-year risk of developing breast cancer among the study population was 4.03%. The trial opened for participant entry on July 1, 1999 and completed accrual on November 4, 2004.

Table 1 STAR Trial: Participant Characteristics at Time of Randomization

	Tamoxifen		Raloxifene	
Participant Characteristic	**N**	**%**	**N**	**%**
Age (y)				
≤ 49	884	9.1	877	9.0
50–59	4850	49.9	4848	49.7
60–69	3133	32.2	3173	32.6
≥ 70	859	8.8	847	8.7
Race/ethnicity				
Caucasian	9096	93.5	9108	93.5
African American	233	2.4	241	2.5
Hispanic	191	2.0	193	2.0
Other	206	2.1	203	2.1
N first-degree relatives with breast cancer				
0	2835	29.1	2789	28.6
1	5041	51.8	5130	52.6
2	1532	15.8	1559	16.0
≥ 3	318	3.3	267	2.7
History of hysterectomy				
No	4732	48.7	4712	48.4
Yes	4994	51.3	5033	51.6
History of lobular carcinoma in situ				
No	8833	90.8	8849	90.8
Yes	893	9.2	896	9.2
History of breast atypical hyperplasia				
No	7540	77.5	7505	77.0
Yes	2186	22.5	2240	23.0
5-year predicted breast cancer risk (%)				
≤ 2.00	1055	10.8	1097	11.3
2.01–3.00	2988	30.7	2893	29.7
3.01–5.00	3039	31.2	3082	31.6
≥ 5.01	2644	27.2	2673	27.4

Abbreviation: STAR, Study of Tamoxifen and Raloxifene.
Source: Adapted from 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. Erratum in JAMA 2006;296:2926.

The study's goal was to compare the relative effects and safety of raloxifene and tamoxifen on the risk for developing invasive breast cancer and other disease outcomes,[12] with invasive breast cancer the primary end point. In situ breast cancer, uterine cancer, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attacks, cardiac disease (e.g., fatal and nonfatal myocardial infarction, severe angina, acute ischemic syndrome), osteoporotic fractures, cataract, and death were secondary end points.

Findings

Raloxifene was found to be equivalent to tamoxifen in reducing the incidence of breast cancer but with fewer risks.[12] The raloxifene group developed 168 invasive breast cancers compared with 163 in the tamoxifen group (incidence 4.30 vs. 4.41 per 1000; RR, 1.02; 95% CI, 0.82–1.28). Both groups had statistically equivalent numbers of invasive breast cancers (Table 2). When the treatment groups were

Table 2 STAR Trial: Breast Cancers and Other Major Adverse Events

End Points	Tamoxifen (n = 9872)	Raloxifene (n = 9875)	Risk Ratio (95% CI)
Invasive breast cancer	163	168	1.02 (0.82–1.28)
ER status (invasive cancers)			
ER-positive	115	109	0.93 (0.72–1.24)
ER-negative	44	51	1.15 (0.75–1.77)
ER status unknown	4	8	1.99 (0.53–9.02)
In situ breast cancer	57	80	1.40 (0.98–2.00)
Invasive uterine cancer	36	23	0.62 (0.35–1.08)
Uterine hyperplasia	84	14	0.16 (0.09–0.29)
Hyperplasia with atypia	12	1	0.08 (0.00–0.55)
Hyperplasia without atypia	72	13	0.18 (0.09–0.32)
Hysterectomy	244	111	0.44 (0.35–0.56)
PE and DVT combined	141	100	0.70 (0.54–0.91)
DVT	87	65	0.74 (0.53–1.03)
PE	54	35	0.64 (0.41–1.00)
Stroke	53	51	0.96 (0.64–1.43)
Fractures	104	96	0.92 (0.69–1.22)
Cataracts	394	313	0.79 (0.68–0.92)
Cataract surgery	260	215	0.82 (0.68–0.99)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; ER, estrogen receptor; PE, pulmonary embolus; STAR, Study of Tamoxifen and Raloxifene.
Source: Adapted from 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. Erratum in JAMA 2006;296:2926.

compared using baseline categories of age, history of LCIS and atypical hyperplasia, Gail model-derived 5-year predicted risk for breast cancer, and the number of relatives with a history of breast cancer, no difference according to treatment assignment was found. No differences were seen in the pathologic characteristics of the tumors regarding distributions by tumor size, nodal status, or ER level. Based on the risk reduction seen in BCPT for tamoxifen, both drugs reduced the risk for developing invasive breast cancer by approximately 50%.

In contrast to the findings for invasive breast cancer, substantially fewer noninvasive breast cancers were seen in the tamoxifen arm than in the raloxifene arm (Table 2). The tamoxifen group had 57 cases of noninvasive breast cancer and the raloxifene group had 80 (incidence 1.51 vs. 2.11 per 1000; RR, 1.40; 95% CI, 0.98–2.00). Although tamoxifen has been shown to reduce the incidence of LCIS and ductal carcinoma in situ, raloxifene did not affect these diagnoses. This result confirms earlier data reported in the 2004 CORE trial, although the reasons are unknown.

The incidence of uterine cancer was lower in the raloxifene arm, with the difference approaching statistical significance (RR, 0.62; 95% CI, 0.35–1.08). The tamoxifen arm showed 36 cases of uterine cancer and the raloxifene arm, 23 (Table 2). More than half of the women who joined the STAR trial had previously undergone a hysterectomy and therefore were not at risk for uterine cancer (Table 1), limiting the ability to assess the effect of raloxifene on the uterus. Other differences were observed indicating that the effect of raloxifene on the uterus is less than that for tamoxifen. Among those with no diagnosis of uterine cancer, a statistically significant difference was seen in the incidence of uterine hyperplasia (Table 2). The rates were 84% less in the raloxifene-treated group (14 cases) than in the tamoxifen-treated group (84 cases) (RR, 0.16; 95% CI, 0.09–0.29). This magnitude of difference was evident for hyperplasia both with and without atypia. In the tamoxifen and raloxifene groups, respectively, 12 and 1 cases were seen with atypia (RR, 0.08; 95% CI, 0.00–0.55) and 72 and 13 without atypia (RR, 0.18; 95% CI, 0.09–0.32). A statistically significant difference was also seen for the number of hysterectomies performed during follow-up (Table 2). Among women who were not diagnosed with endometrial cancer, 244 hysterectomies were performed in women assigned to treatment with tamoxifen compared with 111 in those assigned to raloxifene (RR, 0.44; 95% CI, 0.35–0.56), obscuring the effect of raloxifene on the endometrium.

Pulmonary emboli and deep vein thromboses occurred less often in the raloxifene group (Table 2). Pulmonary emboli occurred in 54 women assigned to tamoxifen compared with 35 assigned to raloxifene

(RR, 0.64; 95% CI, 0.41–1.00) and deep vein thromboses in 87 versus 65 (RR, 0.74; 95% CI, 0.53–1.03), respectively. Overall, 141 events occurred with tamoxifen and 100 with raloxifene, indicating that the risk was 30% less for the raloxifene group (RR, 0.70; 95% CI, 0.54–0.91). The numbers of strokes and transient ischemic attacks that occurred in both groups were statistically equivalent. No difference was seen in deaths resulting from strokes. Importantly, women at increased risk for stroke (those with uncontrolled hypertension or uncontrolled diabetes, or a history of stroke, transient ischemic attacks, or atrial fibrillation) were not eligible to participate in the STAR trial.

Raloxifene is FDA approved for osteoporosis prevention and treatment; similar benefits for tamoxifen have been suggested in previous trials of breast cancer treatment and prevention. In the STAR trial, rates of fracture were virtually identical in the raloxifene and tamoxifen arms (Table 2); 104 women in the tamoxifen group and 96 in the raloxifene group experienced a fracture of the hip, wrist (Colles' fracture), or spine (RR, 0.92; 95% CI, 0.69–1.22). Regarding specific types of fracture in the tamoxifen and raloxifene groups, 26 and 23 hip fractures (RR, 0.88; 95% CI, 0.48–1.60), 27 and 23 Colles' fractures (RR, 0.85; 95% CI, 0.46–1.53) occurred, and 53 and 52 spine fractures (RR, 0.98; 95% CI, 0.65–1.46), respectively.

At randomization, 2808 participants reported a history of cataracts. Among those who were cataract-free at baseline, 707 developed cataracts during follow-up. The differences between treatment groups for the incidence of cataracts and cataract surgery were statistically significant, with the raloxifene group showing less occurrence of both (Table 2). Of the women participating in the trial, 394 assigned to tamoxifen and 313 to raloxifene were diagnosed with cataracts. The RR for cataract incidence was 0.79 (95% CI, 0.68–0.92). Cumulative incidence at 6 years for tamoxifen and raloxifene was 77.9 and 56.3 per 1000, respectively ($P = .002$). Of these, 260 in the tamoxifen group and 215 in the raloxifene group underwent cataract surgery. The RR for cataract surgery was 0.82 (95% CI, 0.68–0.99).

Findings were similar between the groups for other invasive cancers, ischemic heart disease events, and total number or causes of deaths.

Side effects of both drugs were mild to moderate in severity and no statistical difference in the quality of life was seen between tamoxifen and raloxifene ($P > 2.0$).[14] Women in the tamoxifen arm reported greater severity of vasomotor symptoms than women in the raloxifene arm (0.96 vs. 0.85; $P < .001$). Vasomotor symptoms increased initially but diminished during treatment. Reports of gynecologic problems (e.g., vaginal discharge, vaginal bleeding, genital itching or irritation) were higher in the tamoxifen group (0.29 vs. 0.19; $P < .001$). Reports of difficulty with urinary bladder control (0.88 vs. 0.73; $P < .001$) and of leg cramps (1.10 vs. 0.91; $P < .001$) were also higher in the tamoxifen group. Sexual function was slightly better for women assigned to tamoxifen than those assigned to raloxifene (1.22%; 95% CI, 1.01–1.46). Pain with intercourse was higher among participants in the raloxifene arm (.078 vs. 0.68; $P < .001$) as were musculoskeletal problems (1.15 vs. 1.10; $P = .002$). Self-reported weight gain was also higher in the raloxifene group (0.82 vs. 0.76; $P < .001$).

Conclusions

In the STAR trial, raloxifene was found to be as effective as tamoxifen in post-menopausal, Caucasian women at increased risk for invasive breast cancer. Although it does not reduce the risk for noninvasive breast cancer like tamoxifen, it has fewer risks. Raloxifene does not have the same effect on the uterus as tamoxifen; concern about the risk for uterine cancer associated with tamoxifen was one of the factors limiting its use for breast cancer risk reduction. The risk for venous thromboembolic events is also less with raloxifene, and the incidence of cataracts in the raloxifene group is similar to that seen for the general population. No significant differences were seen between the tamoxifen and raloxifene arms in patient-reported outcomes for physical health, mental health, and depression, although the tamoxifen arm reported better sexual function. Although quality of life for participants was similar for both drugs, statistically significant differences were seen for specific symptoms. These differences may be an important factor in determining which drug is most appropriate for individual patients. One major limitation of this study is the predominantly Caucasian study population, which limits the application of the findings to non-Caucasian women at risk for breast cancer. Coupled with its known osteoporotic benefits, raloxifene is now an option for breast cancer risk reduction in postmenopausal women at increased risk for the disease.

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