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The NSABP Study of Tamoxifen and Raloxifene (STAR) trial

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Abstract

In the Study of Tamoxifen and Raloxifene (STAR) trial, postmenopausal women at increased risk of breast cancer received either oral tamoxifen (20 mg/day) or raloxifene (60 mg/day) over 5 years. There were an equal number of cases of invasive breast cancer in women assigned to tamoxifen and raloxifene. There were fewer cases of noninvasive breast cancer in the tamoxifen group than in the raloxifene group (risk ratio [RR]: 1.40; 95% confidence interval [CI]: 0.98–2.02). There were more cases of uterine cancer with tamoxifen than with raloxifene (RR: 0.62; 95% CI: 0.35–1.08). Thromboembolic events occurred less often in the raloxifene group (RR: 0.70; 95% CI: 0.54–0.91) and there were fewer cataracts and cataract surgeries in the women taking raloxifene (RR: 0.79; 95% CI: 0.68–0.92). The STAR trial has shown that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of adverse events but a nonstatistically significant higher risk of noninvasive breast cancer. The risk of other cancers, fractures, ischemic heart disease and stroke is similar for both drugs.

Keywords

breast cancer risk reduction; chemoprevention; primary prevention; raloxifene; selective estrogen receptor modulator; tamoxifen

The selective estrogen receptor (ER) modulators (SERMs) approved for clinical use include tamoxifen and raloxifene. SERMs exert estrogen agonist action in some target tissues, while acting as estrogen antagonists in others [1]. Multiple studies have established the role of tamoxifen in treating and preventing breast cancer [2] and of raloxifene in treating and preventing osteoporosis [3-8]. Of the more than 65 million women aged 35–79 years without reported breast cancer in the USA in 2000, more than 10 million women (15.5%) were eligible for tamoxifen chemoprevention using the eligibility criteria of the Breast Cancer Prevention Trial (BCPT) [9-11]. In the USA, there are more than 33 million postmenopausal women and 9 million of these women are currently eligible for risk reduction with a SERM. Of the 50 million white American women aged 35–79 years, more than 2 million (approximately 5%) would have a positive benefit–risk index for SERM-based chemoprevention [11-13].

Approximately 500,000 women worldwide are currently taking raloxifene for the management of osteoporosis. In the osteoporosis trials that led to the approval of raloxifene, preliminary data also suggested a reduction in the risk of breast cancer. These observations led to the design and conduct of the Study of Tamoxifen and Raloxifene (STAR) trial, which will be reviewed in this article.

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Introduction to the trial

The National Surgical Adjuvant Breast and Bowel Project (NSABP) BCPT (also known as P-1) trial demonstrated that tamoxifen could reduce the risk of invasive breast cancer by 49% among risk-eligible women [9,10] and established proof-of-principle that chemoprevention of breast cancer is possible. Nevertheless, primary-care physicians have not broadly accepted the idea of tamoxifen use for breast cancer chemoprevention, in part because the drug has been characterized as too toxic. There is an important distinction to be made between tamoxifen and raloxifene relative to potential use of the latter for breast cancer chemoprevention. Tamoxifen is well known to oncologists who use it extensively in the treatment of receptor-positive breast cancer, but the drug has not been commonly prescribed by primary-care physicians most involved in preventive care. Tamoxifen was viewed as a cancer drug and the news reports highlighting its toxicity may have hampered primary-care physicians' exploration of its use as a preventive agent [14]. By contrast, raloxifene is well known to the primary care community and is prescribed widely for the prevention and treatment of osteoporosis in postmenopausal women [15,16].

The STAR trial was designed to confirm the benefit of raloxifene in reducing the risk of invasive breast cancer reported previously in the osteoporosis trials [4-6]. It was thought that, because the US FDA approved raloxifene for the prevention and treatment of osteoporosis, primary-care physicians may be more willing, given their experience with the drug, to prescribe it for breast cancer chemoprevention than they have been to prescribe tamoxifen if raloxifene could be shown to be as effective and safer than tamoxifen for the reduction of breast cancer risk.

Background & rationale

Tamoxifen has been evaluated thoroughly for the reduction of the risk of both invasive and noninvasive breast cancer in women at increased risk. Raloxifene reduces the incidence of mammary malignancy in preclinical models, and several clinical trials evaluating it for the prevention and treatment of osteoporosis have suggested that it may also have a role in reducing the risk of invasive breast cancer in postmenopausal women.

The Multiple Outcomes Raloxifene Evaluation (MORE) study was designed to test whether raloxifene, at a daily dose of either 60 or 120 mg, reduced the risk of fracture in postmenopausal women with osteoporosis [15]. The primary end point was the development of fracture. A secondary end point in the MORE trial was invasive breast cancer. After 4 years of follow-up, there were 22 cases among 5129 postmenopausal women randomly assigned to raloxifene, compared with 39 cases among 2576 postmenopausal women assigned to placebo. The MORE trial concluded that, among older postmenopausal women with osteoporosis, the risk of ER-positive invasive breast cancer was decreased by 72% during 4 years of raloxifene treatment, with no apparent decrease in the incidence of ER-negative tumors. As with tamoxifen, raloxifene increased the risk of thromboembolic disease but did not appear to increase the risk of endometrial cancer [4-6,16-20].

The Continuing Outcomes Relevant to Evista (CORE) trial was designed to evaluate the efficacy of an additional 4 years of raloxifene therapy in preventing invasive breast cancer in women who participated in the MORE trial [19]. CORE was a multicenter, double-blind, placebo-controlled clinical trial. The CORE trial was conducted in the subset of the MORE women who agreed to participate in what was an extension of the MORE trial, with a change in the primary end point from vertebral fracture incidence to invasive breast cancer. A secondary objective of the CORE trial was to examine the effect of raloxifene (at 60 mg/day) on the incidence of invasive ER-positive breast cancer. Women who had been randomly assigned to receive raloxifene (either 60 or 120 mg/day) in MORE were assigned to receive

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raloxifene (60 mg/day) in CORE (n = 3510), and women who had been assigned to receive placebo in MORE continued on placebo in CORE (n = 1703). Women in the raloxifene group had a 59% reduction in the incidence of all invasive breast cancer compared with women in the placebo group and a 66% reduction in the incidence of invasive ER-positive breast cancers compared with women in the placebo group. By contrast, the incidence of invasive ER-negative breast cancer in women who received raloxifene was not statistically significantly different from that in women who received placebo. The overall incidence of breast cancer, regardless of invasiveness, was reduced by 50% in the raloxifene group compared with the placebo group.

For the 7705 women in the MORE trial, the total number of reported breast cancers from randomization in MORE to the end of their participation in either MORE or CORE was 121 (56 cancers in the raloxifene group and 65 cancers in the placebo group). During these 8 years, 40 invasive breast cancers were reported in the raloxifene group and 58 invasive breast cancers were reported in the placebo group. Thus, the raloxifene group had a 66% reduction in the incidence of invasive breast cancer compared with the placebo group. During these 8 years, the raloxifene group had a 76% reduction in the incidence of invasive ER-positive breast cancer compared with the placebo group. There was no difference in the incidence rates of invasive ER-negative breast cancer between the raloxifene group and the placebo group. During the 8 years of the MORE and CORE trials, the overall incidence of breast cancer, both *in situ* and invasive, was reduced by 58% in the raloxifene group compared with the placebo group [19]. The CORE trial provides additional results indicating that raloxifene reduces breast cancer incidence in postmenopausal women with osteoporosis.

Based on the findings from the NSABP BCPT (P-1) [9,10] and other primary risk-reduction studies [2,21-24], tamoxifen was approved by the FDA for reducing risk in high-risk women. The NSABP STAR trial was launched to directly compare tamoxifen with raloxifene in a population of women at an increased risk for breast cancer [25]. The objective of the STAR trial was to compare raloxifene with tamoxifen in terms of their relative effects on the risk of invasive breast cancer and other diseases influenced by tamoxifen in the BCPT.

Design

The eligibility criteria for participation in the STAR trial are shown in Box 1.

A total of 184,460 women were screened using the modified Gail model [13,26,27] to determine their breast cancer risk. Of these, more than 96,000 had a 5-year risk of at least 1.67%. From this group, 20,616 agreed to be screened to determine full eligibility for the trial based on the medical criteria defined later. In total, 20,168 women were found to meet all eligibility criteria of the study and 19,747 women went forward with participation in the trial, signed a consent form and were randomized to receive either tamoxifen or raloxifene. Treatment assignment was double-blinded and neither participants nor their care providers were aware of their therapy designation until the trial was unblended in April 2006. Participants were screened and enrolled in nearly 200 clinical centers throughout North America.

Data analysis

The primary end point was invasive breast cancer. Secondary end points included endometrial cancer, *in situ* breast cancer, cardiovascular disease, stroke, pulmonary embolism, deep vein thrombosis (DVT), transient ischemic attack, osteoporotic fracture, cataracts, death and quality of life; data on all other invasive cancers were also collected prospectively. The cardiac disease end points included fatal and nonfatal myocardial infarction, severe angina and acute ischemic syndrome. Severe angina was defined as angina requiring revascularization by percutaneous coronary intervention or coronary artery bypass graft surgery. Acute ischemic syndrome was defined as the presence of a new Q-wave on ECG or angina requiring hospitalization without

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surgery. Vascular-related events included stroke and transient ischemic attack, as well as DVT and pulmonary embolism. Three fracture sites known to be indicative of this disease (hip, spine and Colles fractures of the wrist) were selected to judge the impact on osteoporosis.

Follow-up occurred 6 months after treatment initiation and every 6 months thereafter for 5 years. After 5 years, follow-up occurred annually. Clinical breast examination was to be performed every 6 months, and bilateral mammograms were to be performed annually. Gynecologic examinations, complete blood cell counts and routine serum chemistry tests were to be obtained annually. Information regarding the occurrence of all protocol-defined end points was ascertained at each follow-up visit and verified by the collection of pathology reports, mammographic reports, surgical reports, discharge summaries and other medical record documents. Self-reported symptoms were collected at each contact, and in-depth quality-of-life assessments were performed at selected clinical centers on a subset of 1983 participants using the Medical Outcomes Study Short-Form 36, the Center for Epidemiologic Studies-Depression Scale and the Medical Outcomes Study Sexual Functioning Scale [28].

The STAR trial was monitored by an independent data monitoring committee composed of individuals with expertise in research ethics, oncology, clinical trial methodology, gynecology, epidemiology and biostatistics. A consumer representative was also included as a member of the committee. The monitoring plan was based on detecting a statistically significant difference between treatment groups in the incidence of invasive breast cancer – the primary end point of the trial – and included six interim analyses and a final analysis initiated when at least 327 cases of invasive breast cancer were diagnosed in the entire study cohort.

Comparison between treatment groups of the study end points was based on the determination of rates per 1000 person-years, the risk ratio (RR) contrasting the rate in the raloxifene group to the rate in the tamoxifen group, and the 95% confidence intervals (CIs) for the RR. The rate was defined as the number of observed events divided by the total number of observed event-specific person-years at risk. The cumulative incidence was determined accounting for the competing risk due to death.

Results

There was no difference between the effect of tamoxifen and the effect of raloxifene on the incidence of invasive breast cancer; these results are shown in **Tables** 1 & 2. There were 163 cases of invasive breast cancer in the women assigned to tamoxifen and 168 cases in those assigned to raloxifene [25]. The rate per 1000 was 4.30 in the tamoxifen group and 4.41 in the raloxifene group (RR: 1.02; 95% CI: 0.82–1.28). The cumulative incidence through 72 months for the two treatment groups was 25.1 and 24.8 per 1000 for the tamoxifen and raloxifene groups, respectively ($p = 0.83$). When the treatment groups were compared by baseline categories of age, history of lobular carcinoma *in situ* (LCIS), history of atypical hyperplasia, Gail model-derived 5-year predicted risk of breast cancer and the number of relatives with a history of breast cancer, the pattern of no differential effect by treatment assignment was consistent, and none of the RRs in these subsets were statistically significant. Histological characteristics, tumor size and nodal status were derived from submitted pathology reports; there was no central review of pathology slides. When the investigators assessed the pathological characteristics of the tumors in these patients, there were no differences between the treatment groups with regard to distributions by tumor size, nodal status or ER level.

In contrast to the findings for invasive breast cancer, there were fewer noninvasive breast cancers in the tamoxifen group than in the raloxifene group, although this difference did not reach statistical significance (**Tables** 3 & 4). There were 57 incident cases of noninvasive breast cancer among the women who took tamoxifen and 80 among the women who took raloxifene (rate for noninvasive breast cancer, 1.51 per 1000 women assigned to tamoxifen and 2.11 per

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1000 women assigned to raloxifene [RR: 1.40; 95% CI: 0.98–2.02]). Cumulative incidence through 6 years was 8.1 per 1000 in the tamoxifen group and 11.6 in the raloxifene group (p = 0.052). Approximately 36% of the cases were LCIS and 54% were ductal carcinoma *in situ* (DCIS), with the balance being mixed types. The pattern of fewer cases among the tamoxifen group was evident for both LCIS and DCIS.

Box 1

Eligibility criteria for the Study of Tamoxifen and Raloxifene trial

All participants were postmenopausal women who:

- Had at least a 5-year predicted breast cancer risk of 1.66% based on the Gail model. Gail model risk factors include age, race/ethnicity, age at menarche, age at first live birth, family history of breast cancer in first-degree female relatives, number of breast biopsies and whether there was a history of atypical lobular or ductal hyperplasia
- Were at least 35 years of age and not taking tamoxifen, raloxifene, hormone replacement therapy, oral contraceptives or androgens for at least the previous 3 months
- Had no history of stroke, pulmonary embolism or deep vein thrombosis and no history of any malignancy diagnosed less than 5 years before randomization except basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix
- Had no uncontrolled atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension; and had no psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day

Postmenopausal women aged 35 years and older could enter the trial if they had a history of lobular carcinoma *in situ* treated by local excision alone with no other risk factors and regardless of Gail model score

Safety & tolerability

There was a trend toward a decreased incidence of uterine cancer in the raloxifene group: 36 cases with tamoxifen versus 23 with raloxifene. Annual incidence rates were 1.99 per 1000 (tamoxifen) and 1.25 per 1000 women (raloxifene; RR: 0.62; 95% CI: 0.30–0.50). Cumulative incidence rates through 7 years were 14.7 per 1000 (tamoxifen) and 8.1 per 1000 (raloxifene; p = 0.07). Only one case of uterine cancer occurred among women younger than 50 years of age, in a participant in the tamoxifen group. At the time of analysis, clinical–pathological stage was unknown for three cases (one in the tamoxifen group, two in the raloxifene group). The majority of the others who developed uterine cancer were diagnosed with stage I disease (91%).

Among those who did not have a diagnosis of uterine cancer there was a statistically significant difference between the groups in the incidence of uterine hyperplasia. 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) and was evident for hyperplasia both with and without atypia. For the tamoxifen and raloxifene groups, there were 12 cases and one case with atypia (RR: 0.08; 95% CI: 0.00–0.55) and 72 and 13 cases without atypia, respectively (RR: 0.18; 95% CI: 0.09–0.32). There was also a statistically significant difference between the treatment groups in the number of hysterectomies performed during the course of follow-up. Among women who were not diagnosed with endometrial cancer, there were 221 hysterectomies performed in those

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assigned to tamoxifen compared with 87 in those assigned to raloxifene (RR: 0.39; 95% CI: 0.30–0.50).

The difference in total number of strokes was small, with the number of events occurring in women assigned to tamoxifen being only two more than in those assigned to raloxifene (53 vs 51). There was no statistically significant difference between tamoxifen and raloxifene in the number of transient ischemic attacks that occurred (41 in the tamoxifen group vs 50 in the raloxifene group; RR: 1.21; 95% CI: 0.79–1.88), but there was a statistically significant difference between the treatment groups for the incidence of thromboembolic events, with the raloxifene group experiencing fewer cases of pulmonary embolism and DVT. Overall, there were 141 events with tamoxifen and 100 with raloxifene, indicating that the risk was 30% less in the raloxifene group (RR: 0.70; 95% CI: 0.54–0.91). The cumulative incidence at 6 years was 21.0 per 1000 and 16.0 per 1000 for the tamoxifen and raloxifene groups, respectively ($p = 0.01$). Pulmonary embolism and DVT occurred in 54 versus 35 women (RR: 0.64; 95% CI: 0.41–1.00) and in 87 versus 65 women (RR: 0.74; 95% CI: 0.53–1.03) assigned to tamoxifen and raloxifene, respectively.

There were no differences in the rates of myocardial infarction, severe angina, or acute ischemic syndrome between the tamoxifen and raloxifene groups in our study.

Among women in the quality-of-life analysis, mean physical and mental component summaries and depression scores worsened modestly over the study's 60 months, with no significant difference between the tamoxifen and raloxifene groups. Sexual function was slightly better for participants assigned to tamoxifen [28]. Of the women in the symptom assessment analyses, the raloxifene group reported greater mean symptom severity over 60 months of assessments than the tamoxifen group for musculoskeletal problems, dyspareunia and weight gain. Women in the tamoxifen group reported greater mean symptom severity for gynecological problems, vasomotor symptoms, leg cramps and bladder control symptoms. No significant differences existed in the STAR trial between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health and depression, although the tamoxifen group reported better sexual function.

No screening was performed for vertebral fractures, and only data for clinically apparent vertebral fractures were captured. There was no difference between treatment groups in the total number of these fractures or in the number for any of the specific types of fracture. In total, 104 women in the tamoxifen group and 96 in the raloxifene group experienced one of these fractures (RR: 0.92; 95% CI: 0.69–1.22).

At the time of randomization, 2808 participants reported a history of cataracts. Among those who were cataract free at baseline, 707 developed cataracts during the course of follow-up. The differences between treatment groups for the incidence of cataracts and cataract surgery were statistically significant, with occurrence for both being less in the raloxifene group. Of those assigned to tamoxifen, 394 were diagnosed with cataracts and, of those assigned to raloxifene, 313 had 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 ($p = 0.002$). Of these women, 260 in the tamoxifen group and 215 in the raloxifene group had cataract surgery. The RR for cataract surgery was 0.82 (95% CI: 0.68–0.99), favoring raloxifene therapy.

Conclusion

In the several osteoporosis trials and the Raloxifene Use for the Heart Trial of older postmenopausal women [29], raloxifene decreased the risk of ER-positive breast cancer by 44–90%. In the STAR trial, the effect of raloxifene on invasive breast cancer was equivalent

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to that of tamoxifen with more-favorable effects on uterine malignancy and clotting events. Symptomatic side effects are acceptable. In summary, the available data indicate that raloxifene represents an acceptable alternative to tamoxifen for the reduction of the risk of postmenopausal breast cancer in high-risk women [30].

Expert commentary

Compared with placebo in postmenopausal women at average risk of breast cancer in the published osteoporosis trials, raloxifene reduces the risk of invasive breast cancer by 44–76%. Among younger postmenopausal women who are at increased risk of breast cancer, raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer.

Previous studies have shown that raloxifene does not increase the risk of uterine malignancy compared with placebo. In the STAR trial, only 59 invasive uterine cancers were diagnosed in both study groups during more than 76,000 woman-years of follow-up. Approximately 25% fewer cases of uterine cancer were diagnosed in the raloxifene than the tamoxifen group. The rates of uterine cancer were 1.99 per 1000 (tamoxifen) and 1.25 per 1000 (raloxifene). This difference did not reach statistical significance (RR: 0.62; 95% CI: 0.35–1.08). However, endometrial hyperplasia, a risk factor for endometrial cancer, was far more common in the tamoxifen-treated group than in the raloxifene group and was statistically significant (RR: 0.16; 95% CI: 0.09–0.29). The number of participants undergoing a hysterectomy for noncancer-related reasons was significantly reduced in the raloxifene group (RR: 0.39; 95% CI: 0.30–0.50). It is important to note that the difference between the treatment groups in noncancer-related hysterectomies has probably caused an underestimate of the true magnitude of endometrial cancer risk associated with tamoxifen and an underestimate of the true magnitude of difference between the two treatment groups for this end point.

Raloxifene appears to be less effective than tamoxifen in reducing the risk of *in situ* breast cancer (LCIS and DCIS), although the results in the STAR trial were not statistically significant (incidence was 1.51 vs 2.11 per 1000 per year; RR: 1.40; 95% CI: 0.98–2.02). Across all placebo-controlled trials with raloxifene, however, *in situ* cancers occurred more often with raloxifene than with placebo or tamoxifen [4,15,19,29]. The STAR trial may have been underpowered to detect such a difference. Therefore, the clinical impact of this finding remains to be seen. Similar results were observed, however, in the MORE and CORE studies, in which raloxifene did not reduce the risk of noninvasive breast cancer, although the number of events in those studies was very small. All of these results taken together suggest that different SERMs have unique and specific mixes of benefits and risks and that neither a benefit nor a risk seen with one SERM can be generalized across the entire class. Most of the STAR cases were diagnosed as a result of mammograms, demonstrating increasing calcifications. The individuals underwent careful follow-up and, as a result, their cancers were small and most were treated surgically with lumpectomy. Approximately 36% of the cases were LCIS and 64% were DCIS or mixed LCIS and DCIS. The difference between tamoxifen- and raloxifene-treated individuals with DCIS was quite small (0.4 per 1000 per year). The CORE results through 8 years of follow-up show that raloxifene continues to offer a significant reduction in invasive disease, suggesting that raloxifene has a durable benefit despite this lesser impact on noninvasive disease.

Among women in the STAR trial quality-of-life analysis, mean physical, mental and depression component scores worsened modestly over 60 months of observation, with no significant difference between the two groups [28]. Sexual function was slightly better for participants assigned to tamoxifen (age-adjusted repeated measure odds ratio: 1.22; 95% CI: 1.01–1.46). Of the women in the symptom assessment analyses, those in the raloxifene group reported greater mean symptom severity over 60 months of assessments than those in the tamoxifen

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group for musculoskeletal problems, dyspareunia and weight gain, but the differences were not clinically meaningful. Women in the tamoxifen group reported greater mean symptom severity for gynecological problems, vasomotor symptoms, leg cramps and bladder control symptoms. Overall, no significant differences existed between the tamoxifen and raloxifene groups in patient-reported outcomes for physical and mental health, and depression, although the tamoxifen group reported better sexual function.

In high-risk, younger postmenopausal women, raloxifene appears to offer a net benefit when comparing reduction of the risk of breast cancer and the prevention of fractures with the risk of stroke, venous thromboembolic events, uterine events and symptomatic side effects [30].

Given all of these considerations, raloxifene is now the drug of choice for reducing the risk of breast cancer among post-menopausal women who are at increased risk for breast cancer and who have risk/benefit profiles similar to those women who enrolled in the STAR trial. It offers greater net benefit to women with an intact uterus than does tamoxifen. Raloxifene has not been studied in and its use is not appropriate in premenopausal women who are at increased risk of breast cancer; tamoxifen remains the drug of choice for these patients.

Five-year view

Chemoprevention of breast cancer in healthy women offers an attractive potential for prevention of this disease. It is essential to identify women who will benefit from these interventions. Raloxifene has similar risk-reduction activity when compared with tamoxifen but has less toxicity, particularly on the uterus, making it a more attractive option than tamoxifen for use as a breast cancer risk-reduction agent in postmenopausal healthy women. Published clinical trials demonstrate that the greatest clinical benefit with the fewest side effects occur in high-risk, younger postmenopausal women. In this population of women, raloxifene appears to offer a net benefit when comparing reduction of the risk of breast cancer and the prevention of fractures with the risk of stroke, venous thromboembolic events, uterine events and symptomatic side effects. A large net benefit is seen with the use of SERMs in women with LCIS and atypical ductal or lobular hyperplasia. The potential market for a compound shown to reduce the risk of breast cancer in postmenopausal women who are at increased risk for breast cancer is more than 10 million women in the USA alone [11].

The development of the selective aromatase inhibitors (AIs) has had an important impact on the adjuvant treatment of post-menopausal women with receptor-positive breast cancer [31]. In various adjuvant trials, the AIs have improved disease-free survival and overall survival and have had fewer life-threatening side effects than tamoxifen [31-33]. There has been a 35% or greater decrease on primary breast cancers of the opposite breast in the AI trials reported to date, providing strong evidence that these agents may be effective in preventing breast cancer.

The results of a European study, the International Breast Cancer Intervention Study 2 trial, will determine whether the AI anastrozole is effective in preventing breast cancer in high-risk postmenopausal women [32,33]. In this study, anastrozole was compared with placebo in healthy high-risk postmenopausal women. The National Cancer Institute of Canada Clinical Trials Group has also begun its MAP-3 study comparing exemestane to placebo in postmenopausal women at increased risk to determine if exemestane reduces the incidence of invasive breast cancer [34].

Based on all of these considerations, it is likely that an increasing number of postmenopausal women will be screened and identified as being at increased risk of breast cancer. They will have positive net benefit from using either raloxifene or AIs for breast cancer-risk reduction. The burden of morbidity and mortality from breast cancer will, very probably, decline in the

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population as both patients and physicians embrace primary risk reduction and employ these drugs [35].

Key issues

- There are multiple positive considerations for the use of selective estrogen receptor modulators (SERMs) for breast cancer risk reduction.
- Raloxifene is a unique SERM with distinct activity and toxicity profiles.
- Extensive experience from prospective investigations has established its safety and efficacy in the management of postmenopausal osteoporosis.
- Although it has no apparent beneficial effect on coronary heart disease, it has no adverse effect either.
- Three prospective clinical trials have established its benefit in reducing the risk of invasive breast cancer and it offers safety advantages compared with tamoxifen in postmenopausal women who are at increased risk for breast cancer.
- Symptomatic side effects are acceptable as reported in the large, prospectively blinded clinical populations summarized in this article and followed during years of raloxifene administration.
- The risk of other cancers, fractures, ischemic heart disease and stroke are similar for both raloxifene and tamoxifen.
- Raloxifene offers an alternative to tamoxifen for the reduction of breast cancer risk in high-risk postmenopausal women with a superior risk–benefit profile based upon the benefits and risks reviewed here.
- Postmenopausal women over 35 years of age with either Gail model risks of breast cancer greater than 1.67% in 5 years or lobular carcinoma *in situ* should be offered raloxifene for the reduction of breast cancer risk.
- When used for reducing the risk of breast cancer, raloxifene should be administered in a dose of 60 mg once daily; alternate doses and schedules have not been evaluated for either safety or efficacy.
- Chemoprevention with a SERM may be particularly beneficial to women with atypical hyperplasia, a 5-year Gail model risk of more than 5%, lobular carcinoma *in situ*, or two or more first-degree relatives with breast cancer.

Information resources

- American Society of Clinical Oncology offers news and meeting reports, technology assessments, education and training, practice resources, and updates on legislative activities for cancer professionals www.asco.org (Accessed July 2008)
- National Cancer Institute of the United States provides information for both health professionals and the public. Information includes cancer topics and statistics, clinical trials, funding opportunities, advisory boards and groups, and funding opportunities www.cancer.gov (Accessed July 2008)
- The American Cancer Society has comprehensive information for both the public and professionals including cancer facts and figures, statistics, research programs

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and funding opportunities, treatment decision tools, information on clinical trials, a bookstore and an international program www.cancer.org (Accessed July 2008)

- The National Comprehensive Cancer Network (NCCN) is an alliance of 19 of the world's leading cancer centers and provides an authoritative resource for both healthcare professionals and clinicians; information includes Clinical Practice Guidelines in Oncology™ and a compendium of drugs and biologicals. They provide treatment guidelines for patients and resource lines for physicians, including information on clinical trials www.nccn.org (Accessed July 2008)
- Eli Lilly and Company sponsors a web site that reviews the risks and benefits of raloxifene for the prevention and treatment of osteoporosis and the reduction of breast cancer risk www.evista.com (Accessed July 2008)

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Table 1

Average annual rates of invasive breast cancer by treatment group and participant characteristics at baseline in the NSABP STAR trial.

Participant characteristic at baseline	Events (n)		Rate per 1000 individuals			Risk ratio‡	95% confidence interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*		
Age at entry (years)							
≤49	7	8	2.07	2.39	−0.32	1.15	0.37–3.74
50–59	83	77	4.38	4.04	0.34	0.92	0.68–1.29
≥60	73	82	4.69	5.22	−0.53	1.11	0.80–1.55
History of lobular carcinoma in situ							
No	130	134	3.76	3.86	−0.10	1.03	0.81–1.33
Yes	33	33	9.83	9.61	0.22	0.98	0.58–1.63
History of atypical hyperplasia							
No	122	121	4.06	4.03	0.03	0.99	0.76–1.28
Yes	41	46	5.21	5.69	−0.48	1.12	0.72–1.74
5-year predicted breast cancer risk (%)							
≤3.00	32	44	2.03	2.83	−0.80	1.40	0.87–2.28
3.01–5.00	61	46	5.18	3.79	1.39	0.75	0.5–1.11
≥5.01	70	77	6.77	7.35	−0.58	1.09	0.78–1.52
FIrst-degree relatives with breast cancer (n)							
0	52	53	4.99	5.18	−0.19	1.04	0.69–1.55
1	72	77	3.62	3.76	−0.14	1.05	0.75–1.47
≥2	39	37	5.16	5.00	0.16	0.97	0.60–1.56
Total	**163**	**168**	**4.30**	**4.41**	**−0.11**	**1.02**	**0.82–1.28**

NSABP: National Surgical Adjuvant Breast and Bowel Project; STAR: Study of Tamoxifen and Raloxifene. Reproduced with permission from [25].

*Rate in the tamoxifen group minus rate in the raloxifene group.

‡Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.

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Table 2

Distribution and average annual rates of invasive cancer by treatment group and tumor characteristics in the NSABP STAR trial.

Pathological characteristic	Events (n, %)*		Rate per 1000 individuals			Risk ratio§	95% confidence interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference‡		
Tumor size (cm)							
≤1.0	47 (29.7)	62 (37.6)	1.24	1.63	−0.39	1.31	0.88–1.96
1.1–3.0	96 (60.8)	91 (55.2)	2.53	2.39	0.14	0.94	0.70–1.27
≥3.1	15 (9.5)	13 (7.8)	0.40	0.34	0.06	0.86	0.38–1.94
Unknown	5	2	0.13	0.05	0.08	0.40	0.04–2.43
Nodal status							
Negative	117 (75.5)	132 (80.5)	3.09	3.49	−0.37	1.13	0.87–1.46
Positive	38 (24.5)	32 (19.5)	1.00	0.84	0.16	0.84	0.51–1.38
Unknown	8	3	0.21	0.08	0.13	0.37	0.06–1.55
Estrogen receptor status							
Negative	44 (27.7)	51 (32.1)	1.16	1.34	−0.18	1.15	0.75–1.77
Positive	115 (72.3)	108 (67.9)	3.04	2.86	0.18	0.94	0.71–1.24
Unknown	4	8	0.11	0.21	−0.10	1.99	0.53–9.02

NSABP: National Surgical Adjuvant Breast and Bowel Project; STAR: Study of Tamoxifen and Raloxifene.

*Percentage of women with known information.

‡Rate in the tamoxifen group minus rate in the raloxifene group.

§Risk ratio for women in the raloxifene group compared with women in the tamoxifen group.

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Table 3

Average annual rates of noninvasive breast cancer by treatment group and type of noninvasive disease in the NSABP STAR trial.

Type of noninvasive disease	Events (n)		Rate per 1000 individuals			Risk ratio*	95% confidence interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference‡		
DCIS	30	44	0.79	1.16	−0.37	1.46	0.90–2.41
LCIS	21	29	0.56	0.76	−0.20	1.37	0.76–2.54
Mixed	6	7	0.16	0.18	−0.02	1.16	0.33–4.18
Total	**57**	**80**	**1.51**	**2.11**	**−0.60**	**1.40**	**0.98–2.02**

DCIS: Ductal carcinoma *in situ*; LCIS: Lobular carcinoma *in situ*; NSASP: National Surgical Adjuvant Breast and Bowel Project; STAR: Study of Tamoxifen and Raloxifene. Reproduced with permission from [25].

*Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.

‡Rate in the tamoxifen group minus rate in the raloxifene group.

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Table 4

Average annual rates of uterine disease and hysterectomy by treatment group in the NSABP STAR trial.

Type of uterine event	Events (n)		Rate per 1000* individuals			Risk ratio§	95% confidence interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference‡		
Invasive cancer	36	23	1.99	1.25	0.75	0.62	0.35–1.08
Hyperplasia¶	84	14	4.69	0.76	3.93	0.16	0.09–0.29
Without atypia	72	13	4.02	0.71	3.31	0.18	0.09–0.32
With atypia	12	1	0.67	0.05	0.62	0.08	0.00–0.55
Hysterectomy during follow-up¶	221	87	12.24	4.72	7.52	0.39	0.30–0.50

NSABP: National Surgical Adjuvant Breast and Bowel Project; STAR: Study of Tamoxifen and Raloxifene.

*Women at risk were those with an intact uterus at entry.

‡Rate in the tamoxifen group minus rate in the raloxifene group.

§Risk ratio for women in the raloxifene group compared with women in the tamoxifen group.

¶Among women not diagnosed with uterine cancer.