The Role of Selective Estrogen Receptor Modulators on Breast Cancer: From Tamoxifen to Raloxifene

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SUMMARY

The link between hormones and breast cancer growth and development has been recognized for more than a century. Estrogen stimulates the proliferation of breast epithelial cells, and both endogenous and exogenous estrogens have been implicated in the pathogenesis of breast cancer. Classically, estrogen action at target sites around the body is mediated through related but distinct estrogen receptors (ERs), designated ERα and ERβ, to alter gene expression. This accumulating understanding of the mechanism of action of estrogen led ultimately to the design of antiestrogenic agents that work by virtue of their interaction with the ER; these drugs have come to be known as selective estrogen receptor modulators (SERMs). Tamoxifen, a SERM, emerged as the first antiestrogenic agent that is clinically applicable to breast cancer. Tamoxifen became the "gold standard" and established the principles of tumor targeting and identified the appropriate treatment strategy to aid survivorship in breast cancer patients, with enhancement of disease-free survival and a 50% decrease in recurrences observed in ER-positive patients 15 years after diagnosis. However, because of the many adverse events in the use of tamoxifen, some of which have contributed to significant morbidity and mortality, drug modification which has resulted in fewer incidences of adverse events without compromising the therapeutic effect for breast cancer prevention may face an easier road to acceptance. Raloxifene may be a better alternative, since evidence from large clinical trials showed that raloxifene not only decreases the incidence of osteoporosis and related fractures, but also offers benefits for breast cancer prevention. The results from the Study of Tamoxifen and Raloxifene (STAR) trial showed the superiority of raloxifene over tamoxifen, not only for the equal efficacy in the prevention of invasive breast cancer but also for the fewer serious adverse events. Taken together, without other competition so far, raloxifene is recommended for postmenopausal women with osteoporosis who also need breast cancer prevention. [*Taiwan J Obstet Gynecol* 2008;47(1):24–31]

Key Words: breast cancer, estrogen, estrogen receptor, raloxifene, selective estrogen receptor modulator, tamoxifen

Introduction

The link between hormones and breast cancer growth and development has been recognized for more than a century [1]. The concept that hormones are key contributors to carcinogenesis in specific cancers first emerged in relation to breast cancer in 1896, with the observation by George Beatson that elimination of ovarian function, the major source of estrogen, by means of oophorectomy, could benefit women with inoperable disease [2]. Furthermore, an association between the risk of breast cancer and persistently elevated blood levels of estrogen has been consistently found in many studies [3]. Estrogen stimulates the proliferation of breast epithelial cells, and both endogenous and

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exogenous estrogens have been implicated in the pathogenesis of breast cancer [4–8]. The Women's Health Initiative showed that hormone therapy was associated with a 27% relative increase in invasive breast cancer (38 *vs.* 30 cases per 10,000 patient-years) [9], a statistic similar to the 35% increase found in a meta-analysis of 51 observational studies [10]. A summary of 51 epidemiologic studies enrolling 161,116 women with breast cancer and on hormone therapy showed that breast cancer risk increased by 2.3% per year of hormone use (mostly estrogen use) compared with an increased risk of 2.8% per year of natural delay in the onset of menopause [10], suggesting that hormone use increases the risk of developing breast carcinoma and that this risk increases with the increasing duration of hormone use [11]. A review of 19 epidemiologic studies estimated the average breast cancer risk to be 1.18 (95% confidence interval, CI, 1.01–1.38) with current use of estrogen alone, and 1.70 (95% CI, 1.36–2.17) with current use of estrogen–progestin [12]. All these, if not the only, studies suggested that estrogen play an important role in the pathogenesis of breast cancer.

Estrogen and Estrogen Receptors

Classically, estrogen action at target sites around the body is mediated through related but distinct estrogen receptors (ERs) designated ERα and ERβ [13], which then bind as dimers to estrogen-response elements in the regulatory regions of the estrogen-responsive genes and associate with basal transcription factors, coactivators, and corepressors to alter gene expression [14], though recently much evidence has shown the other pathway, since the presence of specific high-affinity estrogen binding in non-nuclear subcellular fractions, including plasma membrane and mitochondria, implies that the ER could be located at these sites [15]. ERα and ERβ have 96% amino-acid identity in their DNA-binding domains, whereas there is only 53% homology in their ligand-binding domains; the latter accounts for differences in the responses of the two receptors to various ligands. For example, tamoxifen (Nolvadex; AstraZeneca, Wilmington, DE, USA) has been reported to be both an agonist and an antagonist for ERα, but only an antagonist for ERβ [3]. The recognition that tamoxifen and other selective estrogen receptor modulators (SERMs) have tissue-specific agonist–antagonist activity led to the realization that the classic model was incomplete and that estrogen action was more complex than had been thought [16,17]. The mechanisms of the tissue-selective, mixed agonist–antagonist action of SERMs, though still only partly understood, are gradually becoming clearer [18]. Most of the unique pharmacology of SERMs can be explained by three interactive mechanisms: differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential expression and binding to the ER of coregulator proteins [18].

Tamoxifen and Breast Cancer

The accumulating understanding of the mechanism of action of estrogen led ultimately to the design of antiestrogenic agents that work by virtue of their interaction with the ER [13]; these drugs have come to be known as SERMs. Tamoxifen, a SERM, emerged as the first antiestrogenic agent that is clinically applicable to breast cancer [18–37].

Efficacy of Tamoxifen on Breast Cancer

Results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial

Initially approved for the treatment of advanced breast cancer, tamoxifen was subsequently shown to reduce contralateral breast cancers by 30–50%, as a secondary endpoint in a series of adjuvant studies on early stage breast cancer [20–23]. Prominent among these was the NSABP B-14 trial of tamoxifen as adjuvant hormonal therapy following initial surgical/radiation treatment of women with localized ER-positive breast cancer and histologically negative axillary lymph nodes. Second cancers in the opposite breast were significantly reduced with tamoxifen versus placebo ($p = 0.007$). These observations of tamoxifen's ability to prevent second primary cancers in the contralateral breast, together with its estrogen-directed mechanism of action and its long half-life, suggested this agent to be a strong candidate for testing in breast cancer prevention in a cancer-free but high-risk population of women [24,25]. The following three randomized trials prospectively evaluated tamoxifen for breast cancer risk reduction [26–28]. The NSABP P-1 trial, Breast Cancer Prevention Trial (BCPT), was conducted by the NSABP and the National Cancer Institute from June 1992 to September 1997, during which time 13,388 women of 35 years of age or older, who were at increased risk of breast cancer, were randomized to either 5 years of tamoxifen (20 mg/day) or placebo [26]. The mean follow-up time was 47 months and the median time in the study was 54 months. During the 69 months of follow-up, 175 invasive breast cancers occurred in the placebo arm, as contrasted with 89 cancers in the tamoxifen

arm (equivalent to a cumulative incidence of 43.4 per 1,000 women given placebo and 22.0 per 1,000 women given tamoxifen), indicating a 49% reduction ($p < 0.00001$) in invasive breast cancers with tamoxifen, which led to the US Food and Drug Administration (FDA)'s approval of tamoxifen for breast cancer risk reduction in high-risk women [19]. The benefit of tamoxifen was also seen in the reduction of noninvasive breast cancers, with 69 in the placebo arm versus 35 in the tamoxifen arm, representing a 50% reduction owing to tamoxifen [29].

Results of the International Breast Cancer Intervention Study I (IBIS-I) trial

The IBIS-I trial showed a 25% reduction in invasive breast cancer with tamoxifen [30]. A meta-analysis of these studies [26–28], of which the NSABP P-1 trial contributed the largest proportion of entered patients, identified a significant 42% reduction in relative risk of developing breast cancer associated with tamoxifen use (relative risk, RR, 0.58; 95% CI, 0.38–0.84) [31]. The absolute risk reduction in these trials was less than 2 per 100 women given tamoxifen for 5 years [33–35]. The absolute risk reduction anticipated in an individual woman depends on her calculated breast cancer risk, with women at higher risk having greater potential benefit. For instance, the average 65-year-old woman with no family history of breast cancer has an anticipated risk reduction of 1 per 100, while a 50-year-old woman with two affected siblings and two prior biopsies but no germline mutation has an anticipated risk reduction of approximately 2.5 per 100. In an overview of 37,000 women with breast cancer from 55 trials of adjuvant therapy, the proportional reduction in recurrence was 47% after 5 years of treatment with tamoxifen and the proportional reduction in mortality was 26% after 10 years [32]. The absolute improvements in 10-year survival were 10.9% in node-positive and 5.6% in node-negative breast cancer. Women with ER-negative disease had little, if any, benefit [33].

Rationale of 5-Year Tamoxifen Use for Preventing Breast Cancer

The question then arises as to how long tamoxifen should be taken. The best results appear to be achieved after 5 years of treatment; thereafter, beneficial effects decrease and toxicity increases [34–37], although the optimal duration of administration is still under investigation [18]. Tamoxifen is mainly cytostatic and slows the proliferation of breast cancer cells by inhibiting their progression from the G1 phase of the cell cycle, but it also induces apoptosis *in vitro* and thus may possess cytocidal properties *in vivo* [29,35]. However, tamoxifen-stimulated breast cancer has been well recognized and provides the rationale for stopping tamoxifen therapy at 5 years [36].

Potential Adverse Events of Tamoxifen

Tamoxifen was also reported to reduce the risk of fractures, though not significantly. However, it was associated with significantly increased risks of endometrial cancer, stroke, pulmonary emboli, deep vein thrombosis, and cataracts, primarily in women 50 years of age or older [26,38–44]. Tamoxifen increased the risk of stroke (RR, 1.75; 95% CI, 0.98–3.20), deep vein thromboembolism (RR, 1.71; 95% CI, 0.85–3.58), and pulmonary emboli (RR, 3.19; 95% CI, 1.12– 11.15), although only the risk of pulmonary emboli reached statistical significance [26]. The incidence of pulmonary emboli was increased from 0.31 per 1,000 women per year to 1 per 1,000 women per year [40]. The incidence of endometrial carcinoma was increased fourfold, but no deaths due to endometrial carcinoma occurred in the tamoxifen arm. Endometrial cancer occurred in 3.05 per 1,000 women per year taking tamoxifen [40]. Bernstein et al examined the effect of the known risk factors for endometrial carcinoma, obesity and previous estrogen use in women taking tamoxifen; they found no increase in endometrial cancer with tamoxifen use in the absence of these factors [41]. Tamoxifen was also noted to increase the risk of cataract surgery from 3 per 1,000 to 4.72 per 1,000 per year [26].

Suggestion of the Use of Tamoxifen for Preventing Breast Cancer

No trial has shown an improvement in survival with tamoxifen; in fact, there were slightly more deaths in the tamoxifen group in the IBIS-I trial owing to an excess of thromboembolic events [30,31]. A recent technology assessment by the American Society of Clinical Oncology concluded that tamoxifen's favorable effect on the risk of breast cancer must be weighed against its potential side effects in individual women, concluding that: (1) for women with a 5-year projected breast cancer risk of ≥ 1.66%, tamoxifen (at 20 mg/day for 5 years) may be offered to reduce risk; (2) consideration of tamoxifen is appropriate for the goal of lowering the short-term risk of developing breast cancer; (3) risk/benefit models suggest that the greatest clinical

benefit with the least side effects are derived from the use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk; and (4) data do not as yet suggest that tamoxifen provides an overall health benefit or increases survival [29].

Comments on Tamoxifen Use in Preventing Breast Cancer

With no other competition, tamoxifen became the "gold standard" and established the principles of tumor targeting and identified the appropriate treatment strategy to aid survivorship in breast cancer patients [1]. A 5-year adjuvant tamoxifen enhances disease-free survival, and there was a 50% decrease in recurrences observed in ER-positive patients 15 years after diagnosis. Adjuvant tamoxifen does not provide an increase in disease-free or overall survival in ER-negative breast cancer. Five years of adjuvant tamoxifen alone is effective in premenopausal women with ER. The benefits of tamoxifen in lives saved from breast cancer far outweigh concerns about an increased incidence of endometrial cancer in postmenopausal women. Tamoxifen does not increase the incidence of second cancers other than endometrial cancer. No non-cancer-related overall survival advantage was noted with tamoxifen when given as adjuvant therapy. Therefore, in the management of breast cancer, translational research with tamoxifen targeting the ER with an appropriate duration (5 years) of adjuvant therapy has demonstrated a contribution to the falling national death rates from breast cancer. However, extensive evaluation of tamoxifen treatment has revealed small but significant side effects, such as endometrial cancer, blood clots and the development of acquired resistance. The solution was to develop drugs, and fortunately, an exploration of the endocrine pharmacology of tamoxifen and related nonsteroidal antiestrogens (e.g. raloxifene) resulted in the laboratory recognition of selective ER modulation and the translation of the concept of using raloxifene for the prevention of osteoporosis and breast cancer. Since tamoxifen and raloxifene are both SERMs which can block estrogen-mediated breast cancer growth and development and also maintain bone mineral density in postmenopausal women and lower circulating cholesterol, the following section will discuss the significant and continuing value of the other SERM, raloxifene, which has fulfilled its promise as an appropriate medicine that targets specific populations for the prevention of breast cancer [45,46]. The main differences seen between tamoxifen and raloxifene in relation to their estrogenic and antiestrogenic properties relates to the ability of the raloxifene side-chain to interact closely with amino acid 351, thus further influencing the function of the ER [1].

Efficacy of Raloxifene on Breast Cancer

Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial

Data on raloxifene's influence on breast cancer come almost exclusively from the MORE study, in which 7,705 postmenopausal women with osteoporosis were randomized to raloxifene at 60 or 120 mg/day (5,129 women) or placebo (2,576 women) for 4 years and monitored for breast cancer development from the safety database [19,29,46–51]. The most important MORE outcome from a cancer perspective is the decrease in breast cancer incidence that was observed as a secondary endpoint in participants taking raloxifene [47,49,50]. During the 40 months of follow-up, a total of 54 cases of breast cancer were confirmed, 22 (0.42%) in the raloxifene group and 32 (1.24%) in the placebo group, with a risk reduction of 65% (RR, 0.35) [47]. Among the 40 invasive breast cancers, the risk reduction of 76% (RR, 0.24; 27 with the placebo *vs.* 13 with raloxifene) was even more striking. The risk reduction was similar for both doses of raloxifene and was limited to ER-positive tumors (RR, 0.10), with no risk reduction occurring in ER-negative tumors (RR, 0.88) [47]. After 48 months, other results from the MORE study on breast cancers were reported, including 77 verified breast cancers of which 59 were invasive [49]. Raloxifene use (combining both dosage arms) continues to be associated with a significant reduction in relative risk of developing invasive breast cancers (RR, 0.28; 95% CI, 0.09–0.30; $p < 0.001$), especially ER-positive breast cancers [49]. The absolute reduction in risk of developing breast cancer was 1.4 per 100 women given raloxifene for 5 years' duration [50]. Continued follow-up of MORE participants using additional annual mammograms at 4 years showed an ongoing breast cancer risk reduction in postmenopausal women treated with raloxifene [50]. Among 61 invasive breast cancers reported as of November 1, 1999, the risk reduction was 72% (RR, 0.28), with 39 (1.51%) using placebo versus 22 (0.43%) using raloxifene. It was more striking to find that the risk reduction was 84% (RR, 0.16) of the ER-positive breast cancers, with 31 (1.20%) in the placebo group versus 10 (0.20%) in the raloxifene group. No difference between the treatment groups was observed in the incidence of

ER-negative tumors. These observations are consistent with a model in which raloxifene antagonized estrogen activity at the ER in the breast [52].

Results from the Continuing Outcomes Relevant to Evista (CORE) trial

The primary objective of the CORE trial was to investigate the effect of additional 4 years of raloxifene (at 60 mg/day) on the incidence of invasive breast cancer in postmenopausal women with osteoporosis [53]. During the 4 years of the CORE trial, 61 cases of breast cancer (30 using placebo *vs.* 31 using raloxifene) were reported and confirmed by adjudication. Of the 61 breast cancer cases, 52 (28 using placebo *vs.* 24 using raloxifene) were invasive breast cancers, with a 59% reduction in the incidence of invasive breast cancer in those using raloxifene versus placebo (2.1 *vs.* 5.2 cases per 1,000 woman-years; hazard ratio, HR, 0.41; 95% CI, 0.24–0.71; $p < 0.001$). Of the 46 invasive breast cancer cases, 36 cases (78%) were ER-positive, with a 66% reduction in the incidence of invasive ER-positive breast cancers with raloxifene use versus placebo (1.3 *vs.* 3.9 cases per 1,000 woman-years; HR, 0.34; 95% CI, 0.18–0.66; $p < 0.001$). However, there was no difference in the incidence rates of invasive ER-negative breast cancer between the raloxifene group and the placebo group (0.55 *vs.* 0.61 per 1,000 woman-years; HR, 1.13; 95% CI, 0.29–4.35; $p = 0.86$). In addition, the incidence of noninvasive breast cancer was also not statistically and significantly different between the raloxifene and placebo groups (HR, 1.78; 95% CI, 0.37–8.61; $p = 0.47$). The overall incidence of breast cancer, regardless of invasiveness, was reduced by 50% in the raloxifene group compared with the placebo group (2.7 *vs.* 5.5 cases per 1,000 woman-years; HR, 0.50; 95% CI, 0.30–0.82; $p < 0.001$) [53].

Results from the MORE and CORE trials

For the 7,705 MORE participants, the total number of reported breast cancers confirmed by adjudication from randomization in the MORE trial to the end of their participation in either the MORE or CORE trial was 121 (56 cancers in the raloxifene group and 65 cancers in the placebo group) [53]. During the 8 years of the MORE and CORE trials, 40 invasive breast cancers were reported in the raloxifene group and 58 in the placebo group, with a 66% reduction in the incidence of invasive breast cancer with raloxifene use versus placebo (1.4 *vs.* 4.2 cases per 1,000 woman-years; HR, 0.34; 95% CI, 0.22–0.50; $p < 0.001$). Of the 88 invasive breast cancer cases, 66 (75%) were ER-positive, with a 76% reduction in the incidence of invasive ER-positive breast cancers with raloxifene use versus placebo (0.8 *vs.* 3.2 cases per 1,000 woman-years; HR, 0.24; 95% CI, 0.15–0.40; $p < 0.001$). There was no difference in the incidence rates of invasive ER-negative breast cancer between the raloxifene group and the placebo group (0.53 *vs.* 0.51 per 1,000 woman-years; HR, 1.06; 95% CI, 0.43–2.59; $p = 0.90$). The incidence of noninvasive breast cancer was also not statistically and significantly different between the raloxifene and placebo groups (16 *vs.* 7 cases; HR, 1.12; 95% CI, 0.46–2.73; $p = 0.80$). The overall incidence of breast cancer, regardless of invasiveness, was reduced by 58% in the raloxifene group compared with the placebo group (1.96 *vs.* 4.9 cases per 1,000 woman-years; HR, 0.42; 95% CI, 0.29–0.60; $p = 0.001$) [53].

Results from the Raloxifene Use for The Heart (RUTH) trial

The two primary objectives of the RUTH trial were to determine the effect of raloxifene as compared with placebo on the incidence of coronary events (i.e. death from coronary causes; nonfatal, including silent, myocardial infarction; or hospitalization for an acute coronary syndrome other than myocardial infarction) and invasive breast cancer [54]. Raloxifene reduced the incidence of the primary outcome of invasive breast cancer (HR, 0.56; 95% CI, 0.38–0.83; $p = 0.003$), principally because of a reduction in ER-positive invasive breast cancer. The absolute risk reduction per 1,000 women treated with raloxifene for 1 year was 1.2 cases of invasive breast cancer and 1.2 cases of ER-positive invasive breast cancer. The results of the as-treated analysis for invasive breast cancer were similar (HR, 0.61; 95% CI, 0.39–0.95; $p = 0.03$). There was no significant difference between treatment groups in the incidence of ER-negative invasive breast cancer.

Comparison of Tamoxifen and Raloxifene for Breast Cancer Prevention

As mentioned above, tamoxifen, the first clinically available SERM, was developed in 1966 and became the first drug to be approved by FDA for use as a preventive agent against cancer in 1998, when it was shown to reduce the incidence of breast cancer in women at increased risk for the disease by 49% in the BCPT [26]. With no other competition, tamoxifen has remained the antihormonal therapy of choice for the treatment of ER-positive breast cancer for the last 30 years. However, although adjuvant tamoxifen produces profound increases in disease-free and overall survival in patients with ER-positive breast cancer, concerns about drug resistance, blood clots and endometrial cancer

have resulted in a change to the use of aromatase inhibitors for the treatment of postmenopausal women [46]. Nevertheless, tamoxifen remains the antihormonal treatment of choice for premenopausal women with ER-positive breast cancer and for risk reduction in premenopausal women who are at high risk for developing breast cancer [46]. However, tamoxifen has presented with many potential adverse events, some of which have contributed to significant morbidity and mortality. Significant improvement in breast cancer prevention with drug modification is possible if other competing drugs, which show fewer incidences of adverse events without compromising the therapeutic effect for breast cancer prevention, are welcome. Based on the CORE, MORE and RUTH studies [47,49,52–54], the efficacy of raloxifene in breast cancer prevention is clear. Therefore, the question is raised regarding the possibility of using raloxifene in place of tamoxifen. Results from the 20,000-women Study of Tamoxifen and Raloxifene (STAR) were released in April 2006 [55,56], more than a year ahead of schedule. Raloxifene's greatest advantage appears to be fewer serious side effects, including uterine cancer, blood clots and cataracts, without compromising the breast cancer chemoprevention strategy. Some important data from the STAR include: (1) the similar incidence of invasive breast cancer in both groups (163 cases in the tamoxifen group *vs.* 168 cases in the raloxifene group, 4.30 per 1,000 *vs.* 4.41 per 1,000; RR, 1.02; 95% CI, 0.82–1.28); (2) fewer incidences of thromboembolic events (141 cases in the tamoxifen group *vs.* 100 cases in the raloxifene group, 3.71 per 1,000 *vs.* 2.61 per 1,000; RR, 0.70; 95% CI, 0.54–0.91); (3) fewer cataracts (394 cases in the tamoxifen group *vs.* 313 cases in the raloxifene group, 12.30 per 1,000 *vs.* 9.72 per 1,000; RR, 0.79; 95% CI, 0.68–0.92) and cataract surgeries (260 cases in the tamoxifen group *vs.* 215 cases in the raloxifene group, 8.03 per 1,000 *vs.* 6.62 per 1,000; RR, 0.82; 95% CI, 0.68–0.99); and (4) fewer endometrial hyperplasia events with atypia or without atypia (84 cases in the tamoxifen group *vs.* 14 cases in the raloxifene group, 4.69 per 1,000 *vs.* 0.76 per 1,000; RR, 0.16; 95% CI, 0.09–0.29) and hysterectomy (244 cases in the tamoxifen group *vs.* 111 cases in the raloxifene group, 13.57 per 1,000 *vs.* 6.04 per 1,000; RR, 0.44; 95% CI, 0.35–0.56) in the women taking raloxifene. Although the results did not achieve statistical significance, they are interesting. There were fewer cases of noninvasive breast cancer in the tamoxifen group than in the raloxifene group (57 *vs.* 80 cases, 1.51 *vs.* 2.11 per 1,000; RR, 1.40; 95% CI, 0.98–2.00), but there were more cases of uterine cancer in the tamoxifen group than in the raloxifene group (36 *vs.* 23 cases, 2.00 *vs.* 1.25 per 1,000; RR, 0.62; 95% CI, 0.35–1.08). In addition, there were no significant differences between tamoxifen and raloxifene in patient-reported outcomes for physical and mental health or depressive symptoms, and scores on all of these measures were well within the normal ranges for healthy women of this age [55], although women in the tamoxifen group reported having better sexual function (age-adjusted repeated measure odds ratio, 1.22%; 95% CI, 1.01–1.46), and less mean symptom severity of 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; $p < 0.001$). However, women in the raloxifene group reported benefits in relation to gynecologic problems, vasomotor symptoms, leg cramps and bladder control, because they had greater mean symptom severity 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; $p < 0.001$) [56].

Conclusion

According to the concept of tamoxifen for chemoprevention of invasive breast cancer and the long-term tolerance of the many adverse events with tamoxifen use, raloxifene is a significantly better alternative since the STAR trial clearly demonstrated the superiority of raloxifene over tamoxifen not only for the equal efficacy in the prevention of invasive breast cancer but also for fewer serious adverse events, including thromboembolism. Since raloxifene is approved by the FDA for the prevention of breast cancer, primary care physicians may be more willing, given their experience with raloxifene, to prescribe it for breast cancer chemoprevention than to prescribe tamoxifen.

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