# To Switch or Not to Switch: Should the Study of Tamoxifen and Raloxifene (STAR) Trial Alter Our Decision?

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We appreciate the interest of Dr Yin on the issue of tamoxifen and breast cancer [1] that we recently presented [2]. This intersection of the widely used tamoxifen and a relatively common cancer of women presents a vexing clinical scenario: How should positive estrogen receptor (ER) breast cancer be managed? Dr Yin introduces another variable into the question with our comment about reconsideration of tamoxifen use for breast cancer [2]. We are happy to provide further evidence to address this. We never overlooked the possible unwanted events of raloxifene use. We do not know why the author should emphasize this, because the author wrote that "the use of raloxifene is not without side effects" [1]. In addition, the author cited the article by Premkumar and colleagues to show the occurrence of ovarian simulation and endometrial polyps in premenopausal women who were treated with raloxifene [3]. Furthermore, the author cited the RUTH (Raloxifene Use for The Heart) trial data to show that there was a small increase in stroke mortality [4]. If the author had considered the effects of other selective estrogen receptor modulators (SERMs) including clomiphene and tamoxifen, these findings would not be so surprising.

In fact, the link between sex hormones and breast cancer growth and development has been recognized for more than a century [5]. Both endogenous and exogenous sex hormones have been implicated in the pathogenesis of breast cancer. Estrogen is mediated through related but distinct ERs, designated ERα and ERβ, to alter gene expression [6–9]. An accumulated understanding of the mechanism of action of estrogen ultimately led to the design of antiestrogenic agents that work by virtue of their interaction with the ER; these drugs have come to be known as SERMs [10]. Tamoxifen, a SERM, emerged as the first antiestrogenic agent that was clinically applicable to breast cancer [2].

We completely agree with Dr Yin's view that the use of tamoxifen to prevent breast cancer and decrease recurrence is not controversial [1]. In fact, in the review of the role of SERMs in breast cancer, we directly pointed out the important value of tamoxifen in treating breast cancer [10]. We wrote that tamoxifen has become the "gold standard", and established the principles of tumor targeting and identified the appropriate treatment strategy to aid survival in breast cancer patients, with enhancement of disease-free survival, and a 50% decrease in recurrence observed in ER-positive patients 15 years after diagnosis [10].

However, due to the many adverse events with the use of tamoxifen, some of which have contributed to significant morbidity and mortality [2], drug modification, which yields a lower incidence 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 has shown that raloxifene not only decreases the incidence of osteoporosis and related fractures, but also offers benefits in breast cancer prevention. The results of the Study of Tamoxifen and Raloxifene (STAR) trial showed the superiority of raloxifene over tamoxifen, not only in its equal efficacy in the prevention of invasive breast cancer but also in having fewer serious adverse events [11]. Some important data from STAR include the similar incidence of invasive breast cancer in both groups (163 cases in the tamoxifen group and 168 in the raloxifene group: 4.30 per 1,000 *vs.* 4.41 per 1,000; relative risk, RR, 1.02; 95% confidence interval, CI, 0.82–1.28); and a lower incidence of thromboembolic events (141 cases in the tamoxifen group and 100 in the raloxifene group: 3.71 per 1,000 *vs.* 2.61 per 1,000; RR, 0.70; 95% CI, 0.54–0.91); fewer cataracts (394 cases in the tamoxifen group and 313 in the raloxifene

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group: 12.30 per 1,000 *vs.* 9.72 per 1,000; RR, 0.79; 95% CI, 0.68–0.92), fewer cataract surgeries (260 cases in the tamoxifen group and 215 in the raloxifene group: 8.03 per 1,000 *vs.* 6.62 per 1,000; RR, 0.82; 95% CI, 0.68–0.99); fewer endometrial hyperplasia events with atypia or without atypia (84 cases in the tamoxifen group and 14 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 fewer hysterectomies (244 cases in the tamoxifen group and 111 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 they did not achieve statistical significance, the data are interesting, nonetheless. There were fewer cases of noninvasive breast cancer in the tamoxifen group (57 cases) than in the raloxifene group (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 (36 cases) than in the raloxifene group (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 [11], although women in the tamoxifen group reported having better sexual functioning (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, and women in the tamoxifen group 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; $p < 0.001$) [12]. In terms of side effects, raloxifene is superior to tamoxifen. Of course, we never suggested that raloxifene could replace tamoxifen in patients who had breast cancer. Before reaching the above conclusion, therapeutic efficacy should be evaluated. Unfortunately, no answer is available for this yet.

Finally, other new adjuvant hormone therapies for breast cancer, such as aromatase inhibitors (AIs) or even ER antagonists, have been available for the management of breast cancer. For example, a recent publication (Arimidex, Tamoxifen, Alone or in Combination trial: ATAC trial) [13] demonstrated the superiority of anastrozole to tamoxifen, by showing its long-term safety outcomes and establishing clearly its long-term efficacy compared with tamoxifen, as an initial adjuvant treatment for postmenopausal women with hormone-sensitive and early breast cancer, and providing statistically significant evidence of it having a longer carryover effect after 5 years of adjuvant treatment [13]. However, regarding the same issue, the editorial comment was that we still need to pay attention to the long-term follow-up findings, not only of this trial but also of other trials containing AIs, because an advantage in terms of overall survival has not yet been confirmed [14]. In addition, the toxicities of the AIs are generally acceptable, with fewer endometrial cancers, gynecologic complaints and thromboembolic events, but there are more bone fractures and arthralgias compared with tamoxifen alone [15].

In summary, with no other competition, tamoxifen became the "gold standard" and established the principles of tumor targeting and identifying an appropriate treatment strategy to aid survival in breast cancer patients [16]. Adjuvant 5-year tamoxifen enhanced disease-free survival, and there was a 50% decrease in recurrence 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, endometrial cancer excepted. 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 to use of raloxifene for the prevention of osteoporosis and breast cancer. 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 significant and continuing value of raloxifene is that it has fulfilled its promise as an appropriate medicine that targets specific populations for the prevention of breast cancer [17,18]. The main differences

seen between tamoxifen and raloxifene in relation to their estrogenic and antiestrogenic properties relate to the ability of the raloxifene side-chain to interact closely with amino acid 351, thus further influencing the function of the ER [16].

Raloxifene is now approved for use as prophylaxis to diminish the risk of breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. Clinical trial data submitted to the Food and Drug Administration (FDA) showed that the drug was effective as prophylaxis and that its effects were comparable to those of tamoxifen, the only drug previously approved for the prevention of breast cancer [19]. Like tamoxifen, raloxifene posed a risk of serious adverse effects including blood clots and stroke, but a lower risk of uterine malignancies. Health care practitioners should note that the expected benefits of raloxifene and the risks posed in its use should be carefully evaluated for each patient, and that the drug does not prevent breast cancer completely [19]. Of course, this limitation is also found in the use of tamoxifen.

Based on the concept of using tamoxifen in the "chemoprevention" of invasive breast cancer and the long-term tolerance of many of the adverse events of tamoxifen, raloxifene is a better alternative choice. Significantly, the STAR trial clearly demonstrated the superiority of raloxifene to tamoxifen not only in its equal efficacy in the prevention of invasive breast cancer but also in a lower incidence of serious adverse events, particularly and most importantly, thromboembolism. However, in patients with breast cancer, the superiority of raloxifene to tamoxifen in terms of decreasing recurrence or prolonging disease-free survival has not been proved as yet. Therefore, there should be caution in choosing raloxifene, since neither the FDA nor clinical trials support this use.

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