The Role of Selective Estrogen Receptor Modulators in the Prevention of Breast Cancer: Comparison of the Clinical Trials

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Abstract

The role of estrogen in the development of breast cancer is well recognized, and the use of selective estrogen receptor modulators (SERMs) to reduce breast cancer risk continues to be evaluated. Tamoxifen is the only SERM approved for the reduction of breast cancer incidence in women at high risk. This approval was based on results from the Breast Cancer Prevention Trial. Although initial results from the Royal Marsden Hospital tamoxifen trial and Italian Tamoxifen Prevention Study did not show a similar overall effect of tamoxifen, recent updates from these two trials and initial results from the International Breast Cancer Intervention Study are consistent with a risk reduction effect of tamoxifen for estrogen-receptor-positive breast cancer.

Raloxifene, approved for the prevention and treatment of postmenopausal osteoporosis, is another SERM being evaluated for breast cancer risk reduction. The recently completed Continuing Outcomes Relevant to Evista® trial and the Raloxifene Use for The Heart trial, have breast cancer risk reduction as

Learning Objectives

After completing this course, the reader will be able to:

1. Discuss the tamoxifen breast cancer prevention trials and the general risk-benefit profile of tamoxifen for breast cancer prevention.

2. Compare and contrast the tamoxifen breast cancer chemoprevention trials with the ongoing raloxifene chemoprevention trials in terms of study design and baseline patient characteristics.

3. Describe the limitations of the completed and ongoing tamoxifen and raloxifene breast cancer chemoprevention trials and the areas for future breast cancer chemoprevention research.

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a primary end point. A third, ongoing trial, the Study of Tamoxifen and Raloxifene trial, is evaluating the relative efficacy and adverse event profile of these two agents in a population at high risk. The study populations of these raloxifene breast cancer prevention trials and the four tamoxifen prevention trials are quite diverse in terms of breast cancer risk. Completion of these trials will provide important information about the occurrence of invasive breast cancer in postmenopausal women and the efficacy of raloxifene for breast cancer risk reduction. The Oncologist 2004;9:116-125

INTRODUCTION

Breast cancer remains a major health problem as incidence rates continue to increase despite recent improvements in the mortality rate. In the U.S., breast cancer has the highest incidence (31%) and second highest mortality rate (15%) of all cancers among women. It is estimated that approximately 211,330 new cases of, and 39,800 deaths from, breast cancer will be reported among U.S. women for 2003 [1]. Worldwide, approximately 1 million new cases of, and over 370,000 deaths from, breast cancer were estimated for the year 2000 [2].

Clinical trials evaluating drugs for the treatment of breast cancer have been ongoing for many decades and have resulted in the development of several effective drugs that can reduce the risk of recurrence and death from this disease. While research to find new drugs to treat breast cancer continues, the focus of breast cancer research over the last decade has expanded to include the evaluation of drugs to reduce the risk of initial clinical development of breast cancer. Selective estrogen receptor modulators (SERMs) are a group of agents being studied for their breast cancer risk reduction effects. SERMs are non-steroidal compounds that elicit estrogen agonist effects in some tissues, such as bone, and estrogen antagonist effects in others, such as breast, through specific, high-affinity binding to the estrogen receptor (ER). Tamoxifen, a triphenylethylene SERM approved for the treatment of breast cancer, is the only agent approved to reduce the incidence of breast cancer in women at high risk for the disease [3]. Raloxifene, a benzothiophene SERM that is chemically distinct from tamoxifen and estradiol, is approved for the treatment and prevention of osteoporosis in postmenopausal women [4] and is currently being studied for breast cancer risk reduction effects in the Continuing Outcomes Relevant to Evista® (CORE), Raloxifene Use for The Heart (RUTH), and Study of Tamoxifen and Raloxifene (STAR) clinical trials. In light of the continuing evaluation of SERMs as therapy to reduce breast cancer risk, it is appropriate to consider the nature and scientific basis for these trials. The design of the RUTH trial [5] and the baseline characteristics of the RUTH participants [6] have been published previously. This paper presents an overview of the CORE trial design and the baseline characteristics of CORE participants and updates the baseline characteristics of those currently enrolled in the STAR trial. In addition, the baseline characteristics of CORE and STAR participants are compared with those of the RUTH trial participants, and the raloxifene breast cancer prevention trials are discussed in relation to the four tamoxifen breast cancer prevention trials conducted in the U.S. and Europe.

ESTROGEN, SERMS, AND BREAST CANCER RISK

The role of estrogen in the pathogenesis of breast cancer is widely recognized [7]. High serum estradiol levels [8-11] and administration of exogenous estrogen to postmenopausal women [12-14] have been associated with a greater breast cancer risk in postmenopausal women. In addition, surrogate clinical markers relating to endogenous hormonal exposure, such as older age at first full-term pregnancy [15-18], early menarche [15], and late menopause [15], are associated with a greater risk for breast cancer. Consistent with the association of high endogenous estrogen levels and greater breast cancer risk, a reduction in endogenous estrogen levels, such as through bilateral oophorectomy, has been shown to decrease breast cancer risk in premenopausal women [19, 20].

Breast cancer risk may also be associated with nonreproductive factors that may be related to estrogen exposure. Obese postmenopausal women tend to have a higher breast cancer risk, which is thought to be related to higher serum concentrations of bioavailable estrogen [21]. Bone mineral density has been shown to be a marker for estrogen exposure with high endogenous estrogen concentrations being associated with greater bone mineral density in elderly women [22]. Postmenopausal women with higher bone mineral densities have been shown to have a greater incidence of breast cancer [22, 23].

Although estrogen is beneficial in reducing some symptoms of menopause, the association between estrogen and greater breast cancer risk is a concern for postmenopausal women. Because the association between estrogen and breast cancer risk is complex, the identification of an individual’s specific modifiable risk factors is difficult. As a result, antagonizing the action of estrogen in breast tissue represents a logical approach to chemoprevention of breast cancer.

While tamoxifen and raloxifene both have estrogen antagonist effects in the breast, their effects on the uterus differ. The competitive antagonist effect of tamoxifen on
the estrogen receptor in the breast is thought to be the mechanism responsible for its breast cancer prevention effects. A lower breast cancer incidence in postmenopausal women receiving raloxifene was observed in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, an osteoporosis treatment trial conducted in postmenopausal women that included breast cancer risk reduction as a pre-defined secondary end point. The difference between raloxifene and tamoxifen in their uterine effects may have important clinical implications. Tamoxifen has estrogen agonist properties in the uterus and increases the risk of endometrial cancer, with the higher risk occurring predominantly in women aged 50 years or older [24]. Unlike tamoxifen, raloxifene has estrogen antagonist effects on the uterus and does not increase the risk for endometrial cancer [25]. This different risk-benefit profile of raloxifene has led to continuing interest in evaluating its efficacy in breast cancer risk reduction. The four tamoxifen breast cancer prevention trials and the ongoing raloxifene trials are discussed in the following sections.

**Tamoxifen Breast Cancer Prevention Trials**

Observations that long-term tamoxifen therapy reduced the risk of contralateral breast cancer in women with primary breast cancer fueled an interest in exploring the effect of tamoxifen in preventing primary breast cancer [26, 27]. The tamoxifen breast cancer prevention trials were randomized, double-blinded, placebo-controlled trials that examined the effect of tamoxifen, 20 mg daily for at least 5 years, on the incidence of breast cancer. The design, results, and patient characteristics for each of these studies are compared in Table 1 and Table 2. The Breast Cancer Prevention Trial (BCPT), conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), is the largest of the four trials and evaluated the effect of tamoxifen on the incidence of invasive breast cancer in women at high risk [24]. Women were considered at high risk for invasive breast cancer if they were 60 years of age or older, were between the ages of 35 and 59 years with a 5-year predicted risk for breast cancer of at least 1.66% based on the Gail model [28], or had a history of lobular carcinoma in situ (LCIS). Approximately 60% of the women participating in the BCPT were postmenopausal, and the overall average 5-year predicted breast cancer risk of the women was 3.6% at baseline. Compared with placebo, tamoxifen resulted in a significantly lower risk for noninvasive breast cancer by 50% and a significantly lower risk for invasive breast cancer by 49% after 4.5 years of follow-up [24]. There was substantial evidence indicating a consistency of treatment effect across age and level of breast cancer risk. When considering age, the estimate of invasive breast cancer risk reduction was 44% in women 49 years of age or younger and 55% in women 60 years of age or older. When considering categories of predicted breast cancer risk, the estimates of

<table>
<thead>
<tr>
<th>Study design and results of the tamoxifen and raloxifene breast cancer prevention trials</th>
<th>MORE with CORE follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>R, DB, PC</td>
</tr>
<tr>
<td>Treatment groups</td>
<td>Tamoxifen, 20 mg, n = 6,681; placebo n = 6,707</td>
</tr>
<tr>
<td>Planned length (years) of treatment</td>
<td>5</td>
</tr>
<tr>
<td>Use of concomitant estrogen</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Invasive breast cancer cases</td>
<td>264</td>
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</tbody>
</table>

*Represents total breast cancer cases; invasive status not reported.

Abbreviations: DB = double-blind; HT = hormone therapy; PC = placebo-controlled; NR = not reported; R = randomized.
invasive breast cancer risk reduction ranged from 32%-66%. Perhaps the most important observation from the BCPT, which supported the hypothesized biological mechanism of action for SERMs, was the finding that tamoxifen resulted in a 69% lower occurrence of invasive, ER-positive breast cancers but did not significantly affect the occurrence of ER-negative cancers.

The Italian Tamoxifen Prevention Study compared tamoxifen with placebo in women who had undergone a hysterectomy for reasons other than cancer [29]. The study population was composed of women aged 35-70 thought to be at either normal risk (hysterectomized without oophorectomy, 26%) or low risk for breast cancer (hysterectomized with bilateral oophorectomy before menopause, 48%). After a median follow-up of 81.2 months, there was no difference in the overall incidence of breast cancer cases between the tamoxifen and placebo groups (34 versus 45, respectively) [30]. However, when women in that study were retrospectively categorized as being at high or low risk for ER-positive breast cancer on the basis of height, age at menarche, parity, age at first full-term pregnancy, and oophorectomy status [31], tamoxifen treatment resulted in a significantly lower incidence of breast cancer (3 cases in the tamoxifen group versus 15 in the placebo group; \( p = 0.003 \)) in the high-risk group but had no effect in the low-risk group (31 cases in the tamoxifen group versus 30 in the placebo group; \( p = 0.89 \)) [31]. The lower breast cancer incidence among high-risk women receiving tamoxifen was statistically significant for ER-positive tumors (1 case in the tamoxifen group versus 11 in the placebo group; \( p = 0.002 \)) but not for ER-negative tumors (\( p = 0.39 \)) [31].

The Royal Marsden Hospital (RMH) trial was a pilot study that examined the effect of tamoxifen on breast cancer incidence in healthy premenopausal and postmenopausal women at high risk for breast cancer [32, 33]. In contrast to the high-risk population studied in the BCPT, which was based primarily on the Gail model, the high-risk population for the RMH study was comprised of women (30-70 years of age) with a family history of breast cancer. Premenopausal women taking oral contraceptives were not eligible for the study, but postmenopausal women taking oral hormone-replacement therapy were eligible without having to discontinue therapy. After approximately 12,200 woman-years of follow-up, 137 total cases of breast cancer (62 in the tamoxifen group and 75 in the placebo group) were diagnosed [33]. Approximately 86% of those cases were invasive breast cancer and 55% were invasive ER-positive breast cancer. Fewer invasive breast cancers and fewer ER-positive breast cancers (54 and 31, respectively) were diagnosed in women receiving tamoxifen than in women receiving placebo (64 and 44, respectively) [33].

The International Breast Cancer Intervention Study (IBIS-I) compared the effect of tamoxifen with that of placebo
on the frequency of breast cancer, including ductal carcinoma in situ [34]. Women aged 35-70 years having at least a twofold higher relative risk for breast cancer were eligible for enrollment. After a median follow-up of 50 months, 170 breast cancers (149 invasive and 21 noninvasive) were diagnosed. Compared with placebo, the overall risk for breast cancer was 32% lower (95% confidence interval [CI] = 8%-50%, \( p = 0.013 \)) in the tamoxifen group. This lower risk in the tamoxifen group was observed for invasive (25% lower) and noninvasive (65% lower) disease and was not affected by age, degree of risk, or prior or concomitant use of hormone-replacement therapy. There was a 31% lower risk for ER-positive invasive breast cancer in the tamoxifen group with no effect on risk for ER-negative invasive disease being observed.

Of the four tamoxifen breast cancer prevention trials, only the BCPT and IBIS-I trials reported a statistically significant overall efficacy of tamoxifen for breast cancer prevention. The RMH and Italian trials did not show a statistically significant overall risk reduction effect of tamoxifen, but a trend toward a lower risk in the tamoxifen group was observed in both trials. These trials differed in terms of sample size, eligibility requirements, breast cancer risk characteristics of the participants, and concomitant use of hormone therapy. Any of these key factors, or a combination thereof, may explain why no overall risk reduction was observed in the RMH and Italian trials. Since results from the tamoxifen prevention trials suggest that tamoxifen may only reduce the risk of ER-positive disease, the true power to show a statistically significant tamoxifen prevention effect should actually be based on the number of women who are likely to develop ER-positive cancer, not the total number of women in the study. Therefore, differences among the study populations in the proportion of women at risk for developing ER-positive breast cancer could alter the observed risk reduction effects of tamoxifen. As shown in Table 3, the placebo group incidence rates of all breast cancer and ER-positive breast cancer were lowest for the Italian trial. These observations suggest that the Italian trial study population may differ from the other study populations in the nature of their overall risk for breast cancer, including ER-positive breast cancer. Indeed, when the Italian trial population was retrospectively dichotomized into two groups of women, one presumed to be at high risk for ER-positive breast cancer and the other presumed to be at low risk, the high-risk group comprised only 13% of the total randomized population [31]. The study population of the RMH trial was chosen primarily on the basis of family history and, therefore, it might be assumed that a lower proportion of women in that trial were at risk for developing ER-positive breast cancer [32]. However, approximately 60% of all the breast cancers in the placebo group of the RMH trial were ER positive, and there was a trend toward a risk reduction effect of tamoxifen for ER-positive invasive breast cancers [33]. The lack of an overall risk reduction effect of tamoxifen in the RMH and Italian trials may also be due to smaller trial populations or simply to chance. Although it is not clear why an overall risk reduction effect of tamoxifen was not observed in the RMH and Italian trials, the results from all four tamoxifen breast cancer prevention trials, when considered together, are consistent with a pooled estimate of a 38% lower (95% CI = 28%-46%, \( p < 0.0001 \)) breast cancer incidence with tamoxifen administration [33].

In addition to evaluating the effect of tamoxifen on breast cancer incidence, the tamoxifen breast cancer prevention trials have provided relevant information regarding side effects. Of these trials, the BCPT specified several secondary end points a priori, including measures of osteoporotic fracture, endometrial cancer, venous thromboembolic events, stroke, and others, to provide the first unbiased estimates of the magnitude of these undesirable effects and a more complete assessment of the risk-benefit profile. In the BCPT, women receiving tamoxifen tended to have fewer hip, Colles’, and spinal fractures; however, these fracture results were not statistically significant. This was likely due to the

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Placebo group (n)</th>
<th>Incidence rate of all breast cancer, placebo group (yearly average per 1,000 woman years)</th>
<th>Incidence rate of ER-positive breast cancer, placebo group (yearly average per 1,000 woman years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCPT [24]</td>
<td>6,599</td>
<td>9.3</td>
<td>5.0(^a)</td>
</tr>
<tr>
<td>RMH [32, 33]</td>
<td>1,233</td>
<td>6.1</td>
<td>3.6(^a)</td>
</tr>
<tr>
<td>Italian [29, 30]</td>
<td>2,708</td>
<td>2.6</td>
<td>1.7(^a)</td>
</tr>
<tr>
<td>IBIS-I [34]</td>
<td>3,566</td>
<td>6.7</td>
<td>4.2(^a)</td>
</tr>
<tr>
<td>MORE [35, 36]</td>
<td>2,576</td>
<td>5.3</td>
<td>3.7(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Incidence rate for invasive ER-positive breast cancer.

\(^a\)Incidence rate for invasive and noninvasive ER-positive breast cancer.
relatively small number of events in a population that, because of its high risk for breast cancer, may have been at a lower risk for osteoporotic fracture [22, 23]. In contrast to these beneficial or neutral effects, tamoxifen has been shown to cause several undesirable side effects that tend to limit its use as a broad-based approach to breast cancer prevention. When results from the four tamoxifen prevention trials were considered together, the rate of endometrial cancer was significantly greater in the tamoxifen group compared with the placebo group (consensus relative risk = 2.4, 95% CI = 1.5-4.0, p = 0.0005) [33]. The majority of the higher risk for endometrial cancer was observed in women 50 years of age and older. Similarly, the occurrence of venous thromboembolism was higher in the tamoxifen group (consensus relative risk = 1.9, 95% CI = 1.4-2.6, p < 0.0001) [33]. Although the absolute risk for venous thromboembolic events was higher in women 50 years of age and older, the risk relative to placebo appeared to be similar in women under and over the age of 50 years at the time of study entry. A greater risk for stroke or cerebrovascular accident was also observed in the BCPT (risk ratio = 1.59, 95% CI = 0.93-2.77), Italian (five cases in the tamoxifen group versus none in the placebo group), and IBIS-I (approximate risk ratio = 1.5) trials [24, 33]. In the RMH trial, four stroke/cerebrovascular accident events were reported in the tamoxifen group, compared with seven in the placebo group [33]. Other side effects observed more often in women receiving tamoxifen than in those receiving placebo include cataract development and cataract surgery and hot flashes [24]. Nonsignificantly lower mortality rates in those receiving tamoxifen were observed in the BCPT and Italian trials, whereas no difference between the tamoxifen and placebo groups was seen in the RMH trial [33]. In the IBIS-I trial, there were significantly more deaths from all causes in the tamoxifen group than in the placebo group [34].

It is clear that the administration of tamoxifen may result in undesirable side effects. Although reducing the risk of breast cancer may outweigh the toxicity of tamoxifen for women at high risk for breast cancer and at low risk for side effects, a compound with a superior benefit-risk profile would be preferable for a broader spectrum of healthy postmenopausal women. Raloxifene may be such a compound. The clinical trials evaluating the effect of raloxifene to reduce the risk of breast cancer are described next.

**Raloxifene Breast Cancer Prevention Trials**

A lower incidence of breast cancer in postmenopausal women receiving raloxifene was observed in the MORE trial, an osteoporosis treatment trial conducted in postmenopausal women [35, 36]. Breast cancer risk reduction was a predefined secondary end point in that trial. Postmenopausal women up to 80 years of age having osteoporosis or at least one moderate or two mild vertebral fractures were eligible. In contrast to the high-risk population in the BCPT, the MORE study population was presumed to be at low to normal risk for breast cancer, although the majority of the women in the MORE trial would have been eligible for the BCPT based on age over 60 years. Women were randomized to receive raloxifene, 60 mg/day, raloxifene, 120 mg/day, or placebo for 4 years. Because the incidences of breast cancer were similar in the 60-mg/day raloxifene (hazard ratio = 0.38, 95% CI = 0.22-0.67) and the 120-mg/day raloxifene (hazard ratio = 0.36, 95% CI = 0.20-0.63) groups, pooled incidences for the raloxifene dose groups were reported. After 4 years of raloxifene treatment (median 3.3 years), 61 cases of invasive breast cancer were reported [37]. Thirty-nine of those cases occurred in the placebo group and 22 in the pooled raloxifene group, resulting in a 72% lower risk (relative risk = 0.28; 95% CI = 0.17-0.46) in those receiving raloxifene [37]. Raloxifene reduced the risk of ER-positive invasive breast cancer by 84%, but had no effect on ER-negative breast cancer [37].

In general, raloxifene was well tolerated in postmenopausal women with a favorable safety profile. The risks for flu syndrome, hot flashes, leg cramps, endometrial cavity fluid, and peripheral edema were higher in the raloxifene group than in the placebo group at 4 years [37]. In general, hot flashes and leg cramps were described as mild to moderate and did not result in the discontinuation of raloxifene [36, 38]. Although the risk for thromboembolic events was higher with raloxifene (1.44, 3.32, and 3.63 events per 1,000 woman-years for placebo, 60-mg/day raloxifene, and 120 mg/day raloxifene, respectively) [37], it was similar in magnitude to the relative risks observed with estrogen-progesterin [39] and tamoxifen [24] therapies. In contrast to tamoxifen, raloxifene has not been associated with a higher risk for endometrial cancer [25, 36, 37] or vaginal bleeding [37] or a greater incidence of new or worsening cataracts or cataract surgery [40].

The significant reduction in risk of invasive breast cancer observed in the MORE trial directly led to the design of the CORE study, the inclusion of breast cancer risk reduction as a primary end point in the RUTH trial, and the development of the STAR trial. The design of these trials and the characteristics of their patient populations are compared in Table 1 and Table 2. The purpose of the CORE trial, a follow-up study to the MORE trial, is to evaluate the long-term efficacy of raloxifene in reducing the incidence of invasive breast cancer in postmenopausal women with osteoporosis who previously were treated with raloxifene for up to 4 years in the MORE trial. All MORE investigation sites were invited to participate in the CORE trial.
From those investigators choosing to participate, all women in the MORE trial were invited to participate in the CORE trial after their completion or discontinuation from the MORE trial, and 4,011 of those women chose to participate. Raloxifene, 60 mg/day, was selected as the only active treatment dose for CORE because the 60-mg/day and 120-mg/day doses of raloxifene had shown similar risk reduction efficacies in the MORE trial. Therefore, women who had been randomized to receive either 60 mg/day or 120 mg/day of raloxifene in the MORE trial received 60 mg/day of raloxifene in the CORE trial. Women who had been randomized to receive placebo in the MORE trial received placebo in the CORE trial. The CORE trial was designed to continue for a maximum of 4 years. Thus, the planned total treatment period will be approximately 8 years from the time of randomization in the MORE trial.

The RUTH trial is designed to determine whether 60 mg/day of raloxifene, compared with placebo, reduces the risk of coronary events and invasive breast cancer in postmenopausal women at risk for a major coronary event. The trial design and methodology have been previously described in detail [5]. Briefly, the RUTH trial is a double-blind, placebo-controlled, randomized clinical trial that completed enrollment of 10,101 women in the summer of 2000. Women were eligible for randomization if they were aged 55 years or older, at least 1 year postmenopausal, and had documented coronary heart disease, peripheral artery disease, or multiple risk factors for coronary heart disease. Eligible women were randomized to receive either 60 mg/day of raloxifene or placebo. Breast cancer incidence will be determined by mammograms performed 2, 4, and 6 years after the qualifying mammogram. The study is planned to end after a prespecified number of participants experience their first acute coronary event. The total duration of treatment is projected to range from 5-7.25 years.

The NSABP is currently conducting its second, large breast cancer prevention trial, the STAR trial, comparing the effect of raloxifene with that of tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women at high risk for the disease [41, 42]. The STAR trial is the first head-to-head trial comparing tamoxifen with raloxifene [42]. Approximately 19,000 postmenopausal women 35 years of age or older having at least a 1.66% estimated Gail risk of developing breast cancer or a history of LCIS are being enrolled. The trial is double blinded, and study participants will be randomized to receive either 20 mg/day of tamoxifen or 60 mg/day of raloxifene for 5 years. The relative potency of tamoxifen and raloxifene in reducing breast cancer risk will be directly compared, as will their relative safety profiles.

**DISCUSSION**

The study of SERMs as potential agents to reduce the risk of breast cancer has arisen from ancillary findings in clinical trials designed to evaluate therapies for the treatment of breast cancer and from trials evaluating therapies to prevent end points other than breast cancer. Within the past few years, research to evaluate SERMs as agents to reduce breast cancer risk has moved from an approved indication for tamoxifen to reduce the incidence of breast cancer in women at high risk to the current complement of three trials evaluating the breast cancer risk reduction effect of raloxifene. The focus of the current research hypothesis is that, like tamoxifen, raloxifene may also be an effective SERM for reducing breast cancer risk but, unlike tamoxifen, does not increase the risk of endometrial cancer.

The CORE, RUTH, and STAR trials will have enrolled women with differing breast cancer risks that, when taken together, comprise a spectrum of women having a wide range of breast cancer risk. Since the MORE trial was an osteoporosis treatment trial conducted in postmenopausal women, with breast cancer risk reduction as a secondary objective, the CORE cohort represents older postmenopausal women with osteoporosis and, therefore, presumed to be at a relatively lower risk for breast cancer [23, 43]. In contrast, participants in the STAR trial were specifically selected to have a 5-year predicted breast cancer risk of at least 1.66%. The RUTH participants were selected based on the presence of documented coronary heart disease (50%) or multiple risk factors increasing their risk for a coronary heart disease event (50%) [6]. Although a Gail breast cancer risk estimate was calculated for the overall RUTH cohort (mean 1.7%) [6], breast cancer risk was not an inclusion criterion for the study. Findings regarding the incidence of breast cancer from these trials will allow assessment of the effects of raloxifene in women having a wide range of breast cancer risks and will be critical to determining the appropriate populations for which raloxifene may be safe and effective. Additionally, findings from the STAR trial, since it is a direct head-to-head comparison, will provide important information regarding the effects of tamoxifen and raloxifene on reducing the incidence of invasive breast cancer and their risk-benefit profiles.

The clinical trials assessing the effects of tamoxifen and those assessing the effects of raloxifene will provide essential information to determine the appropriate use of SERMs as chemopreventive agents to reduce breast cancer risk. However, several important questions regarding aspects of breast cancer chemopreventive therapy in general have not been addressed by these trials. Foremost is the effect on breast cancer mortality. It is reasonable to assume that a 50% reduction in breast cancer incidence will translate into
a mortality benefit. However, evidence to support this assumption would be desirable especially considering the increase in all-cause mortality reported for the tamoxifen group in IBIS-I. In the BCPT, breast cancer incidence was the primary end point and, therefore, when the results were announced, the participants were unblinded and many in the placebo group subsequently initiated active chemopreventive therapy. Therefore, it is unlikely that long-term follow-up of the BCPT will be informative regarding mortality effects from the use of tamoxifen as a chemopreventive therapy. Long-term follow-up of the RMH, the Italian, and the IBIS-I trials may provide such information. If data from the CORE, RUTH, and STAR trials show that raloxifene is as effective as tamoxifen in reducing breast cancer incidence, new trials or unbiased follow-up extensions to the existing trials would be necessary to determine whether a reduction in breast cancer risk translates into a reduced mortality rate.

Other important questions remain regarding the appropriate duration and timing of SERM therapy for breast cancer risk reduction. No trials have addressed the appropriate duration of tamoxifen use to reduce breast cancer risk. As a consequence, the 5-year maximum duration recommended for the use of tamoxifen to treat breast cancer has carried over to its use for breast cancer risk reduction [44-46]. Encouraging evidence from a meta-analysis of all the tamoxifen adjuvant trials suggests that the benefit of reductions in mortality and relapse extends to at least 5 or 10 years after cessation of 5 years of tamoxifen treatment [26]. It is unknown whether this type of an effect would be observed after cessation of therapy to reduce breast cancer risk. If the duration of breast cancer risk reduction therapy is limited, then the next question that arises is when is the best time to receive this therapy? Clinical trials to address this question and the question of possible interactions between therapy duration and the timing of therapy would be desirable. However, considering the complexity of designing and implementing such trials, it may be impractical, if not impossible, to undertake such an endeavor.

Since the mechanism of action for SERMs is the modulation of estrogenic effects, it is not surprising that raloxifene and tamoxifen have been shown to significantly reduce the incidence of ER-positive, but not ER-negative, breast cancer [24, 31, 33, 34, 36, 37]. However, ER-positive breast cancers still were observed in the tamoxifen breast cancer prevention trials and the MORE trial, suggesting that not all ER-positive breast cancers may be altered by modulation of estrogenic effects. Research directed at identifying factors to differentiate among those at risk for ER-positive versus ER-negative breast cancer and those at risk for ER-positive tumors that will or will not respond to SERMs might provide a greater ability to selectively administer therapy. Furthermore, clinical trials evaluating alternative therapies to reduce the risk of ER-negative breast cancer are needed to supplement the ongoing work involving SERMs.
optimal duration; identifying women who are likely to develop estrogen-promoted breast cancers amenable to selective ER modulation; developing therapies directed at reducing the risk of ER-negative breast cancer; and developing therapies applicable to premenopausal women. Answers to these questions are beyond the scope of the ongoing trials. Strategically designed clinical trials are needed to help answer these questions.

REFERENCES