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Breast Cancer Chemoprevention: Progress and Controversy

D. Lawrence Wickerham, MD^{a,b,c,*}

^a National Surgical Adjuvant Breast and Bowel Project (NSABP), Four Allegheny Center – 5th Floor, Pittsburgh, PA 15212, USA

^b Section of Cancer Genetics and Prevention, Allegheny General Hospital, Pittsburgh, PA, USA

^c Pittsburgh Campus, Drexel University School of Medicine, Pittsburgh, PA, USA

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Despite newer, more effective treatments and improvements in detection, there were more than 42,000 deaths from breast cancer in the United States in 2009, according to the American Cancer Society.¹ Because breast cancer is a major health problem for all women, the concept of preventing the disease is an attractive addition to the established roles of screening and treatment. Prophylactic mastectomy is an effective approach that reduces the risk of developing a breast cancer by an estimated 90% or more.² However, it is a drastic and irreversible choice that is perhaps best reserved for women with high risk of the disease, such as those with known deleterious BRCA1 or 2 mutations. This article focuses on nonsurgical approaches to reducing breast cancer risk.

Some of the risk factors associated with breast cancer are modifiable, such as postmenopausal obesity, alcohol intake, and dietary fat. Reducing weight, exercising, low-fat diets, and moderation of alcohol intake are healthy behaviors. Such lifestyle modifications for breast cancer risk reduction remain an active area of research but are not yet of established value. The factors that place a woman at greatest risk (gender, age, and family history) are not amenable to lifestyle modifications.

Hong and Sporn³ have defined chemoprevention as “the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred.”

SELECTED ESTROGEN RECEPTOR MODULATORS

Although the precise mechanism or mechanisms that cause a breast cancer are not fully established, hormones play a significant role in a large percentage of cases, and current chemoprevention strategies have targeted hormonally responsive breast cancers. The selective estrogen receptor modulators (SERMs) are the group of agents that have been evaluated the most, and the best known of these drugs is tamoxifen. Tamoxifen is a well-established adjuvant therapy for receptor-positive breast cancer that has been shown repeatedly to reduce the risk of recurrence and death from this disease.⁴ In the large trials

* National Surgical Adjuvant Breast and Bowel Project (NSABP), Four Allegheny Center – 5th Floor, Pittsburgh, PA 15212. larry.wickerham@nsabp.org.
Dr Wickerham is a consultant to Eli Lilly and Company and has received honoraria from AstraZeneca.

that showed tamoxifen to be an effective adjuvant treatment, there was also a substantial reduction in new primary cancers of the opposite breast. The duration of tamoxifen therapy in these studies varied from 1 to 5 years, but the reduction in opposite breast cancer persisted through at least 15 years of follow-up, showing this to be a durable, if not lifelong, benefit.

TAMOXIFEN CHEMOPREVENTION TRIALS

The findings from the adjuvant trials, combined with extensive laboratory data documenting the potential of tamoxifen as a chemoprevention agent, led to the initial randomized breast cancer chemoprevention trials. The largest of these trials was the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial, P-1, which randomized more than 13,000 healthy women from centers in North America to receive 20 mg of tamoxifen daily or placebo for a 5-year period (Fig. 1A).^{5,6}

Eligible participants for the trial were at increased risk for breast cancer, which was defined as having 5-year projected invasive breast cancer risk of at least 1.66% as determined by the modified Gail model or having a history of lobular carcinoma in situ (LCIS) treated by local excision alone, or being at least 60 years of age. Women were not eligible for the trial if they had a history of deep vein thrombosis (DVT), a pulmonary embolus (PE), or if they had taken hormone therapy, oral contraceptives, or androgens within 3 months before random assignment into the trial. Estrogen or combinations of estrogen-progestin therapy were not permitted during the course of the study. The primary end point of the trial was the incidence of invasive breast cancer. Secondary end points included all other invasive cancers, noninvasive breast cancers, osteoporotic bone fracture, cardiac events, quality of life measurements, and death from any cause.

The initial results were published in 1998, with an average follow-up of approximately 4 years, and showed a highly significant 49% reduction in invasive breast cancer in favor of the tamoxifen-treated women (relative risk [RR] = 0.51, 95% confidence interval [CI] 0.39–0.66).⁵ The rate of noninvasive breast cancers (ductal carcinoma in situ [DCIS] and LCIS combined) was reduced by a similar magnitude. The reduction of invasive breast cancer appeared to be only in estrogen-receptor (ER)-positive cases, with a 69% reduction in incidence; there was no difference between the treatment groups in terms of the incidence of ER-negative disease.

Evaluation of secondary end points showed a 45% reduction in the number of osteoporotic fractures with tamoxifen (79 in the placebo group and 49 in the tamoxifen group). Tamoxifen was known to reduce blood lipids, but there was no reduction in the risk of myocardial infarction, severe angina, or acute ischemic syndrome noted in the tamoxifen-treated group compared with the placebo group. There were 28 cases of myocardial infarction in the placebo group and 39 in the tamoxifen-treated group (RR = 1.11; 95% CI 0.65–1.92). There were no significant statistical differences in the other 2 cardiac end points.

The toxicity associated with tamoxifen has been well documented in the treatment trials for invasive breast cancer and includes increases in the risk of endometrial cancer and thromboembolic events. Both of these toxicities were identified in the P-1 trial as well: the RR of endometrial adenocarcinoma was 2.53 (95% CI 1.35–4.97), with 15 cases occurring in the placebo group compared with 36 in the tamoxifen group. No excess of endometrial cancer was noted in the women younger than the age of 50 years, primarily a premenopausal group, at the time of random assignment. Thromboembolic events were also associated with tamoxifen use, and the magnitude of risk seems to be similar to that for postmenopausal women who take estrogen-replacement therapy. There was a 60% increase in the risk of DVT (RR = 1.60; 95% CI 0.91–2.86), with 22 cases occurring in the placebo group and 35 in the tamoxifen group. The risk of pulmonary embolism was also increased 3-fold (RR =

3.10; 95% CI 1.15–9.27), with 6 cases occurring in the placebo group and 18 in the tamoxifen group. There was a slight increase in strokes among women on tamoxifen, although it did not reach statistical significance. As with the endometrial cancer data, the increase in thromboembolic events appeared predominantly in women older than 50 years at the time they entered the trial.

The data for the use of tamoxifen in women with BRCA1 or BRCA2 inherited mutations are limited, and definitive statements about the effectiveness of tamoxifen in such patients are not available. In the P-1 trial, King and colleagues⁷ identified only 18 women with inherited BRCA1 or BRCA2 mutations. Although tamoxifen reduced breast cancer incidence among BRCA2 carriers by 62%, this reduction was not statistically significant given the small numbers of patients out of the 13,000-plus women who entered the trial. Patients with BRCA2 frequently develop ER-positive breast cancers, although not uniformly. In the patients with BRCA1 noted in the P-1 trial, there was also no significant benefit from tamoxifen; there were numerically more cancers in the tamoxifen group. Narod and colleagues⁸ published a matched case-control study that reported significant protection from contralateral breast cancer in women with BRCA1 mutations who developed an invasive breast cancer and were treated with tamoxifen. A lesser effect was seen in women with BRCA2 mutations. That report and the P-1 data suggest that women with BRCA1 or BRCA2 mutations who have or will develop ER-positive breast cancer are potential candidates for tamoxifen therapy, but at the present time it is not possible to determine which women with BRCA1 or BRCA2 mutations will develop ER-positive disease.

All the various subgroups of women in the P-1 trial appeared to benefit from the use of tamoxifen, including pre- and postmenopausal women as well as those with Gail scores ranging from 1.66% to more than 5%. The group that seems to have the greatest benefit is those women with a biopsy-proven history of LCIS or atypical hyperplasia. Such women are known to have a risk of subsequent invasive breast cancer that is 4- to 10-fold greater. In the P-1 trial, the annual breast cancer rate per 1000 women in the placebo arm with a history of LCIS at the time of entry was 12.99, and for those with a prior history of atypical hyperplasia, 10.11 (Fig. 2A). Both groups showed a substantial benefit from tamoxifen, with a 56% reduction in invasive breast cancer in women with LCIS and an 86% reduction in those with atypical hyperplasia.

ADDITIONAL TAMOXIFEN BREAST CANCER PREVENTION TRIALS

Several additional tamoxifen breast cancer prevention trials have been performed with different designs and sample sizes, and as a result have produced somewhat variable results. The International Breast Cancer Intervention Study (IBIS I) evaluated 7145 women, aged 35 to 70 years, who were at increased risk for breast cancer and randomly assigned them to receive either 20 mg of tamoxifen or placebo for a 5-year period. The initial results published in 2002 with 49 months of median follow-up reported that tamoxifen reduced the risk of ER-positive breast cancer by 31%, and the updated results showed that these benefits persisted with 12 years of follow-up.^{9,10}

The Royal Marsden Trial began as a pilot study in 1986 to evaluate the feasibility of conducting tamoxifen prevention trials. In a 10-year period, 2471 participants entered the study and were assigned either tamoxifen, 20 mg per day, or placebo for an 8-year period. The initial analysis was published in 1998 and reported no reduction in breast cancer incidence.¹¹ However, a more recent paper with a median follow-up of 13 years shows a statistically significant reduction in ER-positive breast cancer.¹²

The Italian Tamoxifen Prevention Study enrolled 5408 women, aged 35 to 70 years, to receive either tamoxifen or placebo, but the study was not restricted to women at increased

risk for breast cancer. The initial results of this trial failed to show an overall benefit of tamoxifen, but in a subset of 1580 women who had used estrogen-replacement therapy at some point during the trial, there were 23 breast cancers (17 in the placebo group and 6 in the tamoxifen group).¹³ This finding led to the Hormone-Replacement Therapy (HRT) Opposed to Tamoxifen (HOT) Study to evaluate tamoxifen, 5 mg per day, in women taking HRT.

An overview of the tamoxifen prevention trials was released in 2003 and reported a 37% decrease in invasive breast cancer in a combined tamoxifen treatment group.¹⁴ An update of this overview is currently being analyzed but has not yet been published.

RALOXIFENE STUDIES

Raloxifene is a second-generation SERM that was originally developed as a breast cancer treatment for receptor-positive tumor. The results of the initial trial showed limited effectiveness, and further examination for its use in breast cancer treatment was discontinued. Raloxifene has well-established favorable effects on bone metabolism in postmenopausal women, and the pivotal raloxifene study that led to its approval by the US Food and Drug Administration for the treatment of osteoporosis was the Multiple Outcomes of Raloxifene Evaluation (MORE) study.¹⁵ The MORE trial randomly assigned 7705 postmenopausal women with osteoporosis to receive raloxifene, 60 mg per day or 120 mg per day, compared with placebo. The participants received the study drug daily for up to 4 years. The primary objective of this multicenter international trial was to evaluate the effects of raloxifene compared with placebo on the incidence of osteoporotic fracture and bone mineral density in this population of women. Breast cancer was a secondary end point, and participants were not selected or prospectively evaluated for their breast cancer risk. The initial MORE results reported a significant reduction in vertebral fractures in the raloxifene-treated women, but the incidence of nonvertebral fractures was not significantly different. In the raloxifene-treated group, the risk of invasive breast cancer was significantly reduced after 4 years by 72% (RR = 0.28; 95% CI 0.17–0.46). As was noted in the tamoxifen trial, the benefits appeared to be specific to receptor-positive invasive breast cancer. An increased risk in thromboembolic events, including DVT and pulmonary embolism, was identified (RR = 3.1; 95% CI 1.5–6.2), but unlike what occurs with tamoxifen, there was no difference in the incidence of endometrial carcinoma. The Continuing Outcomes Relevant to Evista (CORE) trial was a double-blind, placebo-controlled study that evaluated the efficacy of an additional 4 years of raloxifene compared with placebo in reducing the risk of invasive breast cancer in women who had participated in the MORE trial.¹⁶ The primary breast cancer analysis included 3996 patients who had completed MORE and agreed to enter CORE, and data from an additional 1217 patients who were still participating in MORE when CORE began. The incidence of invasive breast cancer was reduced by 59% (hazard ratio [HR] = 0.41; 95% CI 0.24–0.71) in women in the raloxifene-treated group compared with those in the placebo group. During 8 years of both trials, the incidence of invasive breast cancer was reduced by 66% (HR = 0.34; 95% CI 0.22–0.50); no new safety concerns related to raloxifene were identified.

THE STUDY OF TAMOXIFEN AND RALOXIFENE TRIAL, NSABP P-2

The initial results of the NSABP tamoxifen-versus-placebo trial, P-1, were published in 1998 and reported that tamoxifen could reduce the incidence of breast cancer by up to almost 50% in a population of healthy women at increased risk for the future development of breast cancer. The raloxifene studies reported a reduction in breast cancer incidence in an unselected population, making the Study of Tamoxifen and Raloxifene (STAR) trial the next logical step. This study was a double-blind and randomized clinical trial that entered 19,747

postmenopausal women who were at least 35 years of age and had a history of LCIS treated by local incision alone or a modified Gail score showing a 5-year risk for invasive breast cancer of at least 1.66% (see Fig. 1B).¹⁷ Women were randomly assigned to take either tamoxifen, 20 mg per day, plus a placebo, or raloxifene, 60 mg per day, plus a placebo, for a 5-year period. The primary end point of the trial was the development of biopsy-proven invasive breast cancer. The secondary end points included noninvasive breast cancer, uterine malignancies, thromboembolic events, fractures, cataracts, quality of life, and death from any cause. To minimize the risk of stroke or thromboembolic events, eligible participants could not have a history of cerebral vascular accidents, transient ischemic attack (TIA), pulmonary embolism, DVT, uncontrolled diabetes, uncontrolled hypertension, or atrial fibrillation. The median 5-year risk of developing invasive breast cancer based on the modified Gail score was 4.03%, and the projected lifetime risk for these women to age 80 years was 14%. Seven percent of the women entering the trial had 1 or more first-degree relatives with breast cancer, and more than 9% had a history of LCIS. More than 22% had had a breast biopsy before enrollment that showed either atypical ductal or atypical lobular hyperplasia. Slightly more than 6% of the participants had undergone a hysterectomy, with or without oophorectomy, before random assignment.

The initial results from the STAR trial showed there was no difference in the effects in tamoxifen or raloxifene on the incidence of invasive breast cancer: 163 of the women assigned tamoxifen and 168 of those assigned raloxifene developed an invasive breast cancer. The rate per 1000 woman years was 4.3 in the tamoxifen group and 4.4 in the raloxifene group (RR = 1.02; 95% CI 0.82–1.28). Although there was no placebo-alone group in the trial, the Gail model scores of the women who entered the trial allow us to estimate the number of invasive breast cancers that would have occurred in the untreated group and showed that there was a 47% reduction in the incidence of invasive breast cancer. The characteristics of the invasive breast cancers showed no differences between the treatment groups with regard to distribution by tumor size, nodal status, or ER level.

Raloxifene did not seem to be as effective as tamoxifen in reducing the incidence of noninvasive breast cancers (LCIS or DCIS), although the difference did not reach statistical significance. There were 57 cases of noninvasive breast cancer among the women assigned to tamoxifen and 80 among those who took raloxifene (RR = 1.40; 95% CI 0.98–2.00).

More uterine malignancies occurred in STAR in the tamoxifen-treated women than in those treated with raloxifene, but the difference was not statistically significant at the time of the original analysis. There were 36 cases in the tamoxifen group and 23 in the raloxifene group, with an annual incidence rate of 1.99 per 1000 and 1.25 per 1000, respectively (RR = 0.63; 95% CI 0.35–1.08). Uterine hyperplasia with and without atypia was significantly less common in the raloxifene-treated group. There were also significantly fewer hysterectomies performed for nonmalignant indications in the raloxifene group (244 tamoxifen; 111 raloxifene [RR = 0.29; 95% CI 0.30–0.50]). There was no statistically significant difference between the groups in regard to other malignancies.

No statistically significant differences were noted between the 2 groups relative to the incidence of ischemic heart disease, TIA, stroke, or fracture; however, there were significantly fewer thromboembolic events (DVT or PE) in the raloxifene-treated group. Fewer women on raloxifene developed cataracts during treatment, and fewer underwent surgical removal of those cataracts. Mortality within the 2 groups was similar, with 101 deaths in those assigned to tamoxifen and 96 deaths in those assigned to raloxifene (RR = 0.94; 95% CI 0.71–1.26). The distribution by cause of death did not differ by treatment.

Data from the STAR trial and the other raloxifene/placebo trial resulted in the approval of raloxifene by the US Food and Drug Administration for a reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer. No data are currently available on the use of raloxifene in patients with BRCA1 or BRCA2 mutations, nor was raloxifene approved for women with a previous invasive breast cancer or for the treatment of invasive breast cancer. However, the approval of raloxifene gives an important new option to postmenopausal women beyond that of tamoxifen, one that avoids an excess of endometrial cancers and reduces the risk of thromboembolic events. The optimum duration of raloxifene therapy for breast cancer prevention has not been established. The drug was used for a period of 5 years in the STAR trial based on the standard 5-year duration of treatment with tamoxifen. The MORE/CORE combined results of 8 years of treatment reported a continued benefit of breast cancer risk reduction as well as risk reduction in bone fractures without increased or new toxicities being identified. In the MORE trial, the number needed to treat to prevent 1 invasive breast cancer in the population of postmenopausal women with osteoporosis was 91, which compares favorably with the number needed to prevent a myocardial infarction with a statin.

There continues to be a concern that raloxifene does not seem to be as effective as tamoxifen in preventing the development of noninvasive breast cancer; this is different from saying there is no effect. At the time of the initial STAR publication, the difference between tamoxifen and raloxifene was not quite statistically significant. A mechanism to explain the difference in noninvasive breast cancer incidence is unknown, but long-term follow-up results for the STAR trial may result in additional information regarding this issue.

ADDITIONAL SERMS

At least 2 additional SERMs are in development and may prove to be of value in breast cancer chemoprevention. The first is lasofoxifene. At the 2008 San Antonio Breast Cancer Symposium, the results of the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) Study were presented.¹⁸ This trial included 8556 postmenopausal women with osteoporosis randomly assigned to receive either a placebo or lasofoxifene 0.5 mg per day or 0.25 mg per day. Lasofoxifene reduced the incidence of vertebral and nonvertebral fracture, but there was an increased risk of thromboembolic events. The results showed a significant reduction in invasive breast cancers in the group that received lasofoxifene 0.5 mg per day (HR = 0.15; 95% CI 0.04–0.50). The other SERM being studied is arzoxifene. A large multicenter, placebo-controlled double-blind trial, the Generations Trial, compared arzoxifene, 20 mg per day, versus placebo in 9254 postmenopausal women with osteoporosis or low bone mass.¹⁹ A total 75 breast cancers were identified, 53 in the placebo group and 22 in the arzoxifene group (HR = 0.14; 95% CI 0.25–0.68, $P < .001$). As with the other SERMs, the reduction in breast cancer was primarily in receptor-positive disease. There was a significant reduction in vertebral fractures in favor of the arzoxifene-treated individuals but no significant reduction in nonvertebral fractures.

AROMATASE INHIBITORS

High circulatory estrogen levels, as well as high aromatase levels in breast tissue, have been known to increase breast cancer risk.²⁰ In postmenopausal women, aromatase inhibitors (AIs) block the production of estrogens in extragonadal peripheral tissues. Circulatory estrogen levels are dramatically reduced, and aromatase activity in the breast may also be influenced. The development of third-generation selective AIs has had a profound effect on the adjuvant treatment of postmenopausal women with receptor-positive breast cancer. In adjuvant trials of various designs, these AIs have resulted in improved disease-free survival

and are associated with fewer life-threatening side effects than is tamoxifen.^{21–25} Women in these adjuvant trials who received AIs had a decrease in new primary breast cancers of the opposite breast when compared with those who received tamoxifen, which we know to be effective in reducing risk compared with no treatment. A 35% to 50% decrease in opposite breast cancer in AI trials reported to date provides strong clinical evidence that these agents may be superior to tamoxifen in breast cancer chemoprevention.

The adjuvant trial results reporting a reduction in opposite breast cancers in AI-treated women has led to 2 primary prevention trials evaluating AIs in healthy persons at increased risk for the development of breast cancer. The first of these studies is the IBIS II trial, which will randomize 6000 postmenopausal women to receive anastrozole, 1 mg per day, or placebo. The primary end point of the study is the development of breast cancer. Other cancers, toxicities, cognition, and bone effects will also be evaluated. The IBIS II trial is being conducted in 40 centers in the United Kingdom and around the world. The second trial, the MAP-3 study being led by the National Cancer Institute of Canada Clinical Trials Group, will enter 4560 postmenopausal women assigned to receive exemestane, 25 mg per day, or placebo for a 5-year period. Eligible women are those at increased risk for breast cancer, which is defined as being older than 60 years of age or having a Gail score greater than 1.65%, or having a previous breast biopsy documenting atypical hyperplasia of the breast, or LCIS. Also eligible are women who were treated with mastectomy for DCIS. The main objective of this trial is to compare the incidence of breast cancer in the 2 groups. Data will also be collected on bone fractures, cardiovascular events, tolerability and safety, and the incidence of other malignancies.

The IBIS II and MAP-3 trials have placebo-alone control groups. Although this design is scientifically compelling, a direct comparison of either tamoxifen or raloxifene would allow a better risk/benefit evaluation. The IBIS II study does have a separate component for DCIS patients that compares anastrozole with tamoxifen and should allow some insight into the risk/benefit issues. The NSABP has already completed accrual of 3000 patients in the B-35 study, which also evaluates anastrozole and tamoxifen in ER-positive DCIS. The primary study end points of the B-35 trial include ipsilateral and contralateral invasive and noninvasive breast cancers. The B-35 results may be available before those from IBIS II or the MAP-3 prevention trials.

2009 AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINES ON THE USE OF PHARMACOLOGIC INTERVENTION, INCLUDING TAMOXIFEN, RALOXIFENE, AND AIs, FOR BREAST CANCER RISK REDUCTION

The American Society of Clinical Oncology updated its Clinical Practice Guidelines regarding breast cancer risk reduction in 2009.²⁶ The original 1999 guidelines and the 2002 update suggest women at increased risk for breast cancer may be offered tamoxifen (20 mg per day for 5 years) to reduce the risk of invasive ER-positive breast cancer, with benefits that persist for at least 10 years.^{27,28} Since the publication of the STAR results, the guidelines have been updated and state that for postmenopausal women raloxifene at 60 mg per day may be considered as an additional option. A discussion of risks and benefits by health care providers is believed to be critical to a patient's decision making. The use of AIs and other potential chemopreventive agents is not recommended outside clinical trials.

SUMMARY

Compared with breast cancer screening and treatment, the chemoprevention of this disease is in its infancy. However, SERMs have shown substantial clinical benefit in several large, well-conducted randomized clinical trials. For women with LCIS or atypical hyperplasia of the breast, tamoxifen, and to a lesser degree, raloxifene, are highly effective in reducing the risk of subsequent invasive breast cancer (see Fig. 2B). Thus the option of SERM therapy should be considered for these women.

The history of medicine has shown us that the greatest advances in care are often through prevention of disease as opposed to treatment. Although there are issues with the current breast cancer chemoprevention agents, such as side effects, costs, and the identification of proper candidates for use, these are not insurmountable barriers, and efforts are under way to address them. Over the years, cardiologists have recognized and refined the role of disease prevention in their practices; they can serve as a model. The oncology community has always been supportive of cancer prevention strategies, and chemoprevention offers an opportunity to expand those strategies beyond behavior and lifestyle modifications.

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Fig. 1.
(A) NSABP BCPT P-1 Schema. (B) NSABP STAR P-2 Schema.

Fig. 2.

(A) BCPT Results: Invasive Breast Cancer by Previous Pathology. (B) STAR Results: Invasive Breast Cancer by Previous Pathology (Data from Fisher B, Costantino J, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–62; and Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–41.).