Follow-Up of the Breast Cancer Prevention Trial and the Future of Breast Cancer Prevention Efforts

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Abstract

Women who are at increased risk for developing breast cancer can be identified using quantitative risk assessment models that provide valid estimates of risk. The Breast Cancer Prevention Trial (BCPT, P-1) demonstrated that tamoxifen can reduce the incidence of both invasive and noninvasive breast cancer as well as of bone fractures in women at increased risk. These benefits accrue at the expense of increased risk of endometrial cancer, thromboses, cataracts, and possibly diminished quality of life in postmenopausal women. All premenopausal women with a 5-year risk of developing invasive breast cancer greater than 1.67% derive net benefit from using tamoxifen to reduce the risk. Subset analyses of older postmenopausal women taking raloxifene for the treatment of osteoporosis indicate reduction of breast cancer incidence by more than 70%. These findings led the National Surgical Adjuvant Breast and Bowel Project (NSABP) to design and launch the STAR trial (P-2, the Study of Tamoxifen and Raloxifene). Eligible women are at least 35 years of age and postmenopausal, and they must have either lobular carcinoma in situ (LCIS) or a 5-year risk of invasive breast cancer of at least 1.67% as determined by the Gail model [M. H. Gail et al., J. Natl. Cancer Inst. (Bethesda), 81: 1879–1886, 1989]. Subjects are randomly assigned to receive either tamoxifen 20 mg or raloxifene 60 mg daily in a double-blind, double-dummy design. The trial is designed to recruit a total of 22,000 postmenopausal women and is powered to demonstrate superior efficacy of either agent or their equivalence in reducing the incidence of primary breast cancer. Additional end points will include the incidence of cardiovascular events and bone fractures. Thromboembolic events and endometrial cancer are the predicted toxicities. Ancillary studies of cognitive function will also be performed. Raloxifene should not be used for the reduction of breast cancer risk outside the context of the STAR trial.

Introduction

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the progression of premalignant lesions to invasive carcinoma (1, 2). Because the lifetime probability of developing breast cancer is high among women with known epidemiological risk factors for breast cancer, there is considerable interest in identifying agents that can reduce this risk by using the mechanism of prospective clinical trials. Our basic understanding of human carcinogenesis indicates that the process proceeds through multiple discernible stages of molecular and cellular alterations, a concept that provides the scientific rationale for clinical cancer chemoprevention. We shall review the basic science and clinical data that point us to several potentially active agents for the reduction of breast cancer risk.

Hormones, especially estrogens, have been linked to breast cancer, and their role has been attributed to their ability to stimulate cell proliferation, which in turn leads to accumulation of random genetic errors that result in neoplasia. Epidemiological studies indicate that estrogen-mediated events play a role in the development of breast cancer (3) and support the hypothesis that intact ovarian function is required to develop breast cancer. Prior investigations also show that oophorectomy or radiation-induced ovarian ablation can reduce the incidence of breast cancer by up to 75%. These observations suggest that SERMs acting as estrogen antagonists might play a role in the primary prevention of breast cancer by reducing the rate of cell division.

The BCPT

The National Cancer Institute, in collaboration with the NSABP, launched the BCPT in 1992 to evaluate the ability of tamoxifen to prevent breast cancer in women who were at increased risk (4). Women eligible for the trial were either older than 60 years at entry, were age 35 or older with a breast biopsy showing LCIS, or were between the ages of 35 and 59 years with an estimated annual risk for developing breast cancer equal to that of a 60-year-old woman. The 5-year predicted risk of breast cancer required to enter the trial, therefore, was at least 1.66%. Risk was estimated using the model, developed by Gail and colleagues (5–7), that considers current age, ages at menarche, and first live birth, number of first-degree relatives with breast cancer, and the number of breast biopsies ever done. A previous diagnosis of atypical hyperplasia doubles the estimated risk; there are interaction terms for age and the number of breast biopsies, and for family history and the age at first live birth.

Between June 1, 1992, and September 30, 1997, 13,388...
women, ages 35 years and older, entered the trial and were randomly assigned to receive tamoxifen 20 mg daily versus placebo therapy. Approximately 40% were between the ages of 35 and 49 years; 30% were 50 to 59 years old; and 30% were 60 years or older. The trial was stopped in late March 1998 and results reported because statistical significance had been achieved in a number of study end points.

**Reduction in Incidence of Invasive Breast Cancer.** Through July 1998, a total of 368 invasive and noninvasive breast cancers occurred among 13,175 women with evaluable end points in BCPT. There were a total of 175 cases of invasive breast cancer in the placebo group as compared with 89 in the tamoxifen group (risk ratio, 0.51; 95% CI, 0.39–0.66; P < 0.00001). The annual event rate for invasive breast cancer among women taking tamoxifen was 3.4 per 1000 women compared with 6.8 per 1000 women taking placebo. There was a reduced risk of developing invasive breast cancer among all age groups in the trial. Risk ratios were 0.56 for women ≤49 years of age; 0.49 for women 50–59 years; and 0.45 for women 60 years old or older. All of the 95% CIs for these observations excluded 1.0 and were statistically significant. A benefit was also seen for women with a history of LCIS (risk ratio, 0.44; 95% CI, 0.16–1.06); for women with a history of atypical lobular or ductal hyperplasia, the risk ratio was markedly diminished at 0.14 (95% CI, 0.03–0.47). Reduced risk ratios were seen at all projected levels of risk and among women with 1, 2, or more first-degree relatives with a history of invasive breast cancer.

The reduction in the risk of invasive breast cancer was seen within the 1st year of the trial, and lower incidence rates for women taking tamoxifen compared with those taking placebo were seen for each subsequent year of the trial throughout 6 years of maximum follow-up at the time the results were reported. There was a substantial difference when comparing the proportion of estrogen receptor-positive tumors that occurred among women taking tamoxifen. The incidence rate of estrogen receptor-positive breast cancers was 5 per 1000 women in the placebo group compared with only 1.6 per 1000 women in the tamoxifen group, a 69% reduction. Concordant with this observation, rates of estrogen receptor-negative tumors were not significantly different in the two treatment groups (1.46 per 1000 women in the tamoxifen group compared with 1.20 per 1000 women in the placebo group).

The breast cancer incidence curves for the two treatment groups in the P-1 study began to separate after the 1st year of tamoxifen administration, and they continued to diverge throughout the 5 years of drug administration. Although the early benefit from tamoxifen could have been a treatment effect on small, clinically occult breast cancers, the continued reduction of breast cancer incidence during years 3–5 of tamoxifen administration suggests a true preventive effect. This observation is consistent with the prolonged suppression of second, contralateral breast primary malignances seen among women receiving tamoxifen in the adjuvant treatment setting (8). There was also a reduction in the risk of breast cancer occurring in both pre- and postmenopausal women. Some critics of the trial had predicted that little benefit would accrue to these women, but the P-1 data are again consistent with the observations from the overview data of adjuvant tamoxifen treatment trials that show a benefit from tamoxifen in reducing both recurrences and deaths from breast cancer in premenopausal women who have estrogen receptor-positive breast cancer.

**Effect of Tamoxifen in Mutation Carriers.** Mutations in the \(BRCA1\), \(BRCA2\), and other genes increase risk. Whether the absence of the negative regulatory role of intact \(BRCA1\) and \(BRCA2\) molecules may be compensated by the negative modulation of estradiol or by SERMs such as tamoxifen is not known. Although \(BRCA1\) mutation carriers are more likely to develop ER-negative tumors (8–10), prophylactic oophorectomy reduces the risk of breast cancer by ∼30% in women who carry mutations in either the \(BRCA1\) or \(BRCA2\) gene (11). More importantly, Narod et al. (12) compared 209 women with bilateral breast cancer and \(BRCA1\) or \(BRCA2\) mutation (bilateral disease cases), with 384 women with unilateral disease and \(BRCA1\) or \(BRCA2\) mutation (controls) in a matched case-control study (12). History of tamoxifen use for first breast cancer was obtained by interview or by self-administered questionnaire. The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 (95% CI, 0.28–0.89). Tamoxifen protected against contralateral breast cancer for carriers of \(BRCA1\) mutations (odds ratio, 0.38; CI, 0.19–0.74) and for those with \(BRCA2\) mutations (0.63; CI, 0.20–1.50). The greater apparent benefit of tamoxifen in carriers of \(BRCA1\) mutations as compared with carriers of \(BRCA2\) mutations is paradoxical, given the greater prevalence of ER-positive breast cancer reported among carriers of \(BRCA2\) mutations (8). This observation needs to be validated in additional studies. In women who used tamoxifen for 2–4 years, the risk of contralateral breast cancer was reduced by 75%. A reduction in the risk of contralateral cancer was also seen with oophorectomy and with chemotherapy. The protective effect of tamoxifen in carriers of \(BRCA1/2\) mutations seems to be independent of that of oophorectomy.

In BCPT, 57% of participants had only one affected first-degree relative with breast cancer and 20% had two or more affected relatives; blood was collected from the participants before randomization, and DNA was stored for later analysis. Subsequent to the opening of BCPT, both the \(BRCA1\) and \(BRCA2\) genes were cloned, and mutations in both genes are known to increase markedly a woman’s lifetime risk of developing invasive breast cancer. It was important to determine in BCPT whether any benefit accrued to the women with predisposing genetic mutations who received tamoxifen.

A study of anonymous specimens was performed in all of the cases of breast cancer and in selected controls to determine the efficacy of tamoxifen in reducing breast cancer risk in carriers of mutations in either the \(BRCA1\) or \(BRCA2\) genes, and results from this testing were presented at the American Society of Clinical Oncology’s ASCO 2001 meeting. In BCPT, there were 315 cases of breast cancer for which blood specimens were available, and 288 of these specimens were analyzed with complete DNA sequencing. Among these women, 19 (6.6%) with inherited mutations in \(BRCA1\) or \(BRCA2\) were identified. Among eight women with \(BRCA1\) mutations, five had been assigned to tamoxifen and three to placebo. The risk ratio for

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4 Mary-Claire King, personal communication.
developing invasive breast cancer when comparing tamoxifen with placebo was 1.67 (95% CI, 0.41–8.0). Among the 11 subjects found to have BRCA2 mutations, 3 had been assigned to tamoxifen and 8 to placebo; the risk ratio when comparing tamoxifen with placebo was 0.38 (95% CI, 0.06–1.56). Although these data are suggestive of a benefit in BRCA2 but not BRCA1 mutation carriers, the small number of cases makes it essential that the findings be examined in additional populations of women with predisposing genetic mutations.

Fractures. At the time of the report of the BCPT, 955 women had experienced bone fractures. The incidence of osteoporotic fracture events involving the hip, spine, or lower radius was reduced 19% (111 events versus 137 events in the placebo group) among women receiving tamoxifen. Most notable was a 45% reduction in fractures of the hip that missed reaching statistical significance because of the small total number of events reported (n = 34) in a population whose median age at enrollment was 52 years, with only 30% age 60 or older. It is likely that tamoxifen does have a significant effect on fractures in postmenopausal women, but additional data are required to confirm this initial observation.

Incidence of Invasive Endometrial Cancer. Women who received tamoxifen in BCPT had a 2.5 times greater risk of developing invasive endometrial cancer than did women who received placebo; the average annual rate was 2.3 per 1000 women in the former group and 0.9 per 1000 women in the latter group. All 36 invasive endometrial cancers that occurred among women receiving tamoxifen in BCPT were FIGO stages 0 or I and had excellent clinical prognoses, although it is too early to make definitive statements about the long-term outcome of these tumors.

Other Unfavorable Events. There was an increase in the number of thromboembolic events among women taking tamoxifen in the BCPT. Whereas only the event rate for pulmonary embolism reached statistical significance, there is cause for concern when looking at the increased event rates for stroke, transient ischemic attack, and deep vein thrombosis, particularly among women 50 years and older.

In addition to these toxicities, there was a statistically marginal increase of ~14% in the rate of cataract development among women who were free of cataracts at the time of entry into the BCPT. Event rates for cataract surgery were also increased for women taking tamoxifen when compared with those taking the placebo.

Bothersome hot flashes were reported by 46% of women in the tamoxifen group compared with only 29% in the placebo group. Similarly, vaginal discharge reported as moderately bothersome or worse was seen in 29% of the tamoxifen group as compared with 13% of the placebo group.

The Data Monitoring Committee advised that the P-1 trial participants be unblinded to the trial results when a prespecified number of breast cancer events had occurred. After the unblinding, a substantial number of participants from the placebo group requested to begin tamoxifen. Another large group of postmenopausal women from the placebo arm of the trial elected to join the STAR trial, during which they are receiving either tamoxifen or raloxifene. This cross-over removes or substantially confounds, unfortunately, the opportunity to examine the long-term benefit or harm of tamoxifen in the setting of breast cancer risk reduction. It was thought unethical, however, to withhold tamoxifen from the high-risk women in the placebo arm of the trial merely for the purpose of preserving the two treatment groups.

Table 1  Tamoxifen for breast cancer prevention

<table>
<thead>
<tr>
<th>Women who may consider the use of tamoxifen for risk reduction:</th>
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<tbody>
<tr>
<td>History of LCIS</td>
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<tr>
<td>History of ductal carcinoma in situ (DCIS)</td>
<td></td>
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<tr>
<td>History of atypical ductal or lobular hyperplasia</td>
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<tr>
<td>Premenopausal women with mutations in either the BRCA1 or BRCA2 genes, or other predisposing genetic mutations</td>
<td></td>
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<tr>
<td>Women ages &gt;=35 yr with Gail model 5-year P of breast cancer &gt;=1.67%</td>
<td></td>
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<tr>
<td>Women in whom caution should be used when considering the use of tamoxifen:</td>
<td></td>
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<tr>
<td>History of stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolus</td>
<td></td>
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<tr>
<td>History of cataracts or cataract surgery</td>
<td></td>
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<tr>
<td>Current use of hormone replacement therapy</td>
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</tbody>
</table>

Considerations for Using Tamoxifen to Reduce Risk of Breast Cancer

Women who are at increased risk for developing breast cancer can be identified using either individual risk factors or quantitative risk assessment models that provide valid estimates of risk (13, 14). BCPT demonstrated that tamoxifen can reduce the incidence of both invasive and noninvasive breast cancer as well as of bone fractures in women at increased risk. These benefits accrue at the expense of increased risk of endometrial cancer, thromboembolism, cataracts, and possibly diminished quality of life. On the basis of the results of BCPT, the Food and Drug Administration approved tamoxifen for reduction of breast cancer risk in women whose risk of developing breast cancer is equal to the minimum eligibility for the trial, that is, a probability of developing breast cancer of 1.66% or greater in 5 years as determined by the Gail model (Ref. 5, Table 1).

A strategy to weigh risks and benefits of tamoxifen therapy in the setting of breast cancer risk reduction in a semiquantitative manner was developed at a national conference of breast cancer experts, and the methods and recommendations have been published (15). Risk of developing breast cancer is the primary determinant of net benefit with greater net benefits accruing to women at highest risk of breast cancer. Weighting the RRs and benefits associated with tamoxifen has a modest effect on calculated net benefits. Both age and the presence of factors that increase the risk of toxicity have the greatest effect on the net benefit associated with tamoxifen. Importantly, all premenopausal women with a 5-year risk of developing invasive breast cancer greater than 1.67% derive net benefit from using tamoxifen to reduce risk. Among postmenopausal women, in whom there is an increased risk of invasive endometrial cancer associated with tamoxifen and the increased risk of thromboembolic events because the latter risk increases with age), the net benefit derives to those women with substantially increased risk (i.e., >3% in 5 years) or who have had a hysterectomy.

Absolute contraindications to the use of tamoxifen for risk reduction include a history of deep venous thrombosis or pulmonary embolism, a history of stroke or transient ischemic
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attack, a history of uncontrolled diabetes or hypertension, and/or a history of uncontrolled atrial fibrillation. Those women, currently taking estrogen, progesterone, androgens, or birth control pills, should discontinue these medications before initiating tamoxifen therapy. Tamoxifen should also be avoided by women who may be pregnant or become pregnant.

Women with a history of LCIS experienced an annual risk for invasive breast cancer of 1.3% per year in BCPT, and tamoxifen reduced this risk by ~50%. In addition, women with atypical ductal or lobular hyperplasia experience an increased risk of subsequent invasive breast cancer. Women with either LCIS or atypical hyperplasia should be considered candidates for primary prevention with tamoxifen if there are no absolute contraindications to its use.

STAR Trial

Subset analyses of older postmenopausal women taking raloxifene for the treatment of osteoporosis indicates a reduction of breast cancer incidence by more than 70%. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to test whether 3 years of raloxifene therapy reduced the risk of fracture in postmenopausal women with osteoporosis (16). The study was a randomized, double-blind trial, in which women taking raloxifene or placebo were followed from 1994 through 1998 at 180 clinical centers composed of community settings and medical practices in 25 countries, including the United States and Europe. A total of 7705 postmenopausal women with osteoporosis, younger than 81 years (mean age, 66.5 years) were enrolled. Osteoporosis was defined by the presence of vertebral fractures or a femoral neck or spine bone mineral density T-score of at least 2.5 SDs below the mean for young healthy women. Women who had a history of breast cancer or who were taking estrogen were excluded. Participants were assigned to receive raloxifene 120 mg daily, raloxifene 60 mg daily, or placebo. Incident vertebral fracture was determined radiographically at baseline and at scheduled 24- and 36-month visits. Nonvertebral fracture was ascertained by interview at 6-month interim visits. Bone mineral density was determined annually by dual-energy X-ray absorptiometry.

After a median follow-up of 40 months, 13 cases of breast cancer were confirmed among the 5129 women assigned to raloxifene versus 27 among the 2576 women assigned to placebo. The RR of breast cancer was 0.24 (95% CI, 0.13–0.44; P < 0.001). Raloxifene did not increase the risk of endometrial cancer (RR, 0.8; 95% CI, 0.2–2.7). Raloxifene at either 60 or 120 mg daily was also associated with statistically significant increases in the incidence of influenza-like symptoms, hot flashes, leg cramps, and endometrial cavity fluid. Women receiving raloxifene had increased risk of venous thromboembolism versus placebo (RR, 3.1; 95% CI, 1.5–6.2), but raloxifene did not cause vaginal bleeding or breast pain.

These findings led the NSABP to design and launch the STAR trial with the support of the National Cancer Institute, Astra-Zeneca Pharmaceuticals, and Eli Lilly & Company. The primary aim of the STAR trial is to determine which of the following three statements is true: (a) compared with tamoxifen, raloxifene significantly reduces the incidence rate of invasive breast cancer; (b) compared with raloxifene, tamoxifen significantly reduces the incidence rate of invasive breast cancer; and (c) the statistical superiority of one of the treatments cannot be demonstrated, and the choice of therapy should be based on risk/benefit considerations.

Secondary aims of the trial include evaluation of the following end points: the incidence of LCIS and ductal carcinoma in situ; the incidence of endometrial cancer; the incidence of ischemic heart disease and bone fractures; and the overall quality of life.

The trial design for STAR is shown in Fig. 1. Because there are no data regarding the safety or efficacy of raloxifene in premenopausal women, the trial is restricted to postmenopausal women whose projected 5-year risk of developing invasive breast cancer is 1.66% or higher. Postmenopause is defined as being 12 or more months without spontaneous menstrual bleeding; having a prior documented hysterectomy and bilateral oophorectomy; being greater than 55 years of age with a prior hysterectomy, with or without oophorectomy; or being less than 55 years of age with a history of prior hysterectomy and an elevated serum follicle-stimulating hormone (FSH) level.

Women 60 years or older are members of the risk-eligible group because of their high age-specific incidence of breast cancer, as are women with LCIS, which was associated with an annual incidence of invasive breast cancer of 1.3% in BCPT. Women ages 35 years or older who are postmenopausal will have their risk of breast cancer evaluated using the model of Gail and colleagues (5). Eligible women are stratified by age, RR, race, and history of LCIS. They are randomly assigned to receive tamoxifen 20 mg p.o. daily or raloxifene 60 mg p.o. daily for 5 years. Because of the difference in the shapes of raloxifene and tamoxifen, each subject receives two tablets, one containing tamoxifen or its placebo, and the other containing raloxifene or its placebo. There is no “placebo group” in the STAR trial because of the positive and dramatic findings in BCPT that now make a placebo control unethical in a trial of SERMs for the reduction of breast cancer incidence.

Women who are ineligible to participate in the STAR trial include those with a prior history of invasive breast cancer, a history of ductal carcinoma in situ, a history of deep venous thrombosis or pulmonary embolism, a history of stroke or tran-
sient ischemic attack, and/or a history of uncontrolled atrial fibrillation. Those women currently taking estrogen, progesterone, androgens, or birth control pills are also ineligible, but risk-eligible subjects may enter the trial if they discontinue hormonal medications for 3 months prior to randomization.

After 22 months of active recruitment for the STAR trial at 193 clinical centers in North America through April 30, 2001, risk assessments have been performed in 83,057 women and 47,325 (57.0%) were eligible for the trial. Of the eligible subjects, 9,710 (20.5% of those eligible) have been randomized. The median age of randomized women is 58 years (mean age, 58 years), 94.6% are white, and their median 5-year risk of breast cancer is 3.3% (mean, 4.0%). LCIS was reported by 8.5% of subjects prior to randomization. The proportion of randomized subjects with Gail model risk ≥ 3.0% by race was: white, 27.9%; black, 44.1%; Hispanic, 59.3%. The trial is designed to recruit a total of 22,000 postmenopausal women and is powered to demonstrate superior efficacy of either agent or their equivalence in reducing the incidence of primary breast cancer. Thromboembolic events and endometrial cancer are the predicted toxicities. Ancillary studies of cognitive function will also be performed. Until results from the STAR trial are available, it is inappropriate to use raloxifene for the purpose of reducing the risk of breast cancer.

Conclusion

A number of promising strategies for reducing the incidence of breast cancer are now available or under active investigation. Additional possibilities will arise from the development of agents that have specific molecular targets for the treatment of breast cancer. It is reasonable to consider interventions to reduce incidence in high-risk populations as being equivalent to the application of very early adjuvant therapies. Future investigation of the biology of hormone-dependent breast cancer will identify additional promising agents, and clinical efficacy will be suggested by studies of new agents in the settings of both adjuvant therapy and the treatment of advanced disease. Additional trials of new agents for reducing the incidence of breast cancer will follow these therapeutic successes.

Open Discussion

Dr. Vogel: Future comparisons (of BCPT P1 subjects) are at this point not possible because of the contamination of the placebo group.

Dr. Kent Osborne: The placebo subjects can be their own control arm, and I’ll bet you that you’ll see a change in the slope of that curve. You’re not going to stop following them, I hope, because the tamoxifen arm is going to go flatter over time. The placebo arm, after they switch, becomes flat and will have the same appearance as the tamoxifen arm but 5 years later.

Dr. Vogel: We will have probably 3000 to 4000 women in the placebo arm. But the problem is that the National Cancer Institute is no longer paying for incident follow-up in the placebo arm. They’re only paying for mortality follow-up. The women taking tamoxifen, or who have taken it, will be followed for mortality, but there will be no cancer incidence or survival comparisons between the two arms.

Dr. Anthony Howell: Can’t you get it from your cancer registries?

Dr. Vogel: In a word, no. It’s possible, but it would be very labor intensive.

Dr. Osborne: We’re seeing the patients every 6 months because they’re high risk. I would be glad to forward that information to you for free. The only thing you have to pay for is the statistical analysis, it seems.

Dr. Vogel: Correct, and that’s the point of contention.

Dr. Paul Goss: Did you say 1800 patients went on tamoxifen?

Dr. Vogel: At last count. It’s probably rising because that opportunity is open continuously. Some of the women in the placebo arm are premenopausal and then when the trial was unblinded, they weren’t yet eligible for STAR and so they will become eligible when they become postmenopausal. So the number who enter STAR or decide to take tamoxifen will continue to rise with time.

Dr. Matthew Ellis: The National Cancer Institute funding decision is the wrong way around, because to see a mortality difference in each arm is extremely unlikely. They should have decided to follow incidence and not mortality.

Dr. Howell: We’re asking for Gail 1.66% to get into the STAR trial, right?

Dr. Vogel: Yes. I should also mention that for all premenopausal women with a Gail model risk of 1.6 or greater, there’s a net benefit using tamoxifen.

Dr. Aman Buzdar: If you use this type of estimated risk/benefit there would be no women to enroll in the study.

Dr. Vogel: Well, in fact, that’s one of the problems in getting African-Americans in the study, because their net benefit is so low. Their baseline age-specific incidence is 30% lower to start with.

Dr. James Ingle: Have you gone back and redone the calculations looking at different weighting schedules? Because I think the African-American recruitment is really a problem, and it’s influenced by that.

Dr. Vogel: Yes, we did that. What really drives it is not so much the weighting but the frequency of the events.

Dr. Osborne: Even in the white population and older age group, you still had to have a fairly high risk to get net benefit. What did you do in that population with the different weightings?

Dr. Vogel: It shifts at about a few percent per year. In the 60 years and older group, you had to have about a 3 or 4% 5-year risk. If you down-weight the endometrial cancers and even the thrombotic events, you’ll move it from needing about a 3 or 4% to get net benefit down to about a 2 or 3%.

Dr. Howell: It’s a pity it’s postmenopausal women only, but I guess that Eli Lilly and Company has no data on raloxifene in premenopausal women.

Dr. Vogel: That’s an interesting story. Lilly had absolutely no data on premenopausal women because they had decided that this was an osteoporosis drug. So they had no trials anywhere in the world that were looking at premenopausal women. There were several proposals to do such a trial, and Joanne Zujewski at the clinical medicine branch at National Cancer Institute started one. In 2 years she has enrolled 23 patients. We met with Lilly as recently as 2 weeks ago, and they have at this point very
little interest in pursuing this in premenopausal women. We pointed out to them that if the STAR trial shows raloxifene is superior to tamoxifen, especially if it’s superior with no endometrial effect, then there will be a clamoring among premenopausal women to use it and they won’t have an indication. Even that argument didn’t sway them very much.

**Dr. Osborne:** The reason you’re seeing a separation of the Kaplan-Meier curves at 3 months has got nothing to do with prevention of breast cancer and everything to do with treatment of subclinical breast cancer. It takes a long time to evolve from atypical ductal hyperplasia, if you believe that scenario. I predicted when I commented on the P1 presentation at American Society of Clinical Oncology 3 years ago that over time the effect will be even greater, and the reason was the ADH data. The slope of that curve is much less steep than it was between years 2 and 3. That’s why I think it’s so important to keep following this study. What you see with the placebo group is that they switch over to tamoxifen, but now their incidence is going to start to plateau and you’ll see a parallel image of the tamoxifen curve delayed by 5 years.

**References**


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* Clin Cancer Res 2001;7:4413s-4418s. 

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