CME CREDIT

BETH A. OVERMOYER, MD
Assistant Professor of Medicine, Case Western Reserve University School of Medicine; Director, Breast Cancer Research Program, Ireland Cancer Center, University Hospitals of Cleveland

THE BREAST CANCER PREVENTION TRIAL (P-1 STUDY)

The role of tamoxifen in preventing breast cancer

ABSTRACT

The recently completed Breast Cancer Prevention Trial found that tamoxifen can reduce the incidence of breast cancer by nearly half in women at high risk, but the benefit comes at a price of increased risk of endometrial cancer and thromboembolism. This article reviews the actions of tamoxifen and the design, findings, and implications of this study.

KEY POINTS

The Food and Drug Administration recently approved tamoxifen as a cancer-prevention treatment, but only for women at increased risk of breast cancer as defined by the Breast Cancer Prevention Trial (BCPT). Physicians can obtain, at no charge, a computer program to calculate risk by calling the National Cancer Institute at 1-800-4-CANCER.

The BCPT was begun before the discovery of the *BRCA1* and *BRCA2* genes, so data are not currently available to support the efficacy of giving tamoxifen to women testing positive for these genes.

Although tamoxifen has estrogen-blocking effects in the breast, it has estrogen-like effects in other organs, with results that are both beneficial (such as increasing bone mineral density and decreasing cardiovascular risk) and harmful (such as increasing the risks of endometrial cancer and thromboembolism).

THE NATIONAL CANCER INSTITUTE'S ambitious study of tamoxifen to prevent breast cancer, which was supposed to last until well into 1999, was terminated early when the benefit of tamoxifen was found to be statistically significant. As a result, tamoxifen was recently approved for breast cancer prevention in some high-risk women. Nonetheless, the use of tamoxifen for prevention remains controversial, as it increases the risk of endometrial cancer, thromboembolism, and other adverse effects.

This article summarizes the results of the study—the Breast Cancer Prevention Trial (BCPT)—and several other studies with seemingly contradictory results. It also reviews the biological rationale for tamoxifen as a preventive agent and discusses its proper use, as well as the promise of other drugs, such as raloxifene, to prevent breast cancer with fewer adverse effects.

RATIONALE FOR TAMOXIFEN IN PREVENTION

Although the mortality rate due to breast cancer is decreasing slightly thanks to better detection and treatment, the disease remains a major problem. In 1998 an estimated 178,700 US women will have been diagnosed with breast cancer and 43,500 women will have died of it.[1] Along with finding better diagnostic and treatment strategies, we need to learn how to prevent this disease.

Certain chemical agents could, in theory, block the carcinogenic process by preventing DNA damage or by inhibiting epithelial cell proliferation.[2] Among these are drugs that interfere with the function of estrogen recep-

TABLE 1

How tamoxifen inhibits epithelial proliferation in the breast

Reduces transforming growth factor alpha
Reduces insulin-like growth factor 1
Stimulates transforming growth factor beta
Binds to calmodulin
Inhibits protein kinase activity

tors, which play a role in initiating and promoting breast cancer.

Tamoxifen, a nonsteroidal triphenylethylene drug, has both estrogen-like and estrogen-blocking effects. Tamoxifen binds to estrogen receptors throughout the body. In some organs—notably, the uterus, bones, and liver—tamoxifen is similar enough to estrogen in its molecular structure to produce estrogen-like effects. However, in the breasts and in breast-cancer tumors it merely occupies the receptor site and thus blocks the effects of endogenous estrogen (FIGURE 1).

About 5% of women stop taking tamoxifen because of side effects

Estrogen-blocking effects

In the breasts, tamoxifen and its metabolite 4-hydroxytamoxifen decrease epithelial cellular proliferation by blocking several processes stimulated by estrogen (TABLE 1).[3–7]

Further, in the liver, tamoxifen stimulates hepatic synthesis of sex hormone-binding globulin (SHBG), which transports estrogen in the circulation. Although this is an estrogen-like effect, increased amounts of circulating SHBG reduce the amount of free estrogen in the circulation.

Estrogen-like effects

In postmenopausal women, tamoxifen reduces basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin; however, plasma estradiol and estrone levels remain normal. In contrast, premenopausal women who take tamoxifen may develop increased serum levels of estradiol, estrone, and progesterone without any significant changes in LH or FSH levels.[3–5]

Like estrogen, tamoxifen has several potentially beneficial effects for postmenopausal women: decreased levels of total cholesterol and low-density lipoprotein cholesterol and increased bone mineral density.[3,7–11] But like estrogen, it has adverse effects as well: increased endometrial proliferation and increased risk of thromboembolism.

PRECLINICAL STUDIES

In studies in rats, tamoxifen both prevented mammary tumors from developing and inhibited established mammary tumors from growing.[3,5,12] It also inhibited the growth of human cancer cells in vitro,[5] and inhibited the development of mammary tumors in mice inoculated with human cancer cells or with mouse mammary tumor virus.[3,5,12]

TAMOXIFEN AS A BREAST CANCER TREATMENT

Tamoxifen is effective for treating both early-stage and metastatic breast cancer. In either situation, its efficacy increases with longer use, as shown in several randomized studies among both premenopausal and postmenopausal patients, with or without axillary lymph node involvement. However, there does not appear to be a dose-response effect.

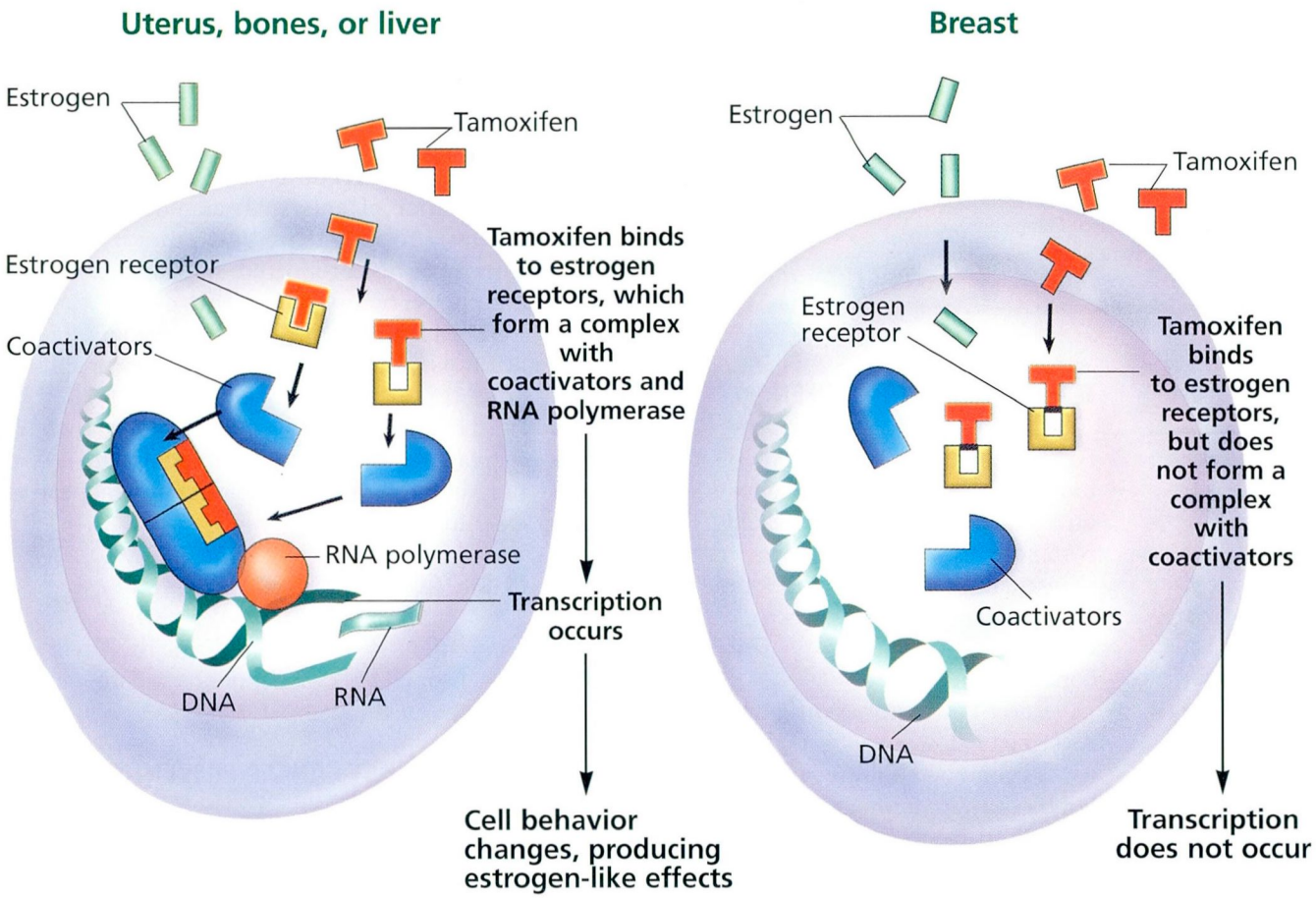
The recommended dosage of tamoxifen as adjuvant therapy in hormone-responsive breast cancer is 20 mg/day for 5 years, regardless of menopausal or nodal status.[4,5,7,13–15]

In metastatic breast cancer, tamoxifen causes a tumor response in approximately 30% of all patients. The response rate is higher—more than 50%—among women with hormone-responsive metastatic disease (ie, whose tumors express estrogen or progesterone receptors).[5,13]

In early-stage breast cancer (ie, stage I or II), tamoxifen reduces the rate of recurrence by approximately 46%, lengthens overall survival by approximately 26%,[16–22] and reduces the incidence of cancer in the contralateral breast by 39% to 49% (TABLE 2).[3,7,15,16–19,22] Again, the benefit appears to increase with duration of use: in an overview analysis of studies, the reduction was 13% in women who took tamoxifen for 1 year, vs 47% in those who took it for 5 years.[16]

How tamoxifen blocks and mimics estrogen

THROUGHOUT THE BODY, tamoxifen competitively binds to receptors for estrogen in the cell nucleus, preventing estrogen from binding. Yet, its effect differs in different organs.



IN MOST ORGANS, notably the uterus, bones, and liver, tamoxifen is similar enough to estrogen to produce estrogen-like effects—endometrial proliferation, bone formation, decreases in harmful lipid levels—although the molecular mechanism may be different from the one used by estrogen.

IN THE BREAST, when tamoxifen occupies the receptor site, the receptor does not go on to bind to coactivators, and DNA transcription does not occur. Thus, tamoxifen reduces the risk of breast cancer in women at high risk.

SOURCE: BASED ON JORDAN VC. DESIGNER ESTROGENS. SCI AM 1998 (OCT); 279(4):60–67.

FIGURE 1

TABLE 2

Effect of tamoxifen on the incidence of contralateral breast cancer

TRIAL*	NO. OF PATIENTS	NO. OF CASES OF CONTRALATERAL CANCER		
		PLACEBO	TAMOXIFEN	*P* VALUE
NSABP B14[15]	2,892	52	28	.002
Scottish[19]	1,312	14	8	NS†
Stockholm[18]	1,846	32	18	.05
CRC[17]	2,230	17	7	.02

*NSABP, National Surgical Adjuvant Bowel and Breast Project; CRC, Cancer Research Campaign
†Not significant

TOXICITY OF TAMOXIFEN

Approximately 5% of women stop taking tamoxifen because of side effects, which are often due to estrogen blockade. The most common are hot flashes, vaginal discharge, menstrual irregularities, and fluid retention. Occasional symptoms include depression, headache, fatigue, and decreased ability to concentrate.

Rarer but more serious adverse effects are described below.

Schedule a yearly pelvic exam for tamoxifen users

Thromboembolic events such as thrombophlebitis, pulmonary embolism, and deep venous thrombosis are increased among tamoxifen users, but the overall incidence remains low at 1% to 3%.[3,6,7,23–25]

Endometrial carcinoma. Several clinical trials demonstrated an increase in endometrial cancer with tamoxifen use, which correlated with longer duration of use and higher doses (40 mg vs 20 mg/day).[3,4,7,13,16,25,26] These studies were not controlled for other risk factors for endometrial carcinoma, such as breast cancer, hypertension, obesity, diabetes, or geographic location, making it difficult to predict the exact risk of endometrial cancer with tamoxifen use in healthy women. However, the risk appears to be at least twice as high in tamoxifen users as in nonusers. In fact, by one estimate, the cumulative incidence is approximately 0.9% among users, compared with 0.2% among nonusers, for an attributable risk of 7 excess cases of endometrial cancer per 1,000 women who take tamoxifen.[13]

Although tamoxifen promotes endometrial carcinoma, it does not appear to cause a more aggressive form of disease. Approximately 80% of cases are low-grade, at stage I at the time of diagnosis. This affects screening recommendations: tamoxifen users should have a pelvic exam once a year, and an endometrial biopsy should be performed if the patient has any postmenopausal bleeding.

Ocular effects such as macular degeneration, retinopathy, and cataract formation have been reported, but have not been conclusively linked to the use of tamoxifen.[24] However, an ophthalmologic evaluation is recommended if ocular problems arise.

Hepatic carcinoma has been shown to increase in incidence with tamoxifen use in rats, but this association does not appear to exist in humans.

METABOLISM

Tamoxifen is metabolized in the liver by cytochrome P450-dependent oxidases and is excreted in the bile.

THE BREAST CANCER PREVENTION TRIAL

A pivotal trial investigating the role of tamoxifen in preventing breast cancer was the Breast Cancer Prevention Trial, also called the "P-1" study, conducted by the National Surgical Adjuvant Bowel and Breast Project (NSABP). The results were discussed at the 34th annual international meeting of the American Society of Clinical Oncology, held on May 16–19, 1998, and subsequently published in the *Journal of the National Cancer Institute*.[27]

More than 131 institutions in the United States and Canada participated. Funding came from the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Tamoxifen and placebo were supplied by Zeneca Pharmaceuticals.

Study aims: Does tamoxifen prevent breast cancer?

The primary aim of the study was to determine whether tamoxifen prevents invasive breast cancer and reduces breast cancer mortality among women at high risk. Secondary aims were to determine whether tamoxifen reduces the incidence of myocardial infarctions and bone fractures, and to evaluate its toxicity in healthy patients.

Study participants: Patients at high risk for breast cancer

Women could enroll in the BCPT study if their 5-year risk of developing breast cancer was at least as high as that of an average 60-year-old woman—1.67%. They could qualify in one of three ways (TABLE 3):

- By being 60 years of age or older.
- By being 35 years of age or older and having a diagnosis of lobular carcinoma in situ on a breast biopsy.
- By being 35 years of age or older and having a sufficiently high score on a risk-assessment model developed by Gail et al,[28] which is based on clinical factors such as the patient's present age, age at menarche, age at first live birth, and the number and pathologic findings of any breast biopsies.

The investigators originally calculated that 16,000 women would need to be enrolled and randomized to receive tamoxifen 20 mg/day or placebo for 5 years to detect a statistically significant benefit. However, an analysis revealed that the participants had more than twice the risk of developing breast cancer than originally estimated. The accrual requirements were subsequently reduced to 13,000, and 13,388 women were enrolled.[29]

At the time of the final report, 13,175 women were available for analysis. Of these, 30% were older than 60 years, and 37% had undergone a hysterectomy prior to enrollment. The patients were at a significantly high risk of developing breast cancer, with 57.6% having a 5-year risk estimated between 2% and 5%.[27]

Controversy from the start

Controversy abounded, even before the study began.[30] Concerns about the toxicity of tamoxifen and its association with secondary malignancies were heatedly debated before several congressional subcommittees. Approval for activation came on April 29, 1992, and accrual was steady until 1994. Then, after 11,000 women were registered, the trial was suspended in March 1994 because of controversy surrounding a previous trial conducted by the National Surgical Adjuvant Bowel and Breast Project. The trial reopened 1 year later after review, but this negative publicity slowed the accrual rate significantly.

TABLE 3

Eligibility for the Breast Cancer Prevention Trial

Age 60 years or older

Age 35 or older, with the diagnosis of lobular carcinoma in situ

Age 35–59 years, with combination of risk factors as identified by Gail et al[28]:

- Family history
- Nulliparity or older age at first live birth
- Number of breast biopsies
- Histologic diagnosis of atypical hyperplasia
- Younger age at menarche

Study results

The BCPT study was stopped early because of clear benefit

Although the investigators had calculated that the BCPT study would need to mature for 5 years, it was stopped after a median follow-up of only 3.6 years when an interim analysis showed that the benefit of tamoxifen was already statistically significant. The median follow-up in the published report was 54.6 months.

Invasive breast cancer. A total of 89 cases of invasive breast cancer occurred in the tamoxifen group, compared with 175 in the placebo group—49% fewer (risk ratio = 0.55; $P < .00001$; FIGURE 2).

Noninvasive breast cancer was also reduced: 35 cases in the tamoxifen group vs 69 in the placebo group (risk ratio = 0.50, $P < .002$).

Effect by subgroup. Among women with a prior diagnosis of lobular carcinoma in situ, tamoxifen reduced the incidence of breast cancer by 56%. Among women with a prior diagnosis of atypical hyperplasia, the reduc-

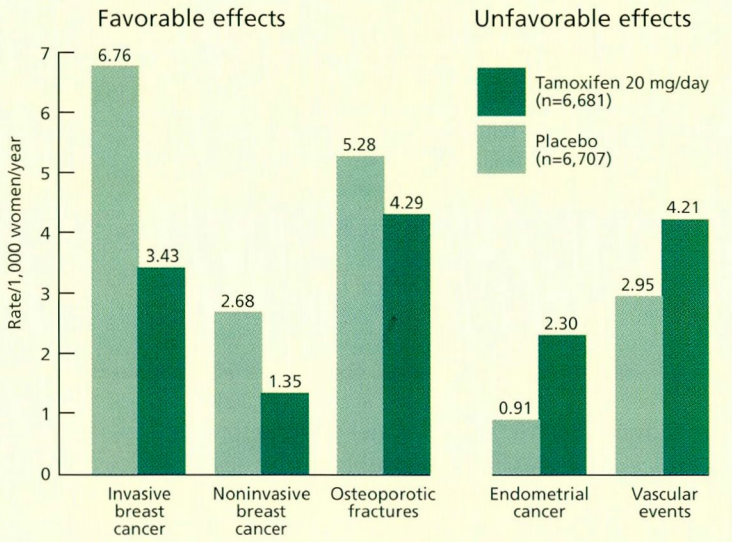


FIGURE 2. Average annual rates of the principal endpoints in the Breast Cancer Prevention Trial.

DATA FROM FISHER ET AL, REFERENCE 27

Toxicity was mainly in patients over age 50

tion was 32% to 66%, depending on other risk factors present.

Although tamoxifen was beneficial in all age groups, older women benefited somewhat more: the risk ratio was 0.56 in women 49 years or younger, vs 0.45 in women 60 years or older.

Tamoxifen had no effect on the incidence of estrogen receptor-negative breast cancers, but reduced the number of estrogen receptor-positive breast cancers significantly: 40 cases in the tamoxifen group vs 130 in the placebo group (risk ratio = 0.31). Approximately 66% of the invasive breast cancers were smaller than 2 cm, and more than 60% were associated with negative lymph nodes, suggesting that tamoxifen significantly reduced the rates of developing larger tumors and lymph node-positive disease.

Cardiovascular disease risk was not affected by tamoxifen.

Vascular events were increased in the tamoxifen group. The risk ratio was 1.59 for strokes, 1.60 for deep vein thrombosis, and 3.01 for pulmonary emboli. The increased risk appeared to be isolated to women older than 50 years.

Fractures of the hip, spine, and wrist were decreased by 19% with tamoxifen use (risk ratio = 0.81).

Endometrial cancer. During the study, 36 cases of endometrial cancer occurred in the tamoxifen group vs 15 in the placebo group (risk ratio = 2.53). The increased risk appeared limited to women 50 years or older. All cases of endometrial cancer were in stage I by the classification system of the International Federation of Gynecology and Obstetrics. The incidence of other malignancies did not appear to increase with tamoxifen use.[27,31]

Survival did not differ between the treatment groups.

INTERPRETING THE BCPT

These findings suggest that 5 years of tamoxifen at 20 mg/day will result in a 49% reduction in the development of breast cancer among high-risk women, regardless of menopausal status. The toxicity of tamoxifen in this patient population appears to be limited to women age 50 years or older, and does not appear to outweigh the benefit of cancer prevention. Although these data are extremely promising, one must approach this information with caution.

Who should get tamoxifen?

On October 29, 1998, the Food and Drug Administration (FDA) approved tamoxifen for preventing breast cancer, but only for women at high risk. In prescribing tamoxifen, physicians should use the same criteria used in the P-1 trial, ie, the patient must be at least 60 years of age, or at least 35 years old with a diagnosis of lobular carcinoma in situ, or at least 35 years old with a sufficiently high score on the Gail risk assessment model. Other risk-assessment tools may not appropriately identify patients who will benefit from tamoxifen as demonstrated by the BCPT study.

The mathematics of the Gail model are somewhat difficult, but the National Cancer Institute has developed a computer program for clinicians to use in counseling patients.[32] Physicians can obtain a copy free of charge by calling 1-800-4CANCER.

Of note: The Gail model was developed before the *BRCA1* and *BRCA2* genes were

discovered, and so does not take genetics into account. Although the NSABP is collecting data on the genetic characteristics of the patients enrolled in the BCPT study, data are not currently available to support the efficacy of giving tamoxifen to women testing positive for the *BRCA1* or *BRCA2* genes.

In view of the possible side effects, the physician should make sure the patient understands the risks and benefits of taking tamoxifen. The decision should be a collaborative one. Patients should also understand that to take tamoxifen they must have close follow-up, and, of paramount importance, they must not become pregnant while taking tamoxifen.

Other studies had negative results

Two other, recent trials of tamoxifen did not arrive at the same conclusion as the BCPT trial.

The Italian Tamoxifen Prevention Study[33] randomized 5,408 women between the ages of 35 and 70 years to receive tamoxifen 20 mg/day or placebo. After a median of 46 months, there was no statistically significant reduction in breast cancer occurrence among the women receiving tamoxifen.

This study had limitations, however. It does not tell us anything about the incidence of endometrial cancer, because all the patients had undergone a total hysterectomy. In addition, some women also had an oophorectomy at the time of hysterectomy, which may have an unknown effect on breast cancer incidence. The investigators also acknowledge that the study had a low statistical power.

The Royal Marsden Hospital Prevention Trial[34] included 2,471 women between the ages of 30 and 70 years with a family history of breast cancer, who received tamoxifen 20 mg/day or placebo. A large number of women in this study also received concurrent hormone replacement therapy. After a follow-up of 70 months, there was no statistically significant reduction in breast cancer among the tamoxifen group.

This study demonstrates the importance of examining the effects of chemoprevention in different high-risk patient populations. The patients in this study all had a significant family history of breast cancer, and familial breast cancer may develop by a mechanism that does not utilize the estrogen receptor as much as sporadic breast cancer does. If this is true, tamoxifen may not have an impact on the development of familial or genetically linked breast cancer. In contrast, patients in the BCPT trial, who were identified by the Gail risk assessment model, may have had a greater number of sporadic breast cancers that were mediated by the estrogen receptor, and had a greater risk reduction when exposed to tamoxifen.

FUTURE PREVENTION STUDIES: TAMOXIFEN VS RALOXIFENE

The promising results of the BCPT P-1 trial are clouded by the increased risk of developing endometrial carcinoma while taking tamoxifen. For this reason, investigators are looking for other drugs that mimic the breast cancer-preventing effects of tamoxifen while having minimal proliferative effects on the endometrium.

One such drug is raloxifene, a selective estrogen receptor modulator that is FDA-approved for preventing and treating osteoporosis. The large Multiple Outcomes of Raloxifene Evaluation (MORE) trial was primarily designed to examine the effects of raloxifene on the incidence of bone fractures among postmenopausal women with known osteoporosis. However, a recent subset analysis of this study demonstrated a 54% reduction in the incidence of breast cancer, without a concomitant rise in endometrial cancers.[35]

A study with raloxifene is underway

Caution must be used in interpreting these data, for two reasons. The patient population studied was estimated to be at a lower risk of developing breast cancer than the general population because they had osteoporosis. Moreover, these data are based on a subset analysis that was not anticipated; therefore, the power of the results are low.

Nevertheless, the findings were provocative enough to prompt the National Cancer Institute to sponsor another trial to compare the chemopreventive effects of tamoxifen vs raloxifene. Study patients will be postmenopausal women age 35 years or older who are at an increased risk of developing breast cancer. This study, called STAR (Study of Tamoxifen and Raloxifene) or NSABP P-2, will enroll 22,000 women at 300 institutions

beginning late in 1998. Data from this trial are not expected for approximately 8 years.

QUESTIONS REMAIN

These and future studies may allow physicians to prescribe agents that prevent breast cancer, but questions remain. Is tamoxifen the optimal chemopreventive agent for breast cancer? Is 5 years the optimal duration of tamoxifen treatment? Are we truly preventing breast cancer, or are we simply changing its natural history by inhibiting the growth of estrogen receptor-positive breast cancer?

That we can even ask these questions shows that cancer therapy has entered a new age, focusing on prevention in addition to treatment. We anxiously await the answers.

REFERENCES

1. **Landis S, Murray T, Bolden S, et al.** Cancer statistics, 1998. Cancer 1998; 48:6–29.
2. **O'Shaughnessy J.** Chemoprevention of breast cancer. JAMA 1996; 275:1349–1353.
3. **Nayfield S, Karp J, Ford L, et al.** Potential role of tamoxifen in prevention of breast cancer. J Natl Cancer Inst 1991; 83:1450–1459.
4. **Love R.** Tamoxifen therapy in primary breast cancer: biology, efficacy, and side effects. J Clin Oncol 1989; 7:803–815.
5. **Furr B, Jordan V.** The pharmacology and clinical uses of tamoxifen. Pharmacol Ther 1984; 25:127–205.
6. **Friedman Z.** Recent advances in understanding the molecular mechanisms of tamoxifen action. Cancer Invest 1998; 16:391–396.
7. **Jaiyesimi I, Buzdar A, Decker D, et al.** Use of tamoxifen for breast cancer: twenty-eight years later. J Clin Oncol 1995; 13:513–529.
8. **Decensi A, Fontana V, Bruno S, et al.** Effect of tamoxifen on endometrial proliferation. J Clin Oncol 1996; 14:434–440.
9. **Love R, Weibe D, Feyzi J, et al.** Effects of tamoxifen on cardiovascular risk factors in postmenopausal women after 5 years of treatment. J Natl Cancer Inst 1994; 86:1534–1539.
10. **Powles T, Hickish T, Kanis J, et al.** Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996; 14:78–84.
11. **Love R, Wiebe D, Newcomb P, et al.** Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. Ann Intern Med 1991; 115:860–864.
12. **Greenwald P, Kramer B, Weed D.** Expanding horizons in breast and prostate cancer prevention and early detection. J Cancer Education 1993; 8:91–107.
13. **Legha S.** Tamoxifen in the treatment of breast cancer. Ann Intern Med 1988; 109:219–228.
14. **Tormey D, Gray R, Falkson H.** Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. J Natl Cancer Inst 1996; 88:1828–1833.
15. **Fisher B, Dignam J, Bryant J, et al.** Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 1996; 88:1529–1542.
16. **Early Breast Cancer Trialists' Collaborative Group.** Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998; 351:1451–1467.
17. **Cancer Research Campaign Breast Cancer Trials Group.** Preliminary results from the Cancer Research Campaign Trail evaluating tamoxifen duration in women aged fifty years or older with breast cancer. J Natl Cancer Inst 1996; 88:1834–1839.
18. **Swedish Breast Cancer Cooperative Group.** Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. J Natl Cancer Inst 1996; 88:1543–1549.
19. **Breast Cancer Trials Committee, Scottish Cancer Trials.** Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. Lancet 1987; 2:171–175.
20. **Tormey D, Gray R, Abeloff M, et al.** Adjuvant therapy with a doxorubicin regimen and long-term tamoxifen in premenopausal breast cancer patients: an eastern cooperative oncology group trial. J Clin Oncol 1992; 10:1848–1856.
21. **Ribeiro G, Swindell R.** The Christie Hospital tamoxifen (Nolvadex) adjuvant trial for operable breast carcinoma—7-year results. Eur J Cancer Clin Oncol 1985; 21:897–900.
22. **Nolvadex Adjuvant Trial Organization.** Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer. Br J Cancer 1988; 57:608–611.
23. **Love R, Cameron L, Connell B, et al.** Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Intern Med 1991; 151:1842–1847.
24. **Nayfield S, Gorin M.** Tamoxifen-associated eye disease: a review. J Clin Oncol 1996; 14:1018–1026.
25. **Stearns V, Gelmann E.** Does tamoxifen cause cancer in humans? J Clin Oncol 1998; 16:779–792.
26. **Fisher B.** Commentary on endometrial cancer deaths in tamoxifen-treated breast cancer patients. J Clin Oncol 1996; 14:1027–1039.
27. **Fisher B, Costantino J, Wickerham DL, et al.** Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998; 90:1371–1388.
28. **Gail M, Brinton L, Byar D, et al.** Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81:1879–1886.
29. **Fisher B, Costantino J.** Highlights of the NSABP breast cancer prevention trial. Cancer Control 1997; 4:78–86.
30. **Smigel K.** Breast cancer prevention trial under scrutiny (again) (editorial). J Natl Cancer Inst 1992; 84:1692–1694.
31. **Horton J.** Breast cancer care: developments in 1998. Cancer Control. 1998; 5:338–345.
32. **Smith J.** New computer program assesses a woman's risk for developing breast cancer. J Natl Cancer Inst 1998; 90:1332.
33. **Veronesi U, Maisonneuve P, Costa A, et al.** Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Lancet 1998; 352:93–97.
34. **Powles T, Eeles R, Ashley S, et al.** Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998; 352:98–101.
35. **Cummings S, Norton L, Eckert S, et al.** Raloxifene reduces the risk of breast cancer and may decrease the risk of endometrial cancer in postmenopausal women. Two-year findings from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (abstract). Proc ASCO 1998; 17:2a.

ADDRESS: *Beth A. Overmoyer, MD, Ireland Cancer Center, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106.*