

EMBARGOED FOR RELEASE  
4 p.m., EDT  
Monday, September 14, 1998

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## **Questions and Answers: The Breast Cancer Prevention Trial**

### **1. What is the Breast Cancer Prevention Trial?**

The Breast Cancer Prevention Trial (BCPT) is a clinical trial (a research study conducted with people) designed to see whether taking the drug tamoxifen (Nolvadex®) can prevent breast cancer in women who are at an increased risk of developing the disease. The BCPT is also looking at whether taking tamoxifen decreases the number of heart attacks and reduces the number of bone fractures in these women. The study began recruiting participants in April 1992 and closed enrollment in September 1997; 13,388 women ages 35 and older are enrolled. Researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting the study in more than 300 centers across the United States and Canada. The study is funded by the National Cancer Institute (NCI), the United States' primary agency for cancer research.

### **2. What is tamoxifen?**

Tamoxifen is a drug, taken by mouth as a pill. It has been used for 25 years to treat patients with breast cancer. Tamoxifen works against breast cancer, in part, by interfering with the activity of estrogen, a female hormone that promotes the growth of breast cancer cells. For this reason, tamoxifen is often called an "anti-estrogen." In treatment, the drug slows or stops the growth of these cancer cells.

### **3. Why was tamoxifen tested to prevent breast cancer?**

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Research had shown that taking tamoxifen as adjuvant therapy for breast cancer not only helps prevent the original breast cancer from returning but also helps to prevent the development of new cancers in the opposite breast. Researchers believed that tamoxifen might have a similar beneficial effect for women at increased risk of breast cancer. While tamoxifen acts *against* the effects of estrogen in breast tissue, it acts *like* estrogen in other organs. Tamoxifen's estrogen-like effects include the lowering of blood cholesterol and the slowing of bone loss.

**4. Who participated in the BCPT?**

Women at increased risk for developing breast cancer participated in the study. These included women 60 years of age and older who qualified to participate based on age alone, and women between the ages of 35 and 59 with an increased risk of breast cancer equivalent to or greater than that of a 60-year-old woman. At age 60, about 17 of every 1,000 women are expected to develop breast cancer within five years.

About 40 percent of the women on the trial were ages 35 to 49, about 30 percent were ages 50 to 59, and about 30 percent were age 60 or older. Almost 4 percent of the participants were minorities, including Black American, Asian American, Hispanic, and other groups.

**5. Did every woman in the study receive tamoxifen?**

No. Participants in the BCPT were randomized (selected by chance) to receive either tamoxifen or a placebo (an inactive pill that looked like tamoxifen). In a process known as "double blinding," neither the participant nor her physician knew which pill she was receiving. Setting up a study in this way allowed the researchers to clearly see the true benefits and side effects of tamoxifen without the influence of other factors. According to the design, all women in the study were to take two pills a day for five years, either a 20-mg dose of tamoxifen (two 10-mg pills) or placebo pills.

**6. Why were women 60 years of age or older eligible for the BCPT based on age alone?**

Many diseases, including breast cancer, occur more often in older persons. The risk of developing breast cancer increases with age, so breast cancer occurs more commonly in women over 60 years of age. The risk of developing heart disease or osteoporosis also increases with age, and those diseases are also being studied in the BCPT.

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**7. What factors were used to determine increased risk of breast cancer for the participants aged 35 to 59?**

To enroll in the study, women between 35 and 59 years of age needed to have a risk of developing breast cancer within the next five years that was equal to or greater than the average risk for 60-year-old women. This increased risk was determined in one of two ways. Women diagnosed as having lobular carcinoma in situ, a condition that is not cancer but indicates an increased chance of developing invasive breast cancer, were eligible based on that diagnosis alone. The risk for other women was determined by a computer calculation based on the following factors:

- Number of first-degree relatives (mother, daughters, or sisters) who had been diagnosed as having breast cancer;
- Whether a woman had any children and her age at her first delivery;
- The number of times a woman had breast lumps biopsied, especially if the tissue showed a condition known as atypical hyperplasia; and
- The woman's age at her first menstrual period.

**8. What proportion of women in the United States are estimated to be at the level of risk required for participation in the BCPT?**

At age 35, about three women in 1,000 or .3 percent, would have qualified for the study based on their estimated breast cancer risk.

At age 40, the proportion is about 27 women in 1,000, or 2.7 percent.

At age 45, the proportion is about 71 women in 1,000, or 7.1 percent.

At age 50, the proportion is about 93 women in 1,000, or 9.3 percent.

At age 55, the proportion is about 125 women in 1,000, or 12.5 percent.

At age 60 and beyond, all women would have met the breast cancer risk criteria.

**9. Did other factors affect eligibility for the study?**

Certain health conditions affected eligibility for the study. For example, women at increased risk for blood clots could not participate. Also, women taking hormone replacements and women using oral contraceptives ("the pill") could not take part in the trial unless they stopped taking these medications. Those who stopped taking these hormones were eligible for the study three months after they discontinued the drugs.

Women who were pregnant or who planned to become pregnant were not eligible to participate. Animal studies have suggested that the use of tamoxifen during pregnancy might harm the fetus. Premenopausal women participating in the BCPT were required to

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use some method of birth control other than oral contraceptives. Oral contraceptives may change the effects of tamoxifen and may also affect the risk of breast cancer.

**10. What are the results of the BCPT?**

At this point (data to March 31, 1998), women on the trial have been followed on the study for about four years (47.7 months). Results show 49 percent fewer diagnoses of invasive breast cancer in women who were randomized to take tamoxifen compared to women who were randomized to take the placebo (89 cases in the tamoxifen group vs. 175 cases in the placebo group). Women on tamoxifen also had 50 percent fewer diagnoses of noninvasive breast cancer, such as ductal or lobular carcinoma in situ (35 cases in the tamoxifen group vs. 69 cases in the placebo group). Nine women have died of breast cancer, three women in the tamoxifen group and six women in the placebo group.

Women in the tamoxifen group had almost 20 percent fewer bone fractures of the hip, wrist, and spine than women in the placebo group (111 cases in the tamoxifen group vs. 137 cases in the placebo group), a result that nearly reached statistical significance. There was no difference in the number of heart attacks between the two groups.

Tamoxifen did increase the women's chances of three rare but serious health problems: endometrial cancer (cancer of the lining of the uterus) 36 cases in the tamoxifen group vs. 15 cases in the placebo group; pulmonary embolism (blood clot in the lung) 18 cases in the tamoxifen group vs. six cases in the placebo group; and deep vein thrombosis (blood clots in major veins) 35 cases in the tamoxifen group vs. 22 cases in the placebo group.

**11. What were the participants' chances of developing endometrial cancer?**

BCPT participants who were randomized to the tamoxifen group had more than twice the chance of developing endometrial cancer compared with women on placebo (based on 36 cases in the tamoxifen group vs. 15 cases in the placebo group). The increased risk of endometrial cancer was equal to the risk that was expected and is in the same range as (or less than) the endometrial cancer risk for postmenopausal women taking single-agent estrogen replacement therapy. Estrogens and agents that act like estrogens are known to increase the risk of endometrial cancer.

**ALL THE PARTICIPANTS WERE INFORMED ABOUT THE POSSIBILITY OF INCREASED RISK OF ENDOMETRIAL CANCER BEFORE THEY ENTERED THE STUDY.** Like all cancers, endometrial cancer is potentially life-threatening. All but one (in the placebo group) of the endometrial cancers that occurred during the study were found at an early stage, when treatment is very effective. However, one participant (also in the placebo group) died of endometrial cancer. About 38 percent of BCPT participants in both groups had a hysterectomy (surgery to remove the uterus) for a variety of health reasons before

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joining the study. Therefore, these women were not at any known risk for endometrial cancer.

**12. What was done to help diagnose endometrial cancer early?**

Pap smears are very effective at detecting cancer in the cervix but are not useful for detecting endometrial cancer. Therefore, a screening endometrial sampling — removal of cells in the lining of the uterus for examination under a microscope — was used in the BCPT to check for abnormalities in the endometrium. Women who joined the study after October 1994 were required to have a screening endometrial sampling before entering the study if their uterus had not been removed. All women in the study were strongly urged to have screening endometrial sampling done annually throughout the study (at no cost to them), but could decline if they chose. In addition to these annual tests, women in the BCPT were told to see their physicians if they experienced abnormal vaginal bleeding or pain. The vast majority of the endometrial cancers that were diagnosed in the BCPT caused such symptoms.

**13. What were the participants' chances of getting blood clots?**

Women taking tamoxifen had three times the chance of developing a pulmonary embolism (blood clot in the lung) as women on placebo (based on 18 cases in the tamoxifen group vs. six cases in the placebo group). Three women died from these embolisms, all in the tamoxifen group. Women in the tamoxifen group were also more likely to have deep vein thrombosis (a blood clot in a major vein) than women on placebo (35 cases vs. 22 cases). Blood clots occur more often in people with high blood pressure (hypertension) or diabetes, smokers, and in those who are obese.

**14. Is there a relationship between tamoxifen use and the development of eye problems?**

Women in the tamoxifen group, in general, had no more eye problems than women taking the placebo. However, women taking tamoxifen were at a slightly increased risk for developing cataracts (a clouding of the lens inside the eye) according to other research. Over the course of the study, 574 women in the tamoxifen group and 507 women in the placebo group developed cataracts; 114 and 73 women, respectively, had cataract surgery. As women age, they are more likely to develop cataracts whether or not they take tamoxifen.

**15. Was tamoxifen associated with any other cancers?**

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Tamoxifen was not associated with an increased risk of any other cancer other than endometrial cancer.

**16. What were the other adverse effects of tamoxifen?**

Like most medications, whether over-the-counter medications, prescription drugs, or drugs in research studies, tamoxifen causes adverse effects in some women. The effects experienced most often by women in the tamoxifen group were hot flashes and vaginal discharge. Women in *both* groups reported sometimes having side effects — even though the placebo itself would not cause any symptoms. The side effects that some women in both groups reported included: vaginal dryness, itching, or bleeding; menstrual irregularities; depression; loss of appetite; nausea and/or vomiting; dizziness; headaches; and fatigue. Treatments that could minimize or eliminate most side effects were available to the participants.

**17. What is happening to the participants now?**

All participants are being asked to continue with their follow-up examinations. Women who have been randomized to the tamoxifen group who have not completed five years of tamoxifen therapy will have the opportunity to continue on therapy. Postmenopausal women who had been taking the placebo are being invited to participate in the upcoming Study of Tamoxifen and Raloxifene that will compare tamoxifen to the osteoporosis drug raloxifene, which could have similar breast cancer prevention properties, but might be associated with fewer adverse effects. Women in the placebo group also have the option of seeking tamoxifen from their private health care providers.

**18. How can a woman learn more about the Study of Tamoxifen and Raloxifene?**

The NSABP is planning a new breast cancer prevention trial, scheduled to begin recruiting participants in 1999. The trial, known as STAR (Study of Tamoxifen and Raloxifene) would involve about 22,000 postmenopausal women who are at least 35 years old and are at increased risk for developing breast cancer. The study would compare tamoxifen to raloxifene, an osteoporosis drug that appears to have breast cancer prevention effects. Raloxifene (Evista®) is manufactured by Eli Lilly and Company, Indianapolis, Ind.

There are several ways to be placed on a mailing list for more information on this upcoming trial — by Internet, by mail, or by fax. On the Internet, the NSABP homepage (<http://www.nsabp.pitt.edu>) has a form available. By regular mail, send a letter or post

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card with name, mailing address, and a note specifying interest in future breast cancer prevention trials to: NSABP, Box 21, Pittsburgh, PA 15261. Or fax the same information to NSABP at (412) 330-4660. When information about the next prevention trial is available, it will be mailed to the people on this list.

**19. Would it be beneficial for women to take tamoxifen for more than five years?**

Not necessarily: Results of another NSABP study in which women with early stage breast cancer took tamoxifen for five years vs. 10 years (called the B-14 trial) showed no greater benefit from the longer duration of tamoxifen and showed a trend toward more adverse effects.

**20. Based on the BCPT results, should women who are at increased risk of breast cancer take tamoxifen?**

Women who are at increased risk of breast cancer now have the option to consider taking tamoxifen to reduce their chances of developing breast cancer. As with any medical procedure or intervention, the decision to take tamoxifen is an individual one in which the benefits and risks of the therapy must be considered. The balance of these benefits and risks will vary depending on a woman's personal health history and how she weighs the benefits and risks. Therefore even if a woman is at increased risk of breast cancer, tamoxifen therapy may not be appropriate for her. Women who are considering tamoxifen therapy should talk with their health care provider.

**21. How does a woman determine whether she is at increased risk of breast cancer?**

A computer-based tool that allows health professionals to project a woman's individualized estimate of breast cancer risk is being released in a pilot program by the NCI this month. The Breast Cancer Risk Assessment Tool is a computer disk that women and their health care providers can use to estimate a woman's chances of developing breast cancer based on several established risk factors. Researchers from NCI and NSABP developed the tool. The disk is available at no charge and in personal computer (PC) and MacIntosh computer formats. To order, call the NCI's Cancer Information Service at 1-800-4-CANCER or visit NCI's CancerTrials Web site at <http://cancertrials.nci.nih.gov>.

**22. Will women with breast cancer gene alterations (BRCA1 and BRCA2) benefit from tamoxifen?**

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These two breast cancer gene alterations, which increase a woman's risk of the disease, were identified after the BCPT began. Using blood samples taken from participants, analyses are under way to determine whether tamoxifen has the same relative effects on women whether or not they carry alterations in these genes. To maintain strict confidentiality, samples in this study have no identifying labels that could link them to individual women. Therefore, researchers will not be able to give individual results to a participant or her health care provider.

**23. Is tamoxifen a good substitute for hormone replacement therapy?**

No. Every woman has individual health risks that affect her need for interventions such as hormone replacement therapy or tamoxifen therapy. Hormone replacement therapy is intended to help women maintain bone density. Many women benefit from a reduction in hot flashes and other problems that can affect quality of life. Some studies have suggested that hormone replacement therapy increases a woman's chances of developing breast cancer. The BCPT results show that tamoxifen reduces breast cancer risk and may help slow or reduce bone loss, as evidenced by the reduced number of bone fractures.

**24. Should women who are not known to be at increased risk of breast cancer consider taking tamoxifen?**

This question has not been studied. At this time, there is no evidence that tamoxifen is beneficial for women who do not have an increased risk of breast cancer.

**25. Are there any women who should not take tamoxifen?**

Animal studies have suggested that the use of tamoxifen during pregnancy might harm the fetus. Women who were pregnant or who planned to become pregnant were not eligible to participate in the BCPT. Premenopausal women participating in the BCPT were required to use some method of birth control other than oral contraceptives ("the pill") while taking tamoxifen. Oral contraceptives may change the effects of tamoxifen and may also affect the risk of breast cancer. Women with a history of blood clots, hypertension, diabetes, and cigarette smoking must also consider that tamoxifen increases the risk for serious blood clots.

**26. Where were the study results published?**

The study is published in the *Journal of the National Cancer Institute*, Vol. 90, No. 18, Sept. 16, 1998. The study is titled, "Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. The authors are

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B. Fisher, J.P. Costantino, D.L. Wickerham, C.K. Redmond, M. Kavanah, W.M. Cronin, V. Vogel, A. Robidoux, N. Dimitrov, J. Atkins, M. Daly, S. Wieand, E. Tan-Chiu, L. Ford, N. Wolmark, and other NSABP investigators.

**27. What is the National Surgical Adjuvant Breast and Bowel Project?**

The NSABP is a cooperative group with a 40-year-history of designing and conducting clinical trials, the results of which have changed the way breast cancer is treated, and now, potentially prevented. Results of research studies conducted by NSABP researchers have been the dominant force in altering the standard surgical treatment of breast cancer from radical mastectomy to lumpectomy plus radiation. This group was also the first to demonstrate that adjuvant therapy could alter the natural history of breast cancer, thus increasing survival rates. When a breast cancer prevention study was initially conceived, more than 30,000 women with breast cancer had participated in treatment studies conducted by NSABP investigators. Additional research studies to prevent cancer are a logical next step for this research group.

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For more information about cancer visit NCI's Web site for patients, public, and the mass media at <http://rex.nci.nih.gov> or NCI's main web site at <http://www.nci.nih.gov>.