Breast Cancer Prevention Studies

Key Points

- Breast cancer prevention studies are clinical trials involving women who have not had cancer but are at high risk of developing the disease (see Question 1).
- In the Breast Cancer Prevention Trial (BCPT), women who received tamoxifen had a lower incidence of breast cancer than women who did not receive the drug. Initial results of this study were published in 1998 (see Question 2).
- Another trial, the Study of Tamoxifen and Raloxifene (STAR), found that tamoxifen and another drug called raloxifene are equally effective in reducing breast cancer risk in postmenopausal women who are at increased risk of the disease (see Question 3).
- Other breast cancer prevention studies are in progress (see Question 4).

1. What are breast cancer prevention studies?

Breast cancer prevention studies are clinical trials (research studies) that explore ways of reducing the risk, or chance, of developing breast cancer. These studies usually involve women who have not had breast cancer but are at high risk of developing the disease. For example, it is clear that breast cancer occurs more often in women over the age of 60 years; so, these women have a higher risk of developing breast cancer than younger women. Other factors associated with increased risk include a personal or family history of breast cancer and changes in certain genes, such as BRCA1 and BRCA2.

Most breast cancer prevention research is based on evidence linking the development of this disease, in many cases, with exposure to the hormone estrogen. The focus of several breast cancer prevention studies has been on testing the effectiveness of drugs called selective estrogen receptor modulators (SERMs). SERMs are drugs that have some antiestrogen properties and some estrogen-like properties. Their antiestrogen activity may help reduce the risk of breast cancer by blocking the effects of estrogen on breast

tissue. Their estrogen-like properties may help prevent the loss of bone density in postmenopausal women; however, some SERMs may cause bone loss in premenopausal women.

2. What is the Breast Cancer Prevention Trial (BCPT)?

The Breast Cancer Prevention Trial (BCPT) was funded by the National Cancer Institute (NCI), a part of the National Institutes of Health, and conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The BCPT was designed to see whether tamoxifen (Nolvadex®), a SERM, could prevent breast cancer in women who are at an increased risk of developing this disease. The study began recruiting participants in April 1992 and closed to enrollment in September 1997. In the study, 13,388 premenopausal and postmenopausal women were enrolled at more than 300 centers across the United States and Canada and randomly assigned to receive tamoxifen or a placebo orally each day for 5 years.

Initial results of the BCPT were published in September 1998 (1). Among the women randomly assigned to take tamoxifen, there were 49 percent fewer diagnoses of invasive breast cancer than among the women randomly assigned to take the placebo. Women on tamoxifen also had 49 percent fewer diagnoses of noninvasive breast tumors, such as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

Most of the side effects associated with tamoxifen in the study were temporary. However, long-term increased risks were found for several serious health problems: endometrial cancer (cancer of the lining of the uterus), uterine sarcoma (cancer of the muscular wall of the uterus), pulmonary embolism (blood clot in the lung), deep vein thrombosis (blood clot in a large vein), and stroke. These increased risks for serious health problems were generally greater among postmenopausal women than among premenopausal women. The increased risk for endometrial cancer was found only among postmenopausal women.

In November 2005, updated results of the BCPT were published (2). The updated results confirmed tamoxifen's ability to reduce the risk of breast cancer in women at increased risk of developing the disease. Through 7 years of follow-up (that is, at least 2 years past the maximum time that women assigned to take tamoxifen received the drug), there were 43 percent fewer cases of invasive breast cancer diagnosed among the women assigned to tamoxifen than among the women assigned to the placebo. The reduction in risk of developing noninvasive breast tumors also persisted at 7 years, with 27 percent fewer diagnoses of noninvasive breast tumors among the women who took tamoxifen than among the women who took the placebo. In addition, the previously observed increased risks of stroke, pulmonary embolism, and deep vein thrombosis were somewhat reduced at 7 years of follow-up.

In October 1998, based on the initial results of the BCPT, the U.S. Food and Drug Administration (FDA) approved the use of tamoxifen for the prevention of breast cancer in women at high risk of developing the disease.

More information about the BCPT is available on NCI's Web site at http://www.cancer.gov/clinicaltrials/digestpage/BCPT on the Internet.

3. What is the Study of Tamoxifen and Raloxifene (STAR)?

The Study of Tamoxifen and Raloxifene, known as STAR, was a follow-up study to the BCPT. In STAR, another SERM called raloxifene (Evista®) was compared with tamoxifen in preventing breast cancer in postmenopausal women at increased risk of developing the disease. The study, which was funded by NCI and conducted by the NSABP, involved more than 19,000 postmenopausal women who were at least 35 years of age and were at increased risk of developing breast cancer. The women were randomly assigned to receive tamoxifen or raloxifene orally each day for 5 years. STAR began recruiting participants in July 1999 and completed enrollment in November 2004. More than 200 centers across the United States, Canada, and Puerto Rico participated in the study.

Initial results from STAR were published in June 2006 (3). The results showed that raloxifene and tamoxifen are equally effective in reducing breast cancer risk in postmenopausal women who are at increased risk of the disease. Both drugs reduced the risk of developing invasive breast cancer by about 50 percent. However, raloxifene, unlike tamoxifen, did not reduce the risk of noninvasive breast tumors, such as DCIS and LCIS.

Information collected from STAR participants about their physical and mental health revealed no significant differences between the women who took raloxifene and those who took tamoxifen; however, women in the tamoxifen group reported better sexual functioning. Although symptom severity in the study was generally low, women in the tamoxifen group also reported more vasomotor problems (e.g., hot flashes, cold sweats), gynecologic problems (e.g., bleeding or spotting, vaginal discharge), bladder problems (e.g., difficulty with bladder control when laughing or crying), and leg cramps; women in the raloxifene group reported more musculoskeletal problems (e.g., joint pain, muscle stiffness), pain during sexual intercourse, and weight gain (4).

With regard to risks for serious health problems, there were fewer cases of endometrial cancer, pulmonary embolism, and deep vein thrombosis among the women who took raloxifene. There was no difference in the incidence of stroke between the raloxifene group and the tamoxifen group.

More information about STAR is available on NCI's Web site at http://www.cancer.gov/clinicaltrials/digestpage/STAR on the Internet.

In September 2007, the FDA approved raloxifene to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. Raloxifene was approved by the FDA as a treatment for osteoporosis in 1999.

4. What other breast cancer prevention studies are being funded by NCI?

NCI is supporting additional clinical studies to determine whether other drugs or natural products are able to help prevent breast cancer in women who are at increased risk of developing the disease. Drugs called aromatase inhibitors (AIs) are being tested by NCI in a few small studies.

AIs block the activity of an enzyme called aromatase, which the body uses to make estrogen. Although the ovary is the main site of aromatase and estrogen production in a woman's body, other tissues, including adipose (fat), bone, and brain tissue, make these substances as well.

Using AIs to block estrogen production in premenopausal women is not very effective, in part because the ovary is stimulated to make more aromatase (and, therefore, estrogen) when the blood level of estrogen falls below normal. This does not happen in postmenopausal women, whose ovaries have stopped making aromatase and estrogen. Therefore, AIs are being studied primarily in postmenopausal women.

AIs have already been approved by the FDA for the treatment of hormone-sensitive breast cancer in postmenopausal women. All three FDA-approved AIs are being tested in breast cancer prevention studies. These drugs are anastrozole (Arimidex®), exemestane (Aromasin®), and letrozole (Femara®).

In addition, scientists are continuing to study the basic biology and genetics of breast cancer. This research may lead to other, better ways to prevent breast cancer.

For information about ongoing clinical studies of breast cancer prevention, visit NCI's Web site at http://www.cancer.gov or contact NCI's Cancer Information Service (CIS) (see below).

5. What additional options are available for women at increased risk of breast cancer?

Doctors generally suggest that high-risk women be closely monitored and have regular medical checkups, so that if breast cancer develops, it is likely to be detected at an early stage, when it is most treatable (5). These women may also consider participating in breast cancer prevention studies, taking tamoxifen or raloxifene, or undergoing preventive surgery to reduce breast cancer risk.

Preventive mastectomy is surgery to remove one or both breasts in an effort to prevent or reduce the risk of breast cancer (6). Existing data suggest that preventive mastectomy may significantly reduce (by about 90 percent) the chance of developing breast cancer in women at high risk of developing the disease due to BRCA1 or BRCA2 gene mutations (7). Other data suggest that preventive oophorectomy (surgery to remove the ovaries) in women at high risk of ovarian cancer because of BRCA1 or BRCA2 gene mutations may also reduce the risk of breast cancer by about 50 percent (8).

More information about preventive mastectomy can be found in the NCI fact sheet *Preventive Mastectomy: Questions and Answers*, which is available at http://www.cancer.gov/cancertopics/factsheet/Therapy/preventive-mastectomy on the Internet.

The decision to join a clinical study, take medication, or undergo preventive surgery is an individual one. With any medical procedure or intervention, both the benefits and the risks of the treatment must be considered. The balance of these factors will vary depending on a woman's personal and family health history and how she weighs the benefits and risks. Women who are considering surgery or other steps to reduce the risk of breast cancer should discuss their personal risk factors with their doctor.

6. Where can women learn more about estimating their risk for breast cancer?

NCI's *Cancer Risk: Understanding the Puzzle* Web site is an interactive site with information to help women make informed decisions about lowering their risk of cancer. It includes a section on breast cancer where women can find out the basics about breast cancer risk, determine which risk factors apply to them, and identify ways to reduce their risk. It includes questions women can ask their doctors about their risk for breast cancer. The site also includes links to NCI's *Breast Cancer Risk Assessment Tool* and tips on how to analyze stories in the news about cancer. This site is available at http://understandingrisk.cancer.gov on the Internet.

Additional information can be found in the *PDQ® Breast Cancer Prevention* summary for patients. This summary of information from PDQ, NCI's comprehensive cancer information database, provides information about breast cancer and how often it occurs, describes breast cancer prevention methods, and gives current facts about which people or groups of people would most likely be helped by following breast cancer prevention methods. This resource is available at http://www.cancer.gov/cancertopics/pdq/prevention/breast/patient on the Internet.

People who are concerned about their cancer risk are encouraged to talk with their doctor.

Selected References

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2. Fisher B, Costantino JP, 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. *Journal of the National Cancer Institute* 2005; 97(22):1652–1662.

3. 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. *Journal of the American Medical Association* 2006; 295(23):2727–2741.

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5. Thull DL, Vogel VG. Recognition and management of hereditary breast cancer syndromes. *The Oncologist* 2004; 9(1):13–24.

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7. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. *Journal of Clinical Oncology* 2004; 22(6):1055–1062.

8. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *New England Journal of Medicine* 2002; 346(21):1616–1622.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 7.5, *Preventive Mastectomy: Questions and Answers* (http://www.cancer.gov/cancertopics/factsheet/Therapy/preventive-mastectomy)
- National Cancer Institute Fact Sheet 7.16, *Tamoxifen: Questions and Answers* (http://www.cancer.gov/cancertopics/factsheet/Therapy/tamoxifen)
- Breast Cancer Home Page (http://www.cancer.gov/cancertopics/types/breast)
- *If You Want To Find Ways To Prevent Cancer...Learn About Prevention Clinical Trials* (http://www.cancer.gov/clinicaltrials/learning/about-prevention-trials)
- *What You Need To Know About™ Breast Cancer* (http://www.cancer.gov/cancertopics/wyntk/breast)

For more help, contact:

NCI's Cancer Information Service
Telephone (toll-free): 1–800–4–CANCER (1–800–422–6237)
TTY (toll-free): 1–800–332–8615
LiveHelp® online chat: https://cissecure.nci.nih.gov/livehelp/welcome.asp

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