
CANCER FACTS

National Cancer Institute • National Institutes of Health
Department of Health and Human Services

The Study of Tamoxifen and Raloxifene (STAR): Questions and Answers

Key Points

- The Study of Tamoxifen and Raloxifene (STAR) is a clinical trial designed to see how the drug raloxifene (Evista®) compares with the drug tamoxifen (Nolvadex®) in reducing the incidence of breast cancer in women who are at an increased risk for developing the disease (see Question 1).
- The study is closed to new participants. Results are expected in the summer of 2006 (see Question 1).
- Women at increased risk for developing breast cancer, who had gone through menopause, and were at least 35 years old were eligible to participate in STAR (see Question 4).
- Participants in STAR were randomized (assigned by chance) to receive either tamoxifen or raloxifene (see Question 13).

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

The Study of Tamoxifen and Raloxifene (STAR) is a clinical trial (a research study conducted with people) designed to see how the drug raloxifene (Evista®) compares with the drug tamoxifen (Nolvadex®) in reducing the incidence of breast cancer in women who are at an increased risk of developing the disease. Researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting the study at more than 400 centers across the United States, Puerto Rico, and Canada. The study is funded primarily by the National Cancer Institute (NCI), the U.S. Government's main agency for cancer research.

STAR began enrolling participants in 1999. As of June 4, 2004, the study had reached its goal of enrolling 19,000 women. The study is closed to new participants, and results are expected in the summer of 2006.



2. What is tamoxifen?

Tamoxifen is a drug, taken by mouth as a pill. It has been used for more than 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. In October 1998, the U.S. Food and Drug Administration (FDA) approved tamoxifen to reduce the incidence of breast cancer in women at high risk for the disease based on the results of the Breast Cancer Prevention Trial (BCPT). The BCPT studied more than 13,000 pre- and postmenopausal high-risk women age 35 and older who took either tamoxifen or a placebo (an inactive pill that looked like tamoxifen) for up to 5 years. The NSABP conducted the BCPT, which also showed that tamoxifen works like estrogen to preserve bone strength, decreasing fractures of the hip, wrist, and spine in the women who took the drug. Findings from the BCPT were reported in the September 16, 1998, issue of the *Journal of the National Cancer Institute*.

3. What is raloxifene?

Raloxifene is a drug, taken by mouth as a pill. In December 1997, it was approved by the FDA for the prevention of osteoporosis in postmenopausal women. Raloxifene is being studied because large studies testing its effectiveness against osteoporosis have shown that women taking the drug developed fewer breast cancers than women taking a placebo. One of these studies was the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. The MORE trial was designed to study the effects of raloxifene on osteoporosis in postmenopausal women. Researchers also tracked rates of breast cancer and observed a reduction in the risk of breast cancer among the women who took raloxifene. The results of this study were reported in the June 16, 1999, issue of the *Journal of the American Medical Association*.

4. Who was eligible to participate in STAR?

Women at increased risk for developing breast cancer, who had gone through menopause, and were at least 35 years old, were eligible to participate in STAR. All women had to have an increased risk for breast cancer equivalent to or greater than that of an average 60- to 64-year-old woman. In that age group, about 17 of every 1,000 women are expected to develop breast cancer within 5 years.

5. Why couldn't premenopausal women participate?

STAR was limited to postmenopausal women. Raloxifene has not yet been adequately tested for long-term safety in premenopausal women.

6. What factors were used to determine increased risk for breast cancer for the participants?

For most women, the risk was determined by a computer calculation that took into account the following factors:

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

In addition, women diagnosed as having lobular carcinoma in situ (LCIS), a condition that is not cancer but indicates an increased chance of developing invasive breast cancer, were eligible based on that diagnosis alone, as long as their treatment for the condition was limited to local excision. Mastectomy, radiation therapy, chemotherapy, or hormonal therapy made a woman with LCIS ineligible for the study.

7. How was a potential participant's risk of breast cancer determined?

Each potential participant completed a 1-page questionnaire (risk assessment form), which was forwarded to NSABP by the local STAR clinical staff. The NSABP used computer software to generate an individualized risk profile based on the information provided and returned the profile to the local STAR site so that it could be given to the potential participant. The profile estimated the woman's chance of developing breast cancer over the next 5 years and also presented the potential risks and benefits of the study drugs. The woman then used this information to help her decide whether she was interested in participating in STAR.

8. What other factors affected eligibility for the study?

Certain existing health conditions affected eligibility for the study. Health professionals at the STAR site discussed these with each potential participant. For example, women with a history of cancer (except basal or squamous cell skin cancer), blood clots, stroke, or certain types of heartbeat irregularities could not participate. Women with uncontrolled high blood pressure or diabetes were not eligible to participate.

Also, women taking menopausal hormone therapy (estrogen or an estrogen/progesterone combination) could not take part in the trial unless they stopped taking this medication. Those who stopped taking these hormones were eligible for the study 3 months after they discontinued the drugs. Women who had taken tamoxifen or raloxifene for no more than 3 months were eligible for the study, but they also had to stop the medication for 3 months before joining STAR.

9. What are the common side effects of tamoxifen and raloxifene?

Like most medications, including over-the-counter medications, prescription drugs, or drugs used in clinical trials, tamoxifen and raloxifene cause adverse effects in some women. The effects experienced most often by women taking either drug are hot flashes and vaginal symptoms, including discharge, dryness, or itching. It is possible that some women may experience leg cramps, constipation, pain with intercourse, sinus irritation or infection, or problems controlling the bladder upon exertion. Treatments that may minimize or eliminate most of these side effects are available to the participants.

10. Does tamoxifen cause cancers of the uterus?

Tamoxifen increases the risk of two types of cancer that can develop in the uterus: endometrial cancer, which arises in the lining of the uterus, and uterine sarcoma, which arises in the muscular wall of the uterus. Like all cancers, endometrial cancer and uterine sarcoma are potentially life-threatening. Women who have had a hysterectomy (surgery to remove the uterus) and are taking tamoxifen are not at increased risk for these cancers.

Endometrial cancer

In the BCPT, women who took tamoxifen had more than twice the chance of developing endometrial cancer compared with women who took a placebo (an inactive substance that looks the same as, and is administered in the same way as, tamoxifen). The risk of endometrial cancer in women taking tamoxifen was in the same range as (or less than) the risk in postmenopausal women taking single-agent estrogen replacement therapy. This risk is about 2 cases of endometrial cancer per 1,000 women taking tamoxifen each year.

Most of the endometrial cancers that have occurred in women taking tamoxifen have been found in the early stages, and treatment has usually been effective. However, for some breast cancer patients who developed endometrial cancer while taking tamoxifen, the disease was life-threatening.

Uterine sarcoma

Information collected by the FDA indicates that women who have used tamoxifen for breast cancer treatment or prevention have an increased risk of developing uterine sarcoma. Review of all the NSABP clinical trials using tamoxifen confirmed an increased risk of this rare cancer. In the BCPT, there were about 2 cases per 10,000 women taking tamoxifen each year. Research to date indicates that uterine sarcomas are more likely to be diagnosed at later stages than endometrial cancers, and may therefore be harder to control and more life-threatening than endometrial cancer.

Abnormal vaginal bleeding and lower abdominal (pelvic) pain are symptoms of cancers of the uterus. Women who are taking tamoxifen should talk with their doctor about having regular pelvic examinations and should be checked promptly if they have any abnormal vaginal bleeding or pelvic pain between scheduled exams.

11. Does tamoxifen cause other serious side effects?

Women taking tamoxifen in the BCPT had 3 times the chance of developing a pulmonary embolism (blood clot in the lung) as women who took the placebo (18 women taking tamoxifen versus 6 on placebo). Three women taking tamoxifen died from these embolisms. Women in the tamoxifen group were also more likely to have a deep vein thrombosis (a blood clot in a major vein) than women on placebo (35 women on tamoxifen versus 22 on placebo). Women taking tamoxifen also appeared to have an increased chance of stroke (38 women on tamoxifen versus 24 on placebo).

12. Does raloxifene have any serious side effects?

Information about raloxifene is limited compared with the data available on tamoxifen because of the shorter time raloxifene has been studied (about 7 years) and the smaller number of women who have been studied. Studies of raloxifene have generally involved women who received the drug to determine its effect on osteoporosis, and the duration of both therapy and follow-up have been short. Women taking raloxifene in clinical trials have about 3 times the chance of developing a deep vein thrombosis or pulmonary embolism as women on a placebo. In osteoporosis studies of raloxifene, the drug did not increase the risk of endometrial cancer. An important part of STAR is to assess the long-term safety of raloxifene versus tamoxifen in women at increased risk of breast cancer.

13. Who gets which drug?

Participants in STAR were randomized (assigned by chance) to receive either tamoxifen or raloxifene. In a process known as “double blinding,” neither the participant nor her physician knows which pill she is receiving. Setting up a study in this way allows the researchers to directly compare the true benefits and side effects of each drug without the influence of other factors. All women in the study will take two pills a day for 5 years: half are taking active tamoxifen and a raloxifene placebo (an inactive pill that looks like raloxifene); the other half are taking active raloxifene and a tamoxifen placebo (an inactive pill that looks like tamoxifen). All women receive one of the active drugs; no one in STAR receives only the placebo. The dosages are 20 mg of tamoxifen and 60 mg of raloxifene.

14. Why does everyone have to take two pills?

Tamoxifen and raloxifene have different shapes. The trial would not be double blinded if participants or physicians could tell which drug they were receiving because of its shape. The makers of tamoxifen (AstraZeneca in Wilmington, Delaware) and raloxifene (Eli Lilly and Company in Indianapolis, Indiana) are providing the active pills and the look-alike placebos without charge.

15. Are participants required to have any medical exams? Who pays for these exams?

Participants had to have blood tests, a mammogram, a breast exam, and a gynecologic exam before they were accepted into the study. These tests are repeated at intervals during the trial. Physicians' fees and the costs of medical tests are charged to the participant in the same fashion as if she were not part of the trial; however, the costs for these tests generally are covered by insurance. Every effort is made to contain the costs specifically associated with participation in this trial, and financial assistance is available for some women.

16. How did women enroll in the trial?

Postmenopausal women interested in participating in STAR contacted the center nearest to them. In the United States (including Puerto Rico), they learned about nearby centers by calling the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or 1-800-332-8615 for people with TTY equipment.

In Canada, information about participating centers was available from the Canadian Cancer Society's Cancer Information Service at 1-888-939-3333.

STAR centers were also listed on the NSABP's Web site at <http://www.nsabp.pitt.edu> and on the Study of Tamoxifen and Raloxifene (STAR) Trial page on the NCI's Web site at <http://www.cancer.gov/star> on the Internet.

17. How is the safety of participants being ensured? Is the trial monitored?

The safety of participants is of primary importance to STAR investigators. There were strict requirements about who could join the trial, and there is frequent monitoring of participants' health status. An independent Data Safety and Monitoring Committee (DSMC) provides oversight of the trial. The DSMC includes medical and cancer specialists, biostatisticians, and bioethicists who have no other connection to NSABP. The DSMC meets semiannually and reviews unblinded data from all participants. Two other committees also provide oversight. The Participant Advisory Board (PAB) was originally made up of 16 women from the BCPT. As women joined STAR, board membership changed to include STAR participants. The PAB meets semiannually with professionals from NSABP and NCI and provides feedback on many study-related functions such as informed consent, participant recruitment, and communications issues. The STAR Steering Committee is made up of NSABP investigators, breast cancer advocates, and experts from other medical disciplines, as well as NCI and NSABP personnel. The committee, which also meets semiannually, is charged with providing overall administrative oversight of the trial.

In addition, NSABP provides the FDA, NCI, AstraZeneca, and Eli Lilly and Company with annual reports on STAR that summarize the overall data collected to date (only the DSMC receives unblinded data).

18. 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, prevented. Results of clinical trials 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.

Selected References

1. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. *Journal of the American Medical Association* 1999;281(23):2189–2197.
2. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P–1 study. *Journal of the National Cancer Institute* 1998;90(18):1371–1388.

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Related Resources

Publications (available at <http://www.cancer.gov/publications>)

- Cancer Facts 2.11, *Clinical Trials: Questions and Answers*
- Cancer Facts 4.18, *Breast Cancer Prevention Studies*
- Cancer Facts 7.16, *Tamoxifen: Questions and Answers*
- *What You Need To Know About™ Breast Cancer*

National Cancer Institute (NCI) Resources

Cancer Information Service (toll-free)

Telephone: 1–800–4–CANCER (1–800–422–6237)

TTY: 1–800–332–8615

Online

NCI's Web site: <http://www.cancer.gov>

LiveHelp, NCI's live online assistance:

<https://cissecure.nci.nih.gov/livehelp/welcome.asp>

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