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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 postmenopausal women who are at an increased risk of developing the disease (see Question 1).
- Initial results of STAR show that raloxifene is as effective as tamoxifen in reducing a postmenopausal woman's risk of developing invasive breast cancer – a reduction of about 50 percent (see Question 6).
- Participants in STAR who were assigned to take raloxifene had fewer serious side effects from that drug than participants assigned to take tamoxifen, including fewer uterine cancers, blood clots, and cataracts (see Questions 8, 9, and 14).

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) comparing the drug raloxifene (Evista[®]) with the drug tamoxifen (Nolvadex[®]) in reducing the incidence of breast cancer in postmenopausal 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 500 centers across the United States, Canada, and Puerto Rico. The study is funded primarily by the National Cancer Institute (NCI) – part of the National Institutes of Health. NCI is the U.S. Government's main agency for cancer research.

2. Who participated in STAR?

Women at increased risk of developing breast cancer, who had gone through menopause, and were at least 35 years old, took part in STAR. STAR began enrolling participants in 1999. Enrollment was closed on November 4, 2004, with 19,747 women recruited.

The ages of women joining STAR were:

Age Range	Women in STAR Who Fell Into This Age Range
35-49	9.2% (1,815)
50-59	49.7% (9,821)
60+	41.1% (8,111)

All STAR participants had to have an increased risk of breast cancer equivalent to or greater than that of an average 60- to 64-year-old woman. In that age group, 1.66 percent of women -- or about 17 of every 1,000 women -- would be expected to develop breast cancer within five years. The average risk of breast cancer in the women who chose to enter STAR was about twice as high as this minimum risk.

The breast cancer risk of women when they joined STAR was:

Five Year Breast Cancer Risk	Women in STAR Who Fell Into This Risk Category
1.66 - 1.99%	11.0% (2,176)
2.0 - 2.99%	30.2% (5,962)
3.0 - 4.99%	31.5% (6,229)
Greater than 5.0%	27.2% (5,380)

3. What increases a woman's risk of breast cancer? How was it determined that a STAR participant was at increased risk of breast cancer?

A woman's risk of developing breast cancer is determined by many factors. The factors that most affect a woman's risk of the disease are:

- 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 has undergone, especially if the tissue showed a condition known as atypical hyperplasia,
- The woman's age at her first menstrual period, and
- The woman's age when she reached menopause.

STAR researchers used the Breast Cancer Risk Assessment Tool, developed by scientists at NCI and NSABP, to estimate a woman's risk of breast cancer using most of the above factors. The tool can be viewed on NCI's Web site at <http://www.cancer.gov/bcrisktool>. NSABP also has the tool posted at <http://breastcancerprevention.com>. From this Web site, women can also register with the group for information about future breast cancer prevention clinical trials.

In addition, for STAR, 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.

4. What is tamoxifen?

Tamoxifen is a drug, taken by mouth as a pill. It has been used for more than 30 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 the use of tamoxifen to reduce the incidence of breast cancer in women at increased risk of the disease based on the results of the NSABP Breast Cancer Prevention Trial (BCPT). The BCPT studied 13,388 pre- and postmenopausal women age 35 and older at increased risk of breast cancer who took either tamoxifen or a placebo (an inactive pill that looked like tamoxifen) for up to five years. The BCPT 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*.

For more information about tamoxifen, go to <http://www.cancer.gov/cancertopics/factsheet/Therapy/tamoxifen>.

5. 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. In October 1999, it was also approved as an osteoporosis treatment. Raloxifene is being studied for breast cancer prevention 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 incidence 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* and were updated in the Continuing Outcomes Relevant to Evista (CORE) study published in the *Journal of the National Cancer Institute* on December 1, 2004.

6. What were the STAR results in terms of reducing breast cancer risk?

The results of STAR show that raloxifene and tamoxifen are equally effective in reducing breast cancer risk in postmenopausal women at increased risk of the disease. After taking these drugs for an average of almost four years, women in the tamoxifen group and women in the raloxifene group had statistically equivalent numbers of invasive breast cancers (163 cases in 9,726 women in the tamoxifen group versus 167 cases in 9,745 women in the raloxifene group). Tamoxifen is known to be able to reduce breast cancer risk by half, and this study shows that raloxifene can also reduce breast cancer risk by half.

For every 1,000 women similar to those enrolled in STAR, about 40 would be expected to develop breast cancer within five years. The results of STAR show that about 20 of those women would not develop breast cancer if they took tamoxifen or raloxifene for five years.

7. What are the side effects of tamoxifen and raloxifene?

The known, serious side effects of tamoxifen are uterine cancer, blood clots, strokes, and cataracts. Other side effects of tamoxifen include menopause-like symptoms such as hot flashes and vaginal discharge or bleeding.

Raloxifene has not been studied as long as tamoxifen, and one of the goals of STAR was to better assess the drug's long-term effects. The known, serious side effect of raloxifene is blood clots. Other side effects include menopause-like symptoms such as hot flashes and vaginal dryness as well as joint pain or leg cramps.

To read the FDA labels for either drug, visit the Drugs@FDA Web site at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

8. How many participants developed uterine cancer?

In STAR, more than half of the women entered the trial having had a hysterectomy. Women without a uterus are not at risk of uterine cancer. For those women in the trial with a uterus, the women in the raloxifene group developed 36 percent fewer uterine cancers during the trial: 36 of 4,732 women in the tamoxifen group developed uterine cancers compared to 23 of the 4,712 women in the raloxifene group. Tamoxifen is known to increase a woman's chance of developing uterine cancer (mostly in the lining of the uterus or endometrium) by two to three times -- to a rate of about 2 cases per 1,000 women per year -- compared to a woman who does not use the drug. The rate of uterine cancers in women assigned to take tamoxifen in STAR was similar to this rate.

9. How many participants developed blood clots?

Both tamoxifen and raloxifene are known to increase a woman's chance of developing blood clots by up to three times that of women who are not taking either drug. In STAR,

women in the raloxifene group had 29 percent fewer deep-vein thromboses (blood clots in a major vein) and pulmonary embolisms (blood clots in the lung) than women on tamoxifen: 87 of 9,726 women in the tamoxifen group had a deep-vein thrombosis compared to 65 of 9,745 women in the raloxifene group, and 54 of 9,726 women in the tamoxifen group had a pulmonary embolism compared to 35 of 9,745 women in the raloxifene group.

10. How many participants developed other cardiovascular problems?

The numbers of myocardial infarctions (heart attacks), strokes, and transient ischemic attacks (strokes that last only a few minutes) were essentially equivalent between the tamoxifen group and the raloxifene group.

The numbers of women who had strokes in the two groups were statistically equivalent with 53 of 9,726 women in the tamoxifen group and 51 of 9,745 women in the raloxifene group having had a stroke during the trial. There were no differences in deaths from strokes with 6 of 9,726 women in the tamoxifen group and 4 of 9,745 women in the raloxifene group dying from this type of event.

Women at increased risk of cardiovascular problems were not eligible to participate in STAR. This includes women who had uncontrolled high blood pressure or uncontrolled diabetes and those with a prior stroke, transient ischemic attack, or atrial fibrillation (a kind of abnormal heart rhythm).

11. How many women had bone fractures during the trial?

In STAR, women in the tamoxifen group and women in the raloxifene group had similar numbers of bone fractures of the hip, wrist, and spine: 104 of 9,726 women in the tamoxifen group had a bone fracture during the trial compared to 96 of 9,745 women in the raloxifene group. Raloxifene is currently FDA-approved and used for the treatment and prevention of osteoporosis, and data from the BCPT showed that women on tamoxifen have fewer fractures of the hip, wrist, and spine compared to women on placebo. These particular fracture sites were evaluated in the study because they are associated with osteoporosis.

12. Did raloxifene reduce the incidence of lobular carcinoma in situ or ductal carcinoma in situ?

No. While tamoxifen has been shown to reduce the incidence of lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) by half, raloxifene did not have an effect on these diagnoses. (LCIS and DCIS are sometimes called noninvasive or stage 0 breast cancers.) Among the 9,726 women in the tamoxifen group, 57 developed LCIS or DCIS, compared to 81 of 9,745 women in the raloxifene group. This result confirms data reported in 2004 in a large study of raloxifene, the Continued Outcomes Relevant to Evista (or CORE Trial), which showed that raloxifene did not decrease the incidence of LCIS or DCIS in women taking the drug compared to women on a placebo.

13. Does having taken raloxifene change what a woman could do if she developed LCIS or DCIS?

No. Treatment options for LCIS and DCIS would not change if a woman had been taking raloxifene prior to her diagnosis. For more information on treatment options for LCIS and DCIS, visit NCI's Web site at:

<http://www.cancer.gov/cancertopics/pdq/treatment/breast/patient>.

14. How many participants developed a cataract during STAR?

In the BCPT, women in the tamoxifen group had a 14 percent increased risk of developing a cataract. During STAR, 394 of 9,726 women in the tamoxifen group developed a cataract compared to 313 of 9,745 women in the raloxifene group. Based on STAR data and comparing it to data from the BCPT, the risk of cataracts in the raloxifene group does not appear to be elevated over what would be expected if these women were not treated with raloxifene.

15. Did any group of women benefit more from raloxifene than others?

No. Raloxifene reduced breast cancer risk regardless of age, race, family history, or other known breast cancer risk factors.

16. How are the participants being notified about the results?

At the start of the trial, the NSABP made a commitment to make every effort to notify the participants of any major results as soon as possible. Information to "unblind" each participant (telling a woman which drug she is or was taking) was made available on April 17, 2006, to STAR investigators so they can convey the information to the study participants.

17. What do the participants do now that the results are known?

All the women in STAR are being asked to continue their follow-up examinations according to the study protocol. Women who were randomly assigned to the raloxifene group and who have not completed five years of drug will be able to continue on that drug. Women who were randomly assigned to the tamoxifen group will have the option of completing their five years of tamoxifen or switching to raloxifene for the remainder of their five years.

18. Why won't the women who took tamoxifen in STAR now take five years of raloxifene?

There is no evidence that taking more than five years of either drug will further reduce a woman's chance of developing breast cancer.

19. How is this information being made available to physicians, women, and others outside the trial?

The NCI and the NSABP have made the initial results of STAR available by posting information on their websites and by making a public announcement. In addition, the initial results of STAR will be presented at the 42nd annual meeting of the American Society of Clinical Oncology (ASCO), held June 2-6, 2006. A manuscript will be submitted to a peer-reviewed journal for publication.

20. Should postmenopausal women at increased risk of breast cancer take raloxifene based on these results?

At this time, tamoxifen is the only FDA-approved drug for the reduction of breast cancer risk, and it is approved for both pre- and postmenopausal women. Raloxifene is only FDA-approved for the prevention and treatment of osteoporosis in postmenopausal women and is not approved for use in the reduction of breast cancer risk. Should raloxifene receive FDA approval for this use, postmenopausal women who are at increased risk of breast cancer would be able to consider taking either raloxifene or tamoxifen to reduce their risk. As with any medical procedure or intervention, the decision to take one of these drugs is an individual one in which the benefits and risks of 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. Even if a woman is at increased risk of breast cancer, raloxifene or tamoxifen therapy may not be right for her. Women who are considering breast cancer prevention therapy should talk with their health care provider.

21. What is the average monthly cost of tamoxifen or raloxifene?

On average, a month's supply of raloxifene costs \$75 in the United States. A month's supply of tamoxifen can cost from about \$40 a month for the generic version to over \$100 for the brand name version in the United States.

22. What can premenopausal women at increased risk of breast cancer do to reduce their risk of breast cancer?

Tamoxifen has already been shown to reduce a premenopausal woman's risk of developing breast cancer by half in the BCPT and the drug is approved by the FDA to reduce breast cancer risk in premenopausal women. In the BCPT, women under age 50 did not have an increased risk of the most serious side effects seen with tamoxifen use: uterine cancer, blood clots, strokes, and cataracts. Premenopausal women at increased risk of breast cancer can discuss tamoxifen therapy as an option with their physicians. Raloxifene is not FDA-approved for use in premenopausal women.

23. Are there women who should not take raloxifene?

Raloxifene is not approved by the FDA for use in premenopausal women for any indication. It is approved for the prevention and treatment of osteoporosis, and postmenopausal women with a history of blood clots, hypertension, diabetes, and cigarette smoking must also consider that raloxifene increases the risk of serious blood clots.

24. How much did the study cost?

To date, the NCI has spent \$88 million through peer-reviewed grants to NSABP to support STAR. In addition, Eli Lilly and Company, Inc., provided NSABP with \$30 million to defray recruitment costs at the participating centers and to help local investigators conduct the study. The maker of tamoxifen, AstraZeneca Pharmaceuticals, Inc., Wilmington, Del., and the maker of raloxifene, Eli Lilly and Company, Indianapolis, Ind., provided their drugs and matching placebos for the trial without charge to participants.

Background Information**25. What factors affected eligibility for STAR?**

Certain existing health conditions affected eligibility for the study. Health professionals at each 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 three months after they discontinued the drugs. Women who had taken tamoxifen or raloxifene for no more than three months were eligible for the study, but they also had to stop the medication for three months before joining STAR.

26. What determined which participants received tamoxifen or raloxifene?

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 were scheduled to take two pills a day for five years: half took active tamoxifen and a raloxifene placebo (an inactive pill that looks like raloxifene); the other half took 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 received only the placebo. The dosages are 20 mg of tamoxifen and 60 mg of raloxifene per day.

27. Were participants required to have any medical exams? Who paid 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 because the tests are part of routine care for postmenopausal women. Every effort is made to contain the costs specifically associated with participation in this trial, and financial assistance is available for women facing financial hardship.

28. Was any special effort made to include minority women in the trial?

Throughout the trial, many approaches were used to increase participation of women from racial and ethnic minority groups. The majority of women in STAR were white (93.4 percent or 18,446 women). Six percent of women were from racial and ethnic minority groups (2.5 percent African American or 488 women; 2.0 percent Hispanic or 394 women and 2.1 percent other ethnicities or 419 women), an improvement over the 4 percent that participated in BCPT. These categories were determined based on how the women identified themselves when they applied to take part in the trial.

29. How is the safety of participants ensured? Was 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 Monitoring Committee (DMC) provided oversight of the trial. The DMC included medical and cancer specialists, biostatisticians, and bioethicists who have no other connection to NSABP. The DMC met semiannually and reviewed unblinded data from all participants. Two other committees also provide oversight. The Participant Advisory Board (PAB) is made up of 16 women enrolled in STAR. The PAB met semiannually with professionals from NSABP and NCI and provided feedback on many study-related functions such as informed consent, participant recruitment, and communications issues. The STAR Steering Committee was 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 met semiannually, was charged with providing overall administrative oversight of the trial.

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

30. Why is STAR important?

This year, more than 212,000 women will be diagnosed with breast cancer, most of them postmenopausal and more than 40,000 will die of the disease. Since 1998, only tamoxifen has been available to reduce the risk of breast cancer, and this drug has rare, but serious side effects. Women continue to rely on frequent checkups and periodic mammograms to detect breast cancer at an early stage. Doctors sometimes suggest that certain women at very increased risk have preventive (prophylactic) mastectomies (surgeries to remove breast tissues before cancer develops). This operation does not guarantee that breast cancer will be avoided. Some doctors also suggest oophorectomy (surgical removal of the ovaries) to reduce breast cancer risk.

If FDA approves the use of raloxifene to reduce breast cancer risk, postmenopausal women at increased risk of breast cancer would have a choice of drugs to help reduce their risk. These drugs do not replace the need for mammography.

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

The NSABP is a cooperative group funded by NCI 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 and it was the first to demonstrate that healthy women at increased risk of breast cancer could reduce their risk of developing the disease by taking daily medication.

32. Where did women take part in STAR?

Women were enrolled in STAR through clinical centers located in 47 U.S. states, the District of Columbia, Puerto Rico and 5 Canadian provinces. The list of women participating at clinical centers in each location is below, alphabetically by postal code:

[See next page for chart]

UNITED STATES		UNITED STATES	
AL-Alabama	98	NE-Nebraska	208
AR-Arkansas	70	NH-New Hampshire	40
AZ-Arizona	199	NJ-New Jersey	95
CA-California	1369	NM-New Mexico	87
CO-Colorado	349	NV-Nevada	99
CT-Connecticut	307	NY-New York	808
DC-District of Columbia	64	OH-Ohio	959
DE-Delaware	149	OK-Oklahoma	233
FL-Florida	389	OR-Oregon	200
GA-Georgia	185	PA-Pennsylvania	1301
HI-Hawaii	159	PR-Puerto Rico	76
IA-Iowa	352	SC-South Carolina	343
ID-Idaho	38	SD-South Dakota	161
IL-Illinois	1108	TN-Tennessee	271
IN-Indiana	222	TX-Texas	1624
KS-Kansas	337	UT-Utah	83
KY-Kentucky	199	VA-Virginia	170
LA-Louisiana	146	VT-Vermont	79
MA-Massachusetts	616	WA-Washington	552
MD-Maryland	302	WI-Wisconsin	388
ME-Maine	52	WV-West Virginia	68
MI-Michigan	1032	CANADA	
MN-Minnesota	584	AB-Alberta	145
MO-Missouri	795	BC-British Columbia	112
MS-Mississippi	44	MB-Manitoba	139
MT-Montana	122	ON-Ontario	324
NC-North Carolina	915	PQ-Quebec	898
ND-North Dakota	82		
		TOTAL	19,747

Selected References

1. Fisher B, Costantino 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.
2. 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.

3. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing Outcomes Relevant to Evista: Breast Cancer Incidence in Postmenopausal Osteoporotic Women in a Randomized Trial of Raloxifene. *Journal of the National Cancer Institute* 2004; 96(23):1751-1761.
4. 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.

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For more information about STAR, including links to media materials and a fact sheet, visit NCI's STAR home page at <http://www.cancer.gov/star> or at NSABP's Web sites at <http://www.nsabp.pitt.edu> or <http://foundation.nsabp.org/>.

For a press release related to the STAR results, go to:
<http://www.cancer.gov/newscenter/pressreleases/STARresultsApr172006>.

For B-roll related to the STAR results, go to www.thenewsmarket.com for digitized, downloadable B-roll, or call the NCI press office at (301) 496-6641 for a Beta-tape copy.

For tools used to calculate a woman's risk of breast cancer, visit either <http://cancer.gov/bcrisktool> or <http://breastcancerprevention.com>.