

Tamoxifen: Questions and Answers

Key Points

- Tamoxifen (Nolvadex[®]) is a drug that interferes with the activity of estrogen, a female hormone. Tamoxifen has been used for more than 30 years to treat breast cancer in women and men (see Question 1).
- Tamoxifen has been used for almost 10 years to reduce the risk of breast cancer in women who are at increased risk of developing breast cancer (see Question 1).
- The known, serious side effects of tamoxifen are blood clots, strokes, uterine cancer, and cataracts. Other side effects include menopause-like symptoms such as hot flashes, vaginal dryness, joint pain, and leg cramps (see Questions 4–8).
- The benefits of tamoxifen as a treatment for breast cancer are firmly established and far outweigh the potential risks (see Question 11).
- The results of the Breast Cancer Prevention Trial (BCPT) showed a reduction in diagnoses of invasive breast cancer among women who took tamoxifen for 5 years (see Question 12).
- The results of the Study of Tamoxifen and Raloxifene (STAR) clinical trial showed that tamoxifen and another drug, raloxifene, are equally effective in reducing invasive breast cancer risk in postmenopausal women who are at increased risk of the disease (see Question 14).

1. What is tamoxifen?

Tamoxifen (Nolvadex[®]) is a drug, taken orally as a tablet, which interferes with the activity of estrogen, a female hormone. Estrogen can promote the development of cancer in the breast. Tamoxifen is approved by the U.S. Food and Drug Administration (FDA) for the prevention of breast cancer and for the treatment of breast cancer, as well as other types of cancer.

Tamoxifen has been used for more than 30 years to treat breast cancer in women and men. Tamoxifen is used to treat patients with early-stage breast cancer, as well as those with metastatic breast cancer (cancer that has spread to other parts of the body). As adjuvant therapy (treatment given after the primary treatment to increase the chances of a cure), tamoxifen helps prevent the original breast cancer from returning and also helps prevent the development of new cancers in the other breast. As treatment for metastatic breast cancer, the drug slows or stops the growth of cancer cells that are present in the body.

Tamoxifen has been used for almost 10 years to reduce the risk of breast cancer in women who are at increased risk of developing breast cancer. Tamoxifen is also used to treat women with ductal carcinoma in situ (DCIS), a noninvasive condition that sometimes leads to invasive breast cancer.

2. How does tamoxifen work?

Estrogen can promote the growth of breast cancer cells. Some breast cancers are classified as estrogen receptor-positive (also known as hormone sensitive), which means that they have a protein to which estrogen will bind. These breast cancer cells need estrogen to grow. Tamoxifen works against the effects of estrogen on these cells. It is often called an antiestrogen or a SERM (Selective Estrogen Receptor Modulator).



Studies have shown that tamoxifen is only effective in treating estrogen receptor-positive breast cancers. Therefore, the tumor's hormone receptor status should be determined before deciding on treatment options for breast cancer.

Although tamoxifen acts *against* the effects of estrogen in breast tissue, it acts *like* estrogen in other tissue. This means that women who take tamoxifen may derive many of the beneficial effects of menopausal estrogen replacement therapy, such as a decreased risk of osteoporosis.

3. How long should a patient take tamoxifen for the treatment of breast cancer?

Patients with metastatic breast cancer may take tamoxifen for varying lengths of time, depending on the cancer's response to this treatment and other factors. When used as adjuvant therapy for early-stage breast cancer, tamoxifen is generally prescribed for 5 years. However, the ideal length of treatment with tamoxifen is not known.

Two studies have confirmed the benefit of taking adjuvant tamoxifen daily for 5 years. When taken for 5 years, tamoxifen reduces the chance of the original breast cancer coming back in the same breast or elsewhere. It also reduces the risk of developing a second primary cancer in the other breast.

Clinical trials are ongoing to determine whether hormone therapy taken for more than 5 years is beneficial. These studies usually include aromatase inhibitors (AIs) (another type of antiestrogen) (see Question 15). For example, the National Cancer Institute (NCI), a part of the National Institutes of Health, is sponsoring the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 trial. This trial is studying the AI letrozole (Femara[®]) to find out how well it works compared with a placebo in treating postmenopausal women who have received hormone therapy for hormone receptor-positive breast cancer. More information is available in PDQ[®], the NCI's comprehensive cancer information database, at <http://www.cancer.gov/clinicaltrials/NSABP-B-42> on the Internet.

The MA-17R trial, which is being coordinated by the National Cancer Institute of Canada's Clinical Trials Group, is comparing letrozole with placebo in women previously diagnosed with primary breast cancer who participated in another clinical trial of letrozole. Information about the MA-17R trial can be found at <https://www.swogstat.org/ROS/ROSBBooks/Fall%202006/Intergroup/NCIC%20CTG/JMA17R.pdf> on the Internet.

4. What are some of the more common side effects of tamoxifen?

The known, serious side effects of tamoxifen are blood clots, strokes, uterine cancer, and cataracts (see Questions 5–8). Other side effects of tamoxifen are similar to the symptoms of menopause. The most common side effects are hot flashes and vaginal discharge. Some women experience irregular menstrual periods, headaches, fatigue, nausea and/or vomiting, vaginal dryness or itching, irritation of the skin around the vagina, and skin rash. As with menopause, not all women who take tamoxifen have these symptoms. Men who take tamoxifen may experience headaches, nausea and/or vomiting, skin rash, impotence, or a decrease in sexual interest.

5. Does tamoxifen cause blood clots or stroke?

Data from large clinical trials suggest that there is a small increase in the number of blood clots in women taking tamoxifen, particularly in women who are receiving anticancer drugs (chemotherapy) along with tamoxifen. The total number of women who have experienced this side effect is small. The risk of having a blood clot due to tamoxifen is similar to the risk of a blood clot when taking estrogen replacement therapy.

The Breast Cancer Prevention Trial (BCPT), a large research study funded by the NCI, was designed to test the usefulness of tamoxifen in preventing breast cancer in women with an increased risk of developing this disease (see Question 12). This study also found that women who took tamoxifen had an increased chance of developing blood clots and an increased chance of stroke (1, 2).

6. 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

Studies have found the risk of developing endometrial cancer to be about 2 cases per 1,000 women taking tamoxifen each year compared with 1 case per 1,000 women taking placebo (1, 2). 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

Studies have found the risk of developing uterine sarcoma to be slightly higher in women taking tamoxifen compared with women taking placebo. However, it was less than 1 case per 1,000 women per year in both groups (1, 2). Research to date indicates that uterine sarcoma is more likely to be diagnosed at later stages than endometrial cancer, 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.

7. Does tamoxifen cause other types of cancer?

Tamoxifen is not known to cause any types of cancer in humans other than endometrial cancer and uterine sarcoma.

8. Does tamoxifen cause eye problems?

As women age, they are more likely to develop cataracts (clouding of the lens inside the eye). Women taking tamoxifen appear to be at increased risk for developing cataracts. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients.

9. Should women taking tamoxifen avoid pregnancy?

Yes. Doctors advise women receiving tamoxifen to avoid pregnancy because animal studies have suggested that the use of tamoxifen during pregnancy can cause harm to the fetus. Women who have questions about fertility, birth control, or pregnancy should discuss their concerns with their doctor.

10. Does tamoxifen cause a woman to begin menopause?

Tamoxifen does not cause a woman to begin menopause, although it can cause some symptoms that are similar to those that may occur during menopause. In most premenopausal women taking tamoxifen, the ovaries continue to act normally and produce estrogen in the same or slightly increased amounts.

11. Do the benefits of tamoxifen in treating breast cancer outweigh its risks?

The benefits of tamoxifen as a treatment for breast cancer are firmly established and far outweigh the potential risks. Patients who are concerned about the risks and benefits of tamoxifen or any other medications are encouraged to discuss these concerns with their doctor.

12. Can tamoxifen prevent breast cancer?

Research has shown that when tamoxifen is used as adjuvant therapy for early-stage breast cancer, it reduces the chance that the original breast cancer will come back in the same breast or elsewhere. It also reduces the risk of developing new cancers in the other breast. Based on these findings, the NCI funded the BCPT to determine whether taking tamoxifen for at least 5 years can prevent breast cancer in women who have never been diagnosed with breast cancer but who are at increased risk of developing the disease. This study found a reduction in diagnoses of invasive breast cancer among women who took tamoxifen for 5 years. Women who took tamoxifen also had fewer diagnoses of noninvasive breast tumors, such as DCIS or lobular carcinoma in situ (LCIS) (1). After 7 years of follow-up, researchers found similar results (2). The study found that tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69 percent, but no

difference in the occurrence of estrogen receptor-negative tumors was seen (1). More information about the BCPT is available on the NCI's BCPT home page at <http://www.cancer.gov/clinicaltrials/digestpage/BCPT> on the Internet.

13. Who should take tamoxifen to reduce breast cancer risk?

The decision to take tamoxifen is an individual one. A woman and her doctor must carefully consider the benefits and risks of therapy. At this time, there is no evidence that tamoxifen has a net benefit for women who do not have an increased risk of developing breast cancer.

14. What is raloxifene and how does it compare to tamoxifen?

Raloxifene is a drug approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women. Raloxifene is also approved by the FDA for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.

The NCI funded the Study of Tamoxifen and Raloxifene (STAR), a clinical trial comparing raloxifene (Evista[®]) with tamoxifen in preventing breast cancer in postmenopausal women who are at an increased risk of developing the disease. The study found that raloxifene and tamoxifen are equally effective in reducing invasive breast cancer risk in postmenopausal women who are at increased risk of the disease. The study also found that women who took raloxifene had fewer uterine cancers and fewer blood clots than the women who took tamoxifen (3). However, raloxifene did not reduce the risk of noninvasive breast tumors such as DCIS and LCIS (3). Other side effects associated with raloxifene were similar to tamoxifen and included hot flashes, vaginal dryness, joint pain, and leg cramps. Studies of raloxifene to date have only examined its role in breast cancer prevention, not treatment.

More information about STAR is available on the NCI's STAR home page at <http://www.cancer.gov/star> on the Internet.

15. What other hormone therapy may be used for early-stage breast cancer?

Aromatase inhibitors (AIs) are another adjuvant treatment option for some women with early-stage breast cancer. AIs block the action of a protein called aromatase, which helps the body produce estrogen. Most of the estrogen in a woman's body is made in the ovaries, but other tissues can also produce this hormone. AIs are usually used in women who have reached menopause, when the ovaries are no longer producing estrogen.

Although AIs and tamoxifen both help to prevent the growth of estrogen-sensitive breast tumors, they work differently in the body. Tamoxifen blocks the tumor's ability to use estrogen, and AIs reduce the amount of estrogen in the body. Anastrozole (Arimidex[®]), exemestane (Aromasin[®]), and letrozole (Femara[®]) are AIs that have been approved by the FDA.

The American Society of Clinical Oncology (ASCO) recommends that postmenopausal women with hormone-sensitive breast cancer consider one of two adjuvant treatment options (4):

- Begin treatment with tamoxifen for 2 to 3 years or 5 years, and then switch to an AI for another 2 to 3 years or 5 years.
- Forego tamoxifen entirely and begin adjuvant treatment with an AI for 5 years.

ASCO concluded that AIs are appropriate as initial treatment for women who should not take tamoxifen and that patients who cannot take AIs should receive tamoxifen.

Whether an individual patient should start therapy with an AI or begin therapy with tamoxifen and then change to an AI is a subject of medical judgment and clinical research. Patients should talk with their doctors about which drug would be best for them given their particular medical situation.

Question 3 includes information about ongoing clinical trials involving AIs to treat postmenopausal women with hormone receptor-positive breast cancer.

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. 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.
4. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004. *Journal of Clinical Oncology* 2005; 23(3):619–629.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 3.76, *Menopausal Hormone Replacement Therapy Use and Cancer* (<http://www.cancer.gov/cancertopics/factsheet/Risk/menopausal-hormones>)
- National Cancer Institute Fact Sheet 4.18, *Breast Cancer Prevention Studies* (<http://www.cancer.gov/cancertopics/factsheet/Prevention/breast-cancer>)
- National Cancer Institute Fact Sheet, *The Study of Tamoxifen and Raloxifene (STAR): Questions and Answers* (<http://www.cancer.gov/cancertopics/factsheet/STARresultsQandA>)
- Breast Cancer Home Page (<http://www.cancer.gov/cancertopics/types/breast>)
- Breast Cancer Prevention Trial Home Page (<http://www.cancer.gov/clinicaltrials/digestpage/BCPT>)
- Study of Tamoxifen and Raloxifene (STAR) Trial Home Page (<http://www.cancer.gov/star>)
- *Understanding Cancer Series: Estrogen Receptors/SERMs* (<http://www.cancer.gov/cancertopics/understandingcancer/estrogenreceptors>)

How can we help?

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