



# Breast Cancer Chemoprevention

Breast cancer affects 1 in 9 women in the U.S. by the time they reach their 80s. It is caused by several mutations or alterations in the genes found in the DNA of normal breast tissue. It is not always clear what causes these changes. The development of cancer is a multi-step process, which can take years, so interventions at an early point in the process could theoretically prevent cancer from occurring.

## Breast Cancer Prevention

### *Primary Prevention*

“Primary prevention” helps prevent cancer from developing. Primary prevention cancer means avoiding known cancer-causing exposures or adding cancer-preventing activities, supplements, or drugs to your routine. Breast cancer prevention strategies include:

- **Healthy lifestyle:** Regular exercise, a healthy diet, maintaining a healthy weight, and minimal alcohol.
- **Prophylactic surgery:** Mastectomy is an option for women at very high risk for developing breast cancer
- **Chemoprevention:** The use of chemicals or drugs, such as tamoxifen. Antioxidant vitamins have been proposed as another form of cancer chemoprevention. Cancer chemoprevention agents can work by preventing DNA mutations from occurring, or they can help in repairing damaged DNA.

### *Secondary Prevention*

“Secondary prevention” aims to detect cancer at the earliest possible time, to minimize complications, recurrences, and death due to cancer. Screening mammography is an example of secondary breast cancer prevention.

**In the NSABP Breast Cancer Prevention Study, women who took tamoxifen were about 50% less likely to develop breast cancer over a 5-year period. Tamoxifen did cause side effects, some of them serious.**

Breast cancer prevention methods are being tested through clinical research. The best-studied form of breast cancer chemoprevention involves the class of drugs called SERMS (selective estrogen receptor modulators), also known as “designer estrogens.” Drugs in this class have anti-estrogen activity on some tissues (such as breast tissue) and estrogen-like activities on other tissues (such as the bones). The natural hormone, estrogen, stimulates breast cells, leading to increased cell growth, so drugs that have an anti-estrogen effect on breast cells can decrease cell growth in the breast. Drugs in this class have proven to be effective in treating breast cancer. Recent data suggests that SERMS may play a role in preventing breast cancer, as well.

### **The NSABP P-01 Tamoxifen Breast Cancer Prevention Trial**

The drug that has been best studied as a breast cancer chemopreventive agent is tamoxifen (Nolvadex), a drug that has been used to treat breast cancer for more than 20 years. It was observed that women who were treated for cancer in one breast had fewer cancers in the opposite breast. Therefore, the possibility that tamoxifen might be effective at reducing risk of breast cancer was explored. Tamoxifen is a SERM and is able to cause either estrogen-like or anti-estrogen responses in different tissues. In the breast, it acts as an anti-estrogen, slowing down cell growth and division.

The P-01 Breast Cancer Prevention Trial, run by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in the United States and Canada, evaluated the effect of 5 years of tamoxifen versus placebo (a pill without drug) on women at high risk for developing breast cancer. In this study, women taking tamoxifen were about 50% less likely to develop breast cancer over a 5-year period. There were very few deaths due to breast cancer in this study, so it is not yet proven that preventive tamoxifen can improve overall survival. Another benefit of tamoxifen seen in this study is that it reduced fractures related to osteoporosis in post-menopausal women.

Tamoxifen did cause unwanted side effects, some of them serious. It increased the incidence of cancer of the uterus, blood clots that could cause strokes or pulmonary emboli (clots which travel to the lungs), and cataracts. Hot flashes and vaginal discharge were also increased in women taking tamoxifen (see the graphs on page 5). It is felt that the benefits of tamoxifen may outweigh the risks in women at high risk of breast cancer, but that the risks from tamoxifen likely outweigh the benefits in women at low or moderate risk of breast cancer. Women at high risk for breast cancer (see Breast Cancer Risk and the Gail Model, below) who are interested in chemoprevention should talk with

their health care provider about this strategy. At present, tamoxifen is the only drug approved for use in breast cancer chemoprevention.

## **Breast Cancer Risk and the Gail Model**

If you have wondered what your risk of breast cancer is, you should know that most women are at low risk during most of their life. The 2 most significant risk factors are being female, and getting older. Some benign breast disorders (see bottom of this page) can indicate an increased risk, as can a family history of breast cancer. A woman's risk for developing breast cancer can be assessed using a statistical model called the Gail Model.

### ***The Gail Model***

This risk assessment tool uses age, family history, history of pregnancy, prior breast biopsy, and age of menarche (the time when menstrual periods began) to estimate a statistical risk of developing breast cancer for individual women. A woman of 60 with no other risk factors, for example, would have a Gail Model risk of about 1.67% of developing breast cancer in the next 5 years. In other words, of 1,000 women at this level of risk at age 60, about 17 would be predicted to develop breast cancer by their 65th birthday.

Factors included in the Gail Model which increase breast cancer risk include:

- Age: In general, older women are at greater risk.
- Age at menarche: Women who had their first menstrual period at 11 years or younger have a greater risk.
- Pregnancy history: Having a first child after age 30 or never having a child.
- A history of biopsy for benign breast disease (see below).
- A family history of breast cancer (see page 4).

### ***Benign Breast Disease***

Certain breast disorders may indicate a higher than usual risk of breast cancer. *Lobular carcinoma in situ* (LCIS) may indicate a significantly increased risk for later breast cancer, as may breast changes termed "atypia" or "hyperplasia." However, most fibrocystic changes, *fibroadenomas*, and cysts do not indicate an increased breast cancer risk.

### *Family History*

Breast cancer in blood relatives can increase your risk for developing breast cancer. A strong family history, suggesting a higher-than-average risk for developing breast cancer, includes:

- Two or more close family members on the same side of the family (mother's OR father's side) who have had breast and/or ovarian cancer (close family members include mother, sister, daughter, aunt, or grandmother).
- Family members with breast cancer who were younger than 50 when they were diagnosed.
- Family members who developed cancer in both breasts.
- Any man with breast cancer in the family.

About 5% to 10% of women (5 to 10 out of 100) who get breast cancer have an inherited breast cancer-associated gene, such as BRCA1 or BRCA2. Some of these genes can now be detected by genetic testing. (See brochure, "Genetic Testing.")

### **Is tamoxifen right for you?**

When the P-01 trial showed that breast cancer was reduced in high-risk women taking tamoxifen, it was exciting news. But, it is still unknown who will most benefit from tamoxifen, what age to start tamoxifen, what dose to use, and how long to continue its use. It is also not yet known whether tamoxifen entirely prevents some breast cancer, or simply delays it.

It is important to know that breast cancer still occurred in some women taking tamoxifen in the P-01 study, and that deaths due to breast cancer were not proven to be reduced. Also, tamoxifen causes a number of potentially serious side effects, including blood clots, cataracts, and cancer of the uterus, and can worsen menopausal symptoms such as hot flashes and vaginal discharge.

Should you take tamoxifen to reduce your risk of breast cancer? This decision involves weighing the risks from taking the drug against its potential benefits. These risks and benefits vary with each person.

Factors to consider include:

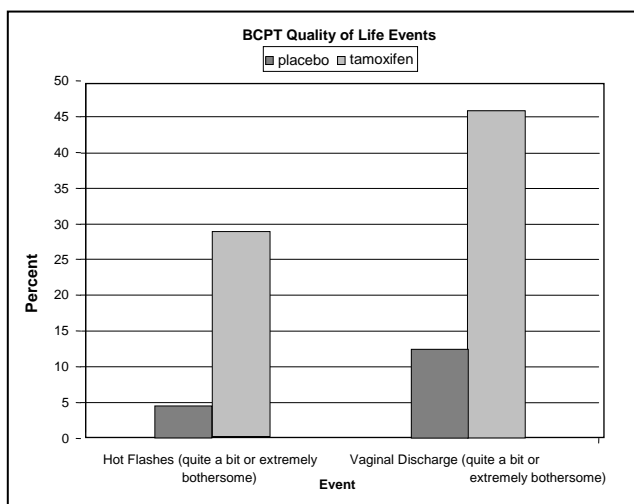
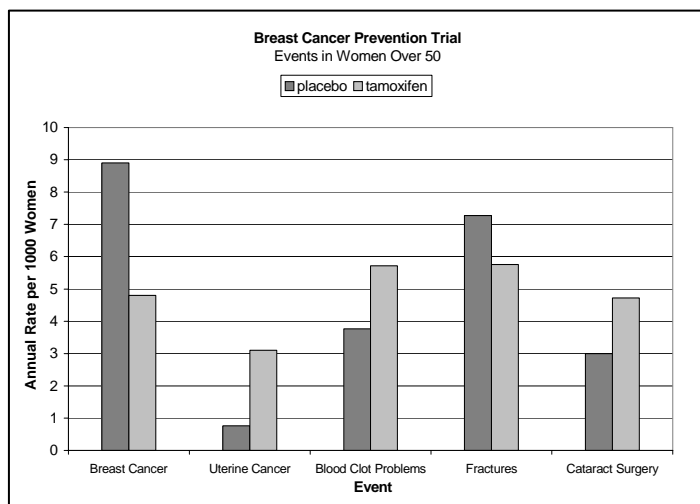
- **Individual risk of breast cancer.** For most women, the risks from taking tamoxifen outweigh the potential benefit. Women whose risk of developing breast cancer is high are those most likely to benefit from taking tamoxifen for chemoprevention of breast cancer. The risk of developing breast cancer in the next 5 years for a 60-year-old woman is reduced from about 1.7% to about half that

(0.85%) if she takes tamoxifen. That means that 98 out of every 100 women who are 60 years old (and do not have other breast cancer risk factors) would not develop breast cancer in the next 5 years even without tamoxifen!

- **Uterine cancer.** Risk is low in most women, and tamoxifen increases this low risk. Women taking tamoxifen and who have not had a *hysterectomy* (surgery to remove the uterus) are advised to have regular monitoring of the uterus and to report any unusual bleeding to their doctor.
- **Risk of blood clots (deep vein thrombus, stroke, and pulmonary embolism).** Since tamoxifen increases risk of clotting in blood vessels, women who smoke or who have a personal or family history of blood clots are usually not advised to take tamoxifen.
- **Risk of osteoporosis (brittle bones).** Women taking tamoxifen had somewhat fewer bone fractures than women who did not take the drug. The osteoporosis benefit was only seen in post-menopausal women on the P-01 study.
- **Risk of cataracts.** Tamoxifen increases risk of cataracts requiring surgery.
- **Hot flashes and vaginal discharge.** Women rated these menopausal symptoms as “quite a lot or extremely bothersome” much more often if they were taking tamoxifen compared to placebo.

The graphs from the P-01 trial give a rough idea of the relative benefits and risks of tamoxifen. All drugs have risks. Tamoxifen is no exception, but it can be a useful drug for some women whose risk of breast cancer is high.

**The risks and benefits of taking tamoxifen vary with each person. All drugs have risks. Talk to your doctor. Think about factors such as risk of blood clots, stroke, cataracts, and other side effects. Then weigh the risks and benefits.**



## **The STAR Trial and Raloxifene**

Raloxifene (Evista) is a SERM similar to tamoxifen. Like tamoxifen, it increases blood clots, which can cause stroke or pulmonary embolism, but it appears less likely to cause uterine cancer. Raloxifene has been studied in clinical trials for about 5 years, and it has been approved for treating and preventing osteoporosis. It has not been well studied with respect to breast cancer treatment or prevention. To learn more about how raloxifene compares to tamoxifen both in preventing breast cancer and in causing complications and side effects, the NSABP is doing a study comparing the 2 drugs in 22,000 women. This study, called the STAR trial (Study of Taxoxifen and Raloxifene), is recruiting postmenopausal women who are at higher than usual risk for breast cancer (see below for information).

### **STAR Trial Eligibility**

The STAR trial will compare the safety and effectiveness of tamoxifen and raloxifene in 22,000 women in the US, Puerto Rico, and Canada.

To be eligible, women must be:

- Postmenopausal
- 35 years of age or over
- At increased risk of breast cancer

Risk is determined by age, family history, and other factors. Women with a Gail Model risk of 1.66% to develop breast cancer in the next 5 years, about the risk of a typical 60-year-old, are eligible. This risk is determined using the STAR Risk Assessment Form. Women who have had lobular carcinoma in situ (LCIS) treated by local excision only (no mastectomy) are also eligible.

Women with the following cannot enter the STAR trial:

- Prior breast cancer.
- Prophylactic mastectomy.
- Hormone medicine (estrogen or progesterone), unless stopped at least 3 months before beginning the study.
- Current use of certain drugs, including coumadin or cholestyramine.

## **Breast Cancer Chemoprevention: The Future**

The ideal method for preventing breast cancer has not yet been found, but more options are available now than existed just a few years ago. One important breast cancer prevention option has always been available: a healthy lifestyle with regular exercise and healthy diet maintaining a healthy weight, and minimal alcohol. Also, tamoxifen is available for women at high risk. As research continues, we are likely to find better ways to prevent breast and other cancers.

### **Glossary**

**Antioxidant** – a chemical which reduces oxidation. Some antioxidants are believed to reduce cancer risk.

**Chemoprevention** – the use of a drug to reduce risk of a disease.

**DNA** – the genetic material within each cell. Damage to DNA can lead to cancer.

**Estrogen** – a hormone important in female reproduction. In excess, it may increase breast cancer risk.

**Pulmonary embolism** – a life-threatening condition caused by blockage of a major artery to the lung due to a blood clot.

**Raloxifene** – a drug which acts like estrogen in some body tissues and acts against estrogen in others. Its ability to reduce risk of breast cancer in women at high risk is being tested.

**Stroke** – loss of coordination, speech, consciousness, or other brain function. It can be caused by blockage of blood circulation to the brain from a blood clot.

**Tamoxifen** – a drug which acts like estrogen in some body tissues and against estrogen in others. It is used to treat breast cancer and sometimes to reduce breast cancer risk.

## Questions?

Your questions are important. Call your doctor or health care provider if you have questions or concerns.

Seattle Cancer Care Alliance (SCCA)  
Call: 206-288-7300

STAR Trial: Fred Hutchinson Cancer Research Center/PSOC  
Joelle Machia, RN  
Call: 206-667-6544

Women's Health Care Center, Roosevelt Clinic  
4245 Roosevelt Way  
Call: 206-598-5500

University of Washington Genetics/  
Genetic Counseling  
Call: 206-616-2135

UNIVERSITY OF WASHINGTON  
**MEDICAL CENTER**  
UW Medicine



**Cancer Center**

Box 356043  
1959 N.E. Pacific St. Seattle, WA 98195  
206-598-4100

## To Learn More

More information is available at:

**UW Breast Care and Cancer Research Center Web site**  
[www.uwbreastcare.org](http://www.uwbreastcare.org)

**National Cancer Institute's Cancer Information Service**  
800-4-CANCER (800-422-6237)  
TTY number: 800-332-8615

**National Cancer Institute's CancerNet Cancer Information**  
<http://cancer.net.nci.nih.gov/>

Some things to keep in mind when using the Web to find out information about your health or illness:

- It should be clear who is providing the medical data – their names and qualifications should be posted.
- Find out who owns the site and consider possible biases.
- Make sure there is a way to contact the site owner(s). If you use the site and need to contact them, keep track to see if they respond in a timely manner.
- Look for sites with recent postings – health information does get outdated.
- If you have questions about something you find on the Web, ask your doctor or health care provider.
- Be aware that as you click-and-link through sites, you may be linked to another site and may need to re-evaluate the source.

There are tools available to help you more thoroughly evaluate Web sites such as:

- <http://healthlinks.washington.edu/hsl/liaisons/schnall/UntanglingTheWeb.pdf>
- <http://www.discern.org.uk/>
- <http://cancertrials.nci.nih.gov/beyond/evaluating.html>

*Seattle Cancer Care Alliance is a collaboration of Fred Hutchinson Cancer Research Center, UW Medicine, and Seattle Children's*