Medicines to Reduce Breast Cancer Risk

What drugs are used to reduce the risk of breast cancer?

When drugs are used to reduce the risk of cancer in healthy people, it's called *chemoprevention*. This is an important area of cancer research.

Many clinical studies have shown that the drugs tamoxifen and raloxifene reduce the risk of breast cancer in women known to have an increased risk. Other studies are looking at newer drugs called aromatase inhibitors to find out if they can help reduce risk. Herbs and dietary supplements are also being studied to find out if they might help reduce risk but to date, none have been shown to be helpful.

Tamoxifen and raloxifene

Tamoxifen and raloxifene belong to a class of drugs known as *selective estrogen response modifiers* (or SERMs). This means that they act against the female hormone, estrogen, in some tissues of the body, but act like estrogen in others.

Both drugs are approved for use in the US to lower the risk of breast cancer. They both act against estrogen in the breast, which is why they are useful in reducing the risk of breast cancer. Other SERMs being studied and used in other countries, won't be discussed in detail here.

Tamoxifen

The main use of tamoxifen is to treat *hormone receptor-positive* breast cancer (breast cancer with cells that have estrogen and/or progesterone receptors on them). When given after a cancer that is hormone receptor-positive has been completely removed by surgery, tamoxifen lowers the chance that the cancer will come back later and helps patients live longer. It also lowers the chance that a new cancer will develop in the other breast.

Because tamoxifen was able to lower the chance of a new breast cancer occurring in women with breast cancer, doctors tested it to see if it could lower the chance of breast cancer in women who hadn't had breast cancer but were at risk for it. Studies showed that, in women at high risk for breast cancer, tamoxifen lowered their relative risk up to 50% (one-half). (See below, "What's relative risk?) This led to tamoxifen being approved by the Food and Drug Administration (FDA) to reduce the risk of breast cancer in women who have an increased risk of breast cancer (and are 35 or older).

Tamoxifen works against breast cancer, in part, by interfering with the activity of estrogen. Estrogen is a female hormone that can fuel the growth of breast cancer cells. Tamoxifen blocks estrogen by keeping it from hooking up to receptors (molecules that control the cells' activity) on cells in the breast. For this reason, tamoxifen is sometimes called an anti-estrogen. But actually, while it acts as an anti-estrogen in the breast, it acts like estrogen in other tissues, such as the bones and the lining of the uterus (the *endometrium*).

This drug may be used by women whether or not they have gone through menopause. It's taken once a day, most often as a pill. Its brand names are Nolvadex® and Soltamox®.

Tamoxifen can rarely cause some serious side effects. Its pro-estrogen effects can lead to cancer of the uterus and problems with serious blood clots, including stroke. (See the section "Weighing risks versus benefits" for more information.)

Raloxifene

Raloxifene (Evista®) is a drug that was first approved by the FDA to prevent and treat osteoporosis (bone thinning) in women past menopause.

Raloxifene helps make bones stronger by acting like estrogen in bone tissue. Like tamoxifen, it also acts as an anti-estrogen in breast tissue. Because it doesn't act much like estrogen in the uterus, it has a much lower risk of causing cancer of the uterus than tamoxifen. It may also cause fewer problems with serious blood clots.

Because it has less serious side effects, it was tested to see if it, too, could lower breast cancer risk. These studies showed that it works almost as well as tamoxifen, lowering the relative risk of breast cancer by up to about 40% (see "What's relative risk?"). This led to the approval of raloxifene by the FDA to help reduce breast cancer risk in women who have an increased risk of the disease. It was also found to lower breast cancer risk in women who have osteoporosis but not an increased risk of breast cancer, so it is approved for this group as well.

It is only approved for use in women past menopause because it was only studied in these women. It's also taken once a day.

How much do these drugs lower the risk of breast cancer?

To understand the effect of these drugs on breast cancer risk, it helps to understand what we mean by relative and absolute risk.

What's relative risk?

An important note about risk reduction: any medicine that reduces a person's risk of a certain cancer type by 50% sounds like a no-brainer – cutting your risk by half must be a good thing. But what that means to you depends on what your baseline risk is – what your risk would be without the drug. The 50% number actually refers to *relative risk*, and to know how much the person's risk changes (the absolute risk reduction) you must know that person's baseline risk of that cancer.

For example, if a group of people are considered at high risk of a certain cancer, they may have a 4% risk over the next 5 years -- meaning that of those 100 people, 4 of them are expected to get that cancer. A 50% relative risk reduction means that the risk would be lowered to 2% - or 2 cases in 100 people over the next 5 years. So having the relative risk lowered by 50% would mean the absolute risk went from 4% to 2%. The absolute risk reduction would be 2%. This may be a good thing, but it is not as dramatic as it might first sound when you hear 50%.

Tamoxifen

The Breast Cancer PreventionTrial: Much of what we know about the effect of tamoxifen on breast cancer risk comes from the Breast Cancer Prevention Trial (BCPT). It began in the early 1990s and was sponsored by the National Cancer Institute (NCI).

In this study, more than 13,000 women who were at higher than average risk of breast cancer were assigned to 1 of 2 groups of about equal size. Each group was to take a pill each day for 5 years. One group took tamoxifen and the other took a placebo (sugar pill), but neither group of women knew which pill they were taking.

After about 7 years total, the study compared the women taking the placebo to those who took tamoxifen:

- Those taking tamoxifen had a lower risk of invasive breast cancer overall. There were 145 cases of breast cancer in the tamoxifen group compared with 250 cases in the placebo group.
- The risk of breast cancer in the tamoxifen group was cut in half during the first 5 years of the study (while they got the drug), with less improvement in risk during the next 2 years (after the drug was stopped).
- The lower risk in the tamoxifen group was only seen for estrogen receptor (ER)-positive breast cancers. The rate of ER-negative breast cancer was the same in both groups.

- The tamoxifen group had a lower risk of non-invasive breast cancer; 38 women had ductal carcinoma in situ (DCIS) in the tamoxifen group and 70 in the placebo group.
- During the 7-year follow-up, there was no major difference between the groups in the risk of death from breast cancer between the 2 groups. Breast cancer caused 11 deaths in the placebo group and 12 in the tamoxifen group.
- The number of women who died (from any cause) was also about the same in the placebo and tamoxifen groups.

A number of other studies have also looked at tamoxifen for breast cancer risk reduction, including the IBIS-I study, the Royal Marsden study, and the Italian Tamoxifen Prevention study. When data from all 4 of these trials were taken together, they showed that tamoxifen lowered the relative risk of invasive breast cancer by about one-third. Again, tamoxifen has no effect on ER-negative breast cancers, but ER-positive cancers were cut by almost half (decreased by 45%) in these studies compared to groups not taking the drug. (See section "What's relative risk?")

The evidence clearly shows that tamoxifen can reduce the risk of ER-positive breast cancer. But the studies did **not** show any effect on death rates, either from breast cancer or any other cause.

Raloxifene

Studies of raloxifene include the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, the Raloxifene Use for the Heart (RUTH) trial, and the Continuing Outcomes Relevant to Evista (CORE) trial. All of these studies compared raloxifene to placebo (sugar pill) in women past menopause.

Taken together, these 3 studies showed a relative risk of invasive breast cancer of more than half (59%).The studies showed about a 70% relative reduction in the risk of ER-positive breast cancer. (See section "What's relative risk?")

The Study of Tamoxifen and Raloxifene (STAR): The largest study to look at the effect of raloxifene on breast cancer risk was the STAR trial. This study compared the effects of tamoxifen and raloxifene on breast cancer risk in more than 19,000 women past menopause who had an increased risk of breast cancer. Half were assigned to take tamoxifen and half were assigned to take raloxifene each day for 5 years. Both drugs reduced the risk of breast cancer, although tamoxifen seemed to reduce the risk more.

Looking at all of the selective estrogen response modifier (SERM) studies

A 2013 analysis put together the data from well-controlled studies (combining all of the studies mentioned above with a couple of newer ones), totaling more than 80,000 women. The investigators concluded that SERM drugs lowered breast cancer risk by 38% over a period of 10 years -- the 5 years of taking the drug plus the next 5 years.

Based on the rate of breast cancer in the studies in the analysis, this would translate to about 1 case of invasive breast cancer being prevented for every 53 women taking a SERM drug. If you include non-invasive breast cancers such as DCIS, only about 42 women must take SERMs for 5 years to prevent 1 case of breast cancer (based on a 10 year risk of breast cancer of around 6%).

For a group of women with higher risk, the number that would need to be treated would be much lower. You would need to treat many more women to prevent one breast cancer if the group started out with a lower risk. Note that some of the SERMs used in this large analysis are only available in Europe, but most of the women took tamoxifen and raloxifene.

Studies continue to show that SERMs don't reduce the risk of ER-negative breast cancers. These cancers are more common in younger women and those with *BRCA1* mutations.

Although these drugs haven't specifically been studied in women with *BRCA* mutations, it isn't clear how helpful they are in those women. In the BCPT trial, tamoxifen didn't seem to help women with *BRCA1* genetic mutations, but did seem to help those with *BRCA2* mutations.

These studies were not designed to find differences in death rates between the groups taking the SERMs and the placebos, and no differences were observed. So far, women who took SERMs had no survival advantage (did not live longer), although more follow-up is needed.

Are there other benefits to taking these drugs?

Both tamoxifen and raloxifene can help prevent osteoporosis, a weakening of the bones that can happen to women after menopause. In addition to its use as a breast cancer risk reduction measure, raloxifene is approved by the FDA to treat or prevent osteoporosis.

What are the risks in taking these drugs?

Tamoxifen

Tamoxifen is a complex drug. It acts like an anti-estrogen in some tissues, but acts like estrogen in others. Its anti-estrogen effects cause the most common side effects, such as hot flashes and night sweats. But because it also acts like an estrogen in some tissues, tamoxifen may increase a woman's chance of some rare but serious health problems.

Cancer of the uterus

Estrogens and agents that act like estrogens are known to raise the risk of cancer of the uterus when they are taken by women after menopause. In the Breast Cancer Prevention Trial (BCPT), the women taking tamoxifen had a higher risk of uterine cancer. Most of these were endometrial cancer (cancer of the lining of the uterus), but a few were uterine sarcoma (cancer of the muscle layer of the uterus).

Overall, the risk of uterine cancer was low. Over 7 years, the risk was higher than that seen in the placebo group, but still less than 2%. This came out to about 16 cases of uterine cancer out of 1,000 women in the tamoxifen group, compared with around 5 out of 1,000 in the placebo group. Most of these cancers were found at a very early stage.

The higher risk seemed to affect the women over 50 and not the younger women. For some women over 50, the increased risk of endometrial cancer may offset the reduction in invasive breast cancer. The higher risk of endometrial cancer seemed to drop after the women finished taking tamoxifen.

It is especially important for women who have taken or are taking tamoxifen to talk about the risk of uterine cancer with their doctors. These women should tell their doctors about any vaginal bleeding or spotting after menopause. Bleeding, spotting, or discharge could be symptoms of these cancers. Women should also talk to their doctors about the possible benefits, risks, and limitations of testing for early endometrial cancer.

Endometrial cancer usually can be found at an early stage, when it hasn't spread and treatment works best. Most endometrial cancers are found when women with symptoms (such as spotting or bleeding) are checked by their doctors. Further testing, with endometrial biopsy and transvaginal ultrasound, is done to see if cancer is present. For more information on this, see our document called *Endometrial (Uterine) Cancer*.

The American Cancer Society recommends that women taking tamoxifen learn about their testing options for endometrial cancer so that they can make informed decisions. But at this time we do not recommend routine testing for these women. This is because studies have not shown that routine testing helps find endometrial cancer at a more curable stage. Also, many studies have found that routine testing for endometrial cancer can lead to unnecessary surgery to check out false-positive test results.

Women who have had a hysterectomy (surgery to remove the uterus) are not at risk for endometrial cancer or uterine sarcoma and do not have to worry about these cancers.

Major blood clots

Tamoxifen is known to increase the risk of major blood clots. In the Breast Cancer Prevention Trial, women taking tamoxifen had a higher risk of a blood clot such as a pulmonary embolism (a blood clot that travels to the lung) or a deep vein thrombosis (a blood clot in a large vein in the leg) than the women on the placebo. These clots can sometimes cause serious problems, and even death. Still, the risk was less than 1%..

Women in the tamoxifen group may have also have been more likely to have a stroke than those the placebo group. But the differences were so small that they may have been due to chance rather than the tamoxifen.

Other possible side effects

Women who take tamoxifen may have a slightly higher risk for cataracts (a clouding of the lens of the eye). This was seen in the BCPT study, but not in the IBIS-I. And as women get older, they are more likely to develop cataracts whether or not they take tamoxifen.

The most common side effects of tamoxifen are the symptoms of menopause. These include hot flashes, night sweats, and vaginal dryness. Some women also report problems with a vaginal discharge.

Tamoxifen use may also cause menopause to start earlier than it may have otherwise. This is more likely in women who were close to menopause when they started taking the drug. In most women who take tamoxifen before menopause, the ovaries work normally and make female hormones (estrogens) in the same or slightly increased amounts. But in some women, menstrual periods will stop.

Raloxifene

Raloxifene has many of the same side effects as tamoxifen, but the risks are not so high.

Problems with menopausal symptoms, such as hot flashes, night sweats, and vaginal dryness occur at about the same rate. But more serious side effects occur less often.

In the Study of Tamoxifen And Raloxifene trial, the risk of uterine cancer was almost half as much in the raloxifene group as in the tamoxifen group. The risk of serious blood clots was also 25% lower than in women taking tamoxifen. Raloxifene also does not seem to be linked to the development of cataracts.

How long should women take these drugs to lower breast cancer risk?

We don’t know the ideal length of time women should take one of these drugs to reduce their risk of breast cancer. The women in the studies took these drugs for 5 years. So, based on this, most doctors recommend that women take tamoxifen or raloxifene for 5 years to lower their risk of breast cancer. The risk was lower during the 5 years the women took the drugs and the lower risk lasted a few years after they’d finished. Researchers are still looking at how long the cancer-lowering effects last.

Do these drugs have the same risks as post-menopausal hormone therapy?

Some women take estrogen (sometimes with progesterone) after menopause to help with symptoms of menopause such as hot flashes, night sweats, and vaginal dryness. This is known as *post-menopausal hormone therapy* (PHT) or *hormone replacement therapy* (HRT). It can also help women maintain bone density and reduce their risk of fractures.

Taking estrogen plus progesterone after menopause is known to raise a woman’s chances of heart disease, blood clots, breast cancer, and other serious health problems. Women who are thinking about taking these hormones after menopause should know about these possible side effects and talk to their doctors about them before making the decision. Those who decide to use HRT should use the lowest dose that works and use it for the shortest possible time.

Neither tamoxifen nor raloxifene reduces symptoms linked to menopause, and may even make them worse. Like PHT, these drugs raise the risk of blood clots. The risk of blood clots in post-menopausal women is about the same for women taking tamoxifen as for those who are taking PHT. The risk is lower for women taking raloxifene.

Both tamoxifen and raloxifene help slow or reduce bone loss and have been shown to help lower the risk of broken bones. These drugs have no clear overall effect on heart disease. Both of these drugs can lower the risk of breast cancer.

Who should consider taking a drug to reduce their breast cancer risk?

All women thinking about taking medicine for breast cancer risk reduction should first have a health care professional assess their risk of developing breast cancer and the risk of serious side effects of the drugs. There are tools that can be used to figure out breast cancer risk – see the "Breast cancer risk assessment" section.

The 2 big studies of these drugs, the Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) looked only at women who had at least a 1.7% risk of developing breast cancer over the next 5 years. 1.7% is the risk of a healthy woman aged 60.

A woman younger than age 60 could have the same risk as a 60-year-old (or even higher) if she has one or more of these factors:

- A *BRCA2* gene mutation (someone with a *BRCA1* mutation also has a high risk, but it isn't clear that these drugs will help in that case)
- Has already had breast cancer
- Any past breast biopsy, especially one that shows either atypical ductal hyperplasia (ADH) or lobular carcinoma in situ (LCIS). These conditions are signs of an increased chance of developing invasive breast cancer.
- Several close relatives – mother, sister(s), daughter(s) with breast cancer – especially if they were diagnosed before menopause
- Never had any children, or had a first child after age 30
- Started menstrual periods before age 12 or went through menopause after age 55

To learn more about your own breast cancer risk and whether you might want to talk to your doctor about taking a drug to reduce your risk see the section called "Breast cancer risk assessment."

Are there women who should NOT take one of these drugs to reduce their breast cancer risk?

Tamoxifen

Tamoxifen should **not** be used to reduce breast cancer risk in women who:

- Have ever had serious blood clots or who develop blood clots that need medical treatment
- Are taking medicines to thin their blood (for instance, warfarin, Coumadin®, heparin – drugs that keep blood from clotting)
- Have or have had high blood pressure, obesity, or diabetes (tamoxifen further increases the risk of blood clots in these women)
- Smoke (tamoxifen further increases the risk of blood clots)
- Are pregnant or planning to become pregnant
- Are breastfeeding
- Are younger than 35 years old
- Are younger than 60 years old and are not at increased risk
- Have not been assessed for breast cancer risk
- Are taking hormone replacement therapy, raloxifene, or an aromatase inhibitor
- Have been diagnosed with any type of uterine cancer

There may be other reasons that a woman should not take tamoxifen, such as cataracts or having been previously found to have atypical hyperplasia of the uterus (a kind of pre-cancer).

Women should talk with their doctors about their total health picture in order to make the best possible choices.

Tamoxifen may cause birth defects if it is taken at the time of conception or during pregnancy. Women taking this drug need to use a barrier or another method of birth control that does not involve hormones. If you are pregnant, breastfeeding, or planning to have children tell your doctor before you start tamoxifen.

Do not take birth control pills (oral contraceptives) or other birth control that contains hormones while taking this drug without checking with your doctor first.

Raloxifene

Raloxifene should not be used to reduce breast cancer risk in women who:

- Have ever had blood clots or who develop blood clots that need medical treatment
- Are taking medicines to thin their blood (for instance, warfarin, Coumadin, or heparin – drugs that keep blood from clotting)
- Have or have had high blood pressure, obesity, or diabetes (these are linked to an increased risk of blood clots)
- Smoke (raloxifene may increase the risk of blood clots)
- Are pre-menopausal (have not yet gone through menopause
- Are younger than 35 years old
- Are younger than 60 years old and are not at increased risk
- Have not had any breast cancer risk assessment (unless they have osteoporosis)
- Are taking hormone replacement therapy, tamoxifen, or an aromatase inhibitor
- Have been diagnosed with any type of uterine cancer (although the risk of uterine cancer is lower with raloxifene than with tamoxifen, it may not be zero.)

There may be other reasons a woman should not take raloxifene. Women who have ever had heart disease and who take raloxifene have an increased risk of stroke.

Women should talk with their doctors about their total health picture in order to make the best possible choices.

Raloxifene has not been studied for safety in pre-menopausal women, so it is only given to women who have gone through menopause. It may cause birth defects if it is taken at the time of conception or during pregnancy.

Should women who have an increased risk of breast cancer take one of these drugs?

Women with an increased risk of breast cancer might think about taking a medicine to reduce their risk. As with any medical procedure or treatment, the decision to take such a drug is a personal one in which the benefits and risks must be discussed with your doctor.

The balance of these benefits and risks vary depending on a woman's risk of developing breast cancer, her personal health history, and how she and her doctor weigh the benefits and risks.

Even if a woman has an increased risk of breast cancer, a drug like tamoxifen or raloxifene may not be right for her. Any woman who is thinking about taking a drug to lower breast cancer risk should talk with her doctor about her personal health situation to make the best decision.

Should women who do NOT have an increased risk of breast cancer take one of these drugs?

The best studies of these drugs were in women with an increased risk of breast cancer or who were at least 60 years old. In those women, the benefits outweighed the risks.

In fact, tamoxifen has never been studied in healthy younger women at average risk for breast cancer, so there's no way to know if it would lower their breast cancer risk and, if so, by how much. Only higher risk or older women were allowed to take part in studies to reduce risk because the overall benefit of taking a drug for breast cancer risk reduction is greatest for them.

The FDA approved tamoxifen to be used for breast cancer risk reduction in women who are at high risk based on age or other risk factors-- not in average-risk women.

Raloxifene was found to lower breast cancer risk in post-menopausal women with osteoporosis who did not have an increased risk of breast cancer, so it is an option for these women.

Women at average breast cancer risk would have the same side effects and risks of the drug, but less benefit because fewer of these women would be likely to develop breast cancer. Women who are not at increased risk may wish to talk with their doctors about their specific situations.

Breast cancer risk assessment

The first step in deciding if you should take a drug to lower your breast cancer risk is to have a health care professional do a breast cancer risk assessment. All drugs have benefits and risks. For women with significant risk of breast cancer, the benefits of chemoprevention often outweigh the risks.

For now, most experts say that a woman's breast cancer risk should be higher than average for her to consider taking tamoxifen or raloxifene. A woman who is at higher than average breast cancer risk needs to compare the benefit of possibly reducing her breast cancer risk with the risk of side effects and problems from taking one of these drugs.

Your risk factors need to be identified to find out if you are at higher than average risk for breast cancer. A risk factor is anything that is linked to a higher chance of getting a disease. For example, smoking is a known risk factor for lung and many other cancers. But keep in mind that not all risk factors actually play a part in causing the cancer, and some risk factors cannot be changed. Having a higher risk because of a certain risk factor does not mean that you will develop breast cancer. In fact, most women who have one or more risk factors will never develop breast cancer.

Age is the major risk factor for breast cancer. The risk goes up as you get older. If you are 60 years old you have a higher risk of having breast cancer than if you are 40. But older women also seem to have more of the serious side effects of tamoxifen. In studies,

the greatest breast cancer risk reduction with the fewest side effects was seen in younger women who were at higher risk for breast cancer. Such women would include those with atypical ductal hyperplasia or those who had a sister or mother with breast cancer. For more, see the section called “Weighing risks versus benefits.”

Another risk factor is family history. If your mother, sister, child, aunt, or grandmother has had breast cancer, or you have a male relative with breast cancer, then you have a higher risk than if you don’t have any close relatives with breast cancer.

Other important risk factors are having a personal history of breast cancer, LCIS (lobular carcinoma in situ), DCIS (ductal carcinoma in situ), ADH (atypical ductal hyperplasia), or a prior breast biopsy. There are other risk factors for breast cancer that are less important, but when they are combined they can influence your risk. Examples of these are age at first menstruation, age at menopause, and age when your first child was born.

Breast cancer risk assessment tools

Researchers have built some statistical models to help predict a woman’s risk of getting breast cancer.

The Gail Model is a tool designed for health professionals. Doctors and nurses can use it to help women make informed decisions about taking a drug to lower the risk of breast cancer. It gives a risk score by calculating a woman’s risk of getting breast cancer in the next 5 years and over her lifetime.

The tool does have some limits, though. For instance, some doctors say it does not count family history enough. It’s also important to note that this tool was created for health professionals, so it uses terms and explanations that patients might not understand. Ask your doctor about using this tool to give you a better idea about your risks and whether you should consider taking medicine to reduce your breast cancer risk.

Other risk tools are based largely on risk factors linked to family history, such as the Tyrer-Cuzick model and the Claus model. These are less available, and are generally used only by professionals to estimate breast cancer risk.

None of these tools is perfect. Each has its strengths and weaknesses, and a woman’s risk result may vary depending on the tool used. Many tools have not been tested on minority women, so they may not work the same for everyone. These tools can give you a rough estimate of risk, but they can’t predict for sure if you will develop breast cancer.

Weighing risks versus benefits

Based largely on the results of the Breast Cancer Prevention Trial (BCPT), the Food and Drug Administration (FDA) approved tamoxifen to reduce the risk of breast cancer in women whose risk of developing the disease was at least 1.7% within the next 5 years based on their Gail score (calculated using the Gail Model risk tool). This included all women over the age of 60, as well as those between 35 and 59 with factors that increased their risk to this level, whether or not they had gone through menopause.

Based largely on the results of the Study of Tamoxifen and Raloxifene (STAR), the FDA approved raloxifene to reduce the risk of breast cancer in post-menopausal women whose risk of developing the disease was at least 1.7% within the next 5 years based on the Gail score (calculated using the Gail Model risk tool). This drug is also approved to lower breast cancer risk in post-menopausal women with osteoporosis who have an average risk of breast cancer.

Still, having a 1.7% risk of developing breast cancer over 5 years is the same as having a 98.3% chance of **NOT** getting breast cancer in the next 5 years. This means that most of the women who take a drug to lower breast cancer risk would never have developed cancer in the first place. Also, because these drugs can have some serious side effects, not everyone who meets the FDA requirements for taking tamoxifen or raloxifene for breast cancer risk reduction would necessarily have an overall benefit from it.

Since these studies came out, researchers have tried to look at more than just a woman's risk of developing breast cancer when trying to decide whether she might benefit. For example, older women are at higher risk of breast cancer than younger women are, which could mean one of these drugs might be more likely to reduce this particular risk. But older women are also more likely to have a stroke or blood clot, which could make the drugs riskier for them.

Pre-menopausal women with a risk of developing breast cancer that is greater than 1.7% in 5 years are likely to have an overall benefit from taking tamoxifen to reduce their risk. (Raloxifene is not an option in these women because it's not approved for women who haven't gone through menopause.)

Most post-menopausal women are likely to have an overall benefit from taking tamoxifen. The benefits will most likely outweigh the risks in groups of women who are not obese or who have had a hysterectomy. Most post-menopausal women are also likely to benefit from taking raloxifene. Though the benefits are not as high, the risks are lower.

Studies estimate that about 3 out of 20 (15%) women over the age of 35 would be eligible to take tamoxifen to reduce their risk of breast cancer, according to the FDA criteria. (Because most of these women are pre-menopausal, few of them would be eligible to take raloxifene.) But only about 1 in 3 of these eligible women would have benefits that would be likely to outweigh the risk.

Generally speaking, younger women at high risk of breast cancer appear to have a better benefit-to-risk ratio from tamoxifen than do older women. As with any drug, it's important to remember that each woman is unique, and the possible benefits and risks for her depend on many factors.

A final word on taking tamoxifen or raloxifene to reduce breast cancer risk

Scientists are working very hard to develop information about competing risks, such as how a woman's risk of heart disease or uterus cancer should affect her decisions about

breast cancer risk reduction. As new information comes in, recommendations about who should and who should not take these drugs may change.

Also keep in mind that your risk changes over time with age, with a new diagnosis of breast cancer in your family, or if you have a breast biopsy.

Some experts think that more research is needed to learn more about the benefits and risks of taking these drugs for breast cancer risk reduction. Although studies have shown a lower risk of breast cancer, this did not translate into any effect on deaths from breast cancer or other causes in women followed for up to 10 years.

More research may be needed to answer the many questions about using one of these drugs to reduce the risk of breast cancer.

Aromatase inhibitors

What are aromatase inhibitors?

Aromatase inhibitors are newer drugs that are sometimes used to treat breast cancer or help keep breast cancer from coming back after surgery. The drugs in this class include:

- Exemestane (Aromasin®)
- Letrozole (Femara®)
- Anastrozole (Arimidex®)

Aromatase inhibitors work differently from tamoxifen and raloxifene. Instead of blocking the estrogen receptors, they stop a key enzyme (called *aromatase*) from changing other hormones into estrogen. This lowers estrogen levels in the body, taking away the fuel that estrogen receptor-positive breast cancers need to grow.

These drugs are only useful in women whose ovaries aren’t making estrogen (such as those who have already gone through menopause).

What are the benefits and risks of taking aromatase inhibitors?

Studies have shown that aromatase inhibitors are better than tamoxifen for treating advanced breast cancer. For keeping breast cancer from coming back after surgery, several studies have found that aromatase inhibitors (used instead of or after tamoxifen) are slightly better than tamoxifen alone.

Some short-term effects of aromatase inhibitors are much like those caused by tamoxifen and raloxifene, including hot flashes and vaginal dryness. Muscle and joint pain and headaches happen more often. Unlike tamoxifen and raloxifene, aromatase inhibitors tend to speed up osteoporosis (bone thinning), which can lead to broken bones.

Aromatase inhibitors seem much less likely to cause serious blood clots. Based on the studies done so far, they do not seem to raise the risk of cancer of the uterus, like tamoxifen and raloxifene do.

Because these drugs have been available for a shorter period of time, less is known about other possible long-term effects they may have, such as on the risk of heart disease. Future research will help define these effects.

Are aromatase inhibitors approved for use in reducing breast cancer risk?

No. At this time, aromatase inhibitors are not approved to be used to reduce breast cancer risk. They are used either to treat advanced breast cancer or given after surgery (instead of or after tamoxifen) to help prevent breast cancer from coming back. The FDA has not approved any of these drugs to reduce the risk of developing breast cancer.

But one of these drugs has been shown to lower breast cancer risk in a clinical trial. The MAP3 study compared exemestane to placebo (sugar pill) in a group of 4,560 post-menopausal women who had an increased risk of breast cancer.

After an average of about 3 years on the study, there were 32 cases of invasive breast cancer in the women on placebo, but only 11 cases in the 2,285 women taking exemestane. This is a 65% lower risk in the exemestane group compared to the placebo group. Exemestane did not have a strong effect on the risk of non-invasive or pre-invasive cancer, such as ductal carcinoma in situ (DCIS).

Side effects of exemestane were usually not severe, the most common being hot flashes and joint pain. The women in the group treated with exemestane did not have more fractures (broken bones) during the 3-year study follow-up. The women did not report more problems with osteoporosis, but the study did not look for these problems, either. (Other studies have shown that women on the drug lose more bone over time than women not taking the drug.)

Other studies are looking at the effect of aromatase inhibitors on breast cancer risk. The British IBIS-II study is comparing anastrozole to placebo for 5 years in 6,000 post-menopausal women who are at increased risk of breast cancer. Recruiting for the study was completed in January 2012. Women will take the drug for 5 years, so it will be some time before results are available. Smaller studies are also being done with letrozole.

Aromatase inhibitors to reduce breast cancer risk: More research is needed

Like raloxifene, aromatase inhibitors may someday prove to be as good as or even better than tamoxifen in reducing breast cancer risk, but more study results will be needed to show this. Much less is known about the possible long-term effects of these drugs. Even if they are shown to reduce risk, each woman and her doctor will still need to weigh the possible benefits and risks when deciding if one of them is right for her.

Other compounds being studied

Some other medicines, such as bexarotene and deslorelin, are in early-stage clinical trials for breast cancer chemoprevention. It is not yet clear how well they may work to reduce breast cancer.

Other clinical trials are looking at breast cancer reduction as an unintended effect of drugs used for other reasons. (This is how raloxifene, used for osteoporosis, was found to be useful in breast cancer.) Drugs currently being researched include bisphosphonates (drugs for osteoporosis), and statins (atorvastatin and lovastatin, drugs used to lower cholesterol).

Two more hormone treatment drugs are being studied for reducing breast cancer risk. A selective estrogen response modifier (SERM) called *arzoxifene* that has been used in Europe is now being studied in the US. A new anti-estrogen called *acolbifene* is also being tested.

Clinical trials were begun some years ago on a few dietary supplements to look at their possible role in reducing breast cancer risk. These included grapeseed extract, folate, omega-3 fatty acids, and vitamins B6 and B12. Although records suggest that some of these human studies have been completed, very little has been published in the available medical literature to date.

This type of research takes many years. It will probably be some time before meaningful results on any of these compounds are available.

What does all of this mean for you?

Chemoprevention with either tamoxifen or raloxifene offers a way to reduce (but not eliminate) the risk of developing invasive breast cancer in women who are at increased risk for the disease. If you've had certain health problems, you may not be able to use either of these drugs. (See subsection "Are there women who should NOT take one of these drugs to reduce their breast cancer risk?" in the section "Who should consider taking a drug to reduce their breast cancer risk?")

Every drug has possible side effects. And these drugs may not be right for all women who have an increased risk for breast cancer. If you are thinking about taking one of them, make sure you have a clear understanding of your breast cancer risk (using a quantitative risk assessment tool), as well as the potential benefits and side effects of these medicines.

Your doctor can help you gather information and make the decision about whether or not chemoprevention is the right choice for you.

To learn more

More information from your American Cancer Society

Here is more information you might find helpful. You also can order free copies of our documents from our toll-free number, 1-800-227-2345, or read them on our website, www.cancer.org.

Prevention and early detection

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention (also available in Spanish)

Breast Cancer: Early Detection (also available in Spanish)

Genetic Testing: What You Need to Know

Learning About New Ways to Prevent Cancer

More on breast cancer and other breast conditions

Breast Cancer Detailed Guide (also available in Spanish)

Breast Cancer Dictionary (booklet)

Non-cancerous Breast Conditions (also available in Spanish)

National organizations and Web sites*

Along with the American Cancer Society, other sources of information and support include:

Facing Our Risk of Cancer Empowered (FORCE)
Toll-free number: 1-866-824 RISK (1-866-824-7475)
Website: www.facingourrisk.org

> Offers breast and ovarian cancer risk assessment information, resources to figure out risk, and support for women at increased risk

Prevent Cancer Foundation (PCF)
Toll-free number: 1-800-227-2732
Website: www.preventcancer.org

> Provides easy-to-understand information about many types of cancer and how to lower cancer risk

National Cancer Institute (NCI)
Toll-free number: 1-800-422-6237 (1-800-4-CANCER)
Website: www.cancer.gov

Offers general cancer information and a tool to help you find professionals who provide cancer genetics services, such as cancer risk assessment, genetic counseling, and more. You can find breast cancer prevention information at www.cancer.gov/cancertopics/prevention-genetics-causes/breast/

National Women's Health Information Center (NWHIC)
Toll-free number: 1-800-994-9662
TTY: 1-888-220-5446
Website: www.womenshealth.gov

Offers information on a broad range of women's health issues from AIDS to violence against women, nutrition, fitness, and mental health, as well as cancer information and referrals to other organizations (also in Spanish)

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

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