National Cancer Institute

FactSheet

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

**Reviewed:** 6/16/2009

# Adjuvant and Neoadjuvant Therapy for Breast Cancer

**Key Points**

- Adjuvant therapy for breast cancer is any treatment given after primary therapy to increase the chance of long-term survival. Neoadjuvant therapy is treatment given before primary therapy.
- Adjuvant therapy for breast cancer can include chemotherapy, hormonal therapy, the targeted drug trastuzumab (Herceptin®), radiation therapy, or a combination of treatments.
- Patients who have a higher risk of breast cancer recurrence are more likely to need adjuvant therapy. Doctors look at both prognostic and predictive factors to decide which patients might benefit from adjuvant treatments.
- Adjuvant and neoadjuvant therapies have side effects, but careful studies have shown that the risks of adjuvant therapy for breast cancer are outweighed by the benefit of treatment—that is, increasing the chance of long-term survival.
- Clinical trials of adjuvant and neoadjuvant therapies for breast cancer are testing new treatments, new combinations of treatments, and whether genetic information can be used to better tailor therapies to individual patients.

## 1. What is adjuvant therapy for breast cancer?

Adjuvant therapy for breast cancer is any treatment given after primary therapy to increase the chance of long-term disease-free survival. Primary therapy is the main treatment used to reduce or eliminate the cancer. Primary therapy for breast cancer usually includes surgery—a mastectomy (removal of the breast) or a lumpectomy (surgery to remove the tumor and a small amount of normal tissue around it; a type of breast-conserving surgery). During either type of surgery, one or more nearby lymph nodes are also removed to see if cancer cells have spread to the lymphatic system. When a woman has breast-conserving surgery, primary therapy almost always includes radiation therapy.

Even in early-stage breast cancer, cells may break away from the primary tumor and spread to other parts of the body (metastasize). Therefore, doctors give adjuvant therapy to kill any cancer cells that may have spread, even if they cannot be detected by imaging or laboratory tests. Studies have shown that adjuvant therapy for breast cancer may increase the chance of long-term survival by preventing a recurrence (1).

## 2. What types of adjuvant therapies are used for breast cancer?

Most adjuvant therapies are systemic: they use substances that travel through the bloodstream, reaching and affecting cancer cells all over the body. Adjuvant therapy for breast cancer can include chemotherapy, hormonal therapy, the targeted drug trastuzumab (Herceptin®), radiation therapy, or a combination of treatments.

- *Adjuvant chemotherapy* uses drugs to kill cancer cells. Research has shown that adjuvant chemotherapy for early-stage breast cancer helps to prevent the cancer from returning (1). Usually, more than one drug is given during adjuvant chemotherapy (called combination chemotherapy).

- *Hormonal therapy* deprives breast cancer cells of the hormone estrogen, which many breast tumors need to grow. A commonly used hormonal treatment is the drug tamoxifen, which blocks

estrogen's activity in the body. Studies have shown that tamoxifen helps prevent the original cancer from returning and also helps to prevent the development of new cancers in the other breast; however, many women develop resistance to the drug over time (1, 2). Tamoxifen can be given to both premenopausal and postmenopausal women.

Postmenopausal women may also receive hormonal therapy with a newer type of drug called an aromatase inhibitor (AI), either after tamoxifen therapy or instead of tamoxifen therapy. Rather than blocking estrogen's activity, as tamoxifen does, AIs prevent the body from making estrogen. Clinical trials suggest that AIs may be more effective than tamoxifen in preventing breast cancer recurrence in some women (3–6). Using AIs to block estrogen production in premenopausal women is not very effective, in part because the ovary is stimulated to make more estrogen when blood levels of estrogen fall below normal. This does not occur in postmenopausal women, whose ovaries have stopped making estrogen.

Some premenopausal women may undergo ovarian ablation or suppression, which greatly reduces the amount of estrogen produced by the body, either permanently or temporarily. Premenopausal women who have *BRCA1* or *BRCA2* gene mutations are at very high risk of breast cancer recurrence as well as of ovarian cancer and may decide to have their ovaries surgically removed as part of adjuvant therapy. The surgical removal of the ovaries also decreases the risk of ovarian cancer. Other premenopausal women who have a lower risk of recurrence may be prescribed drugs that temporarily suppress the function of the ovaries, in addition to tamoxifen.

- *Trastuzumab* is a monoclonal antibody that targets cancer cells that make too much of, or overexpress, a protein called HER2. When cancer cells overexpress HER2 protein, they are said to be HER2 positive. Approximately 20 percent of all breast cancers are HER2 positive. Clinical trials have shown that targeted therapy with trastuzumab in addition to chemotherapy decreases the risk of relapse for women with HER2-positive tumors (7–9).

- *Radiation therapy* is usually given after breast-conserving surgery and may be given after a mastectomy. (When doctors give radiation therapy after breast-conserving surgery, it is usually considered part of primary therapy.) For women at high risk of recurrence, doctors may use radiation therapy after mastectomy to kill cancer cells that may be left in tissues next to the breast, such as the chest wall or nearby lymph nodes. Radiation therapy is a type of local therapy, not systemic therapy.

## 3. How is adjuvant therapy given, and for how long?

*Adjuvant chemotherapy* is given orally (by mouth) or by injection into a blood vessel. It is given in cycles, consisting of a treatment period followed by a recovery period. The number of cycles depends on the types of drugs used. Most patients do not have to stay in the hospital for chemotherapy—they can be treated as an outpatient or at the doctor's office. Adjuvant chemotherapy usually does not last for much more than 6 months.

*Hormonal therapy* is usually given orally, as a pill.

- Most women who undergo hormonal therapy take tamoxifen every day for 5 years.
- Some women may take an aromatase inhibitor every day for 5 years instead of tamoxifen.
- Some women may receive additional treatment with an aromatase inhibitor after 5 years of tamoxifen.
- Finally, some women may switch to taking an aromatase inhibitor after 2 or 3 years of tamoxifen, for a total of 5 or more years of hormonal therapy.

*Trastuzumab* is given by infusion into a blood vessel every 1 to 3 weeks for a year.

*Radiation therapy* given after mastectomy is divided into small doses given once a day over the course of several weeks. Radiation therapy may not be given at the same time as some types of chemotherapy or hormonal therapy.

## 4. How do doctors decide who needs adjuvant therapy?

Not all women with breast cancer need adjuvant therapy. Patients at higher risk of cancer recurrence are more likely to need adjuvant therapy. Doctors look at both prognostic and predictive factors to decide which patients might benefit from adjuvant treatments. Prognostic factors help doctors estimate how likely a tumor is to recur. Predictive factors help doctors estimate how likely cancer cells are to respond to a particular treatment.

In addition to a woman's age and menopausal status, several other prognostic factors are used to determine the risk of recurrence (10).

- *Stage of the cancer*. Cancer stage refers to the size of the tumor and whether it is in the breast only or has spread to nearby lymph nodes or other places in the body. Larger tumors (especially those that are more than 5 centimeters—about 2 inches—in diameter) are more likely to recur than small tumors. Breast cancer often first spreads to the lymph nodes under the arm (axillary lymph nodes). During surgery, doctors usually remove some of these underarm lymph nodes to determine whether they contain cancer cells. Cancer that has spread to these lymph nodes is more likely to recur.

- *Tumor grade*. This term refers to how closely the tumor cells resemble normal breast cells when viewed under a microscope. Tumors with cells that bear little or no resemblance to normal breast cells (called poorly differentiated tumors) are more likely to recur. Women with tumor cells that look like normal breast cells (called well-differentiated tumors) tend to have a better prognosis.

- *Proliferative capacity of the tumor*. Proliferative capacity refers to how fast the tumor cells divide, or multiply, to form more cells. Women who have tumor cells that have a low proliferative capacity (that is, the cells divide less often and grow more slowly) tend to have a better prognosis.

- *Hormone receptor status*. The cells of many breast tumors express receptors for the hormones estrogen and progesterone. Tumors with cells that do not express hormone receptors are more likely to recur. Doctors can determine whether a tumor expresses hormone receptors with laboratory tests.

- *HER2 status*. Tumors that produce too much of a protein called HER2 are more likely to recur. Doctors can determine whether a tumor produces too much HER2 with a laboratory test.

Two major predictive factors are currently used to determine whether cancer cells might respond to particular treatments (11):

- *Hormone receptor status.* As mentioned above, the cells of many breast tumors express receptors for the hormones estrogen and progesterone. These hormones bind to the receptors and help the cancer cells grow. Blocking the activity of these hormones with hormonal therapy stops the growth of the cancer cells. Hormonal therapy will not help patients whose tumors do not express hormone receptors.

- *HER2 status*. Tumors that produce too much of the protein HER2 can be treated with trastuzumab, which can cut the risk of recurrence by up to about half (7). Women whose tumors do not produce too much HER2 do not benefit from treatment with trastuzumab.

Clinical trials are under way to see if genetic information collected from tumors can help predict which women will benefit from adjuvant chemotherapy. See Question 7 for more information about these tests.

Prognostic and predictive factors cannot determine exactly which patients may benefit from adjuvant therapy and which patients may benefit from primary therapy alone. Decisions about adjuvant therapy must be made on an individual basis. This complicated decision-making process is best carried out by consulting an oncologist, a doctor who specializes in cancer treatment. In addition to the factors described above, doctors will take into account a woman's general health and her personal treatment preferences.

## 5. What is neoadjuvant therapy?

Neoadjuvant therapy is treatment given before primary therapy. A woman may receive neoadjuvant chemotherapy for breast cancer to shrink a tumor that is inoperable in its current state, so it can be surgically removed. A woman whose tumor can be removed by mastectomy may instead receive neoadjuvant therapy to shrink the tumor enough to allow breast-conserving surgery (12–14).

Neoadjuvant chemotherapy is given in the same manner as adjuvant chemotherapy (see Question 3). If a tumor does not respond (shrink) or continues to grow during neoadjuvant chemotherapy, the doctor may stop treatment and try another type of chemotherapy or perform surgery instead, depending on the stage of the cancer.

Clinical trials are examining whether hormonal therapy or trastuzumab is effective when given before surgery. See Question 7 for more information about clinical trials of neoadjuvant therapies.

## 6. What are the side effects of adjuvant and neoadjuvant therapy?

*Chemotherapy*: The side effects of chemotherapy depend mainly on the drugs a woman receives. As with other types of treatment, side effects vary from person to person. In general, anticancer drugs affect rapidly dividing cells. These include blood cells, which fight infection, cause the blood to clot, and carry oxygen to all parts of the body. When blood cells are affected by anticancer drugs, patients are more likely to get infections and bruise or bleed easily, and may have less energy during treatment and for some time afterward. Cells in hair follicles and cells that line the digestive tract also divide rapidly. As a result of chemotherapy, patients may lose their hair and may have other side effects, such as loss of appetite, nausea, vomiting, diarrhea, or mouth sores.

Doctors can prescribe medications to help control nausea and vomiting caused by chemotherapy. They also monitor patients for any signs of other problems and may adjust the dose or schedule of treatment if problems arise. In addition, doctors advise women who have a lowered resistance to infection because of low blood cell counts to avoid crowds and people who are sick or have colds. The side effects of chemotherapy are generally short-term. They gradually go away during the recovery part of the chemotherapy cycle or after the treatment is over. However, some chemotherapy drugs, called anthracyclines, can increase the risk of heart problems. Women who receive an anthracycline as part of their treatment should be monitored closely by their doctors for heart problems for the rest of their lives.

*Hormonal therapy*: In general, the side effects of tamoxifen are similar to some of the symptoms of menopause. The most common side effects are hot flashes, vaginal discharge, and nausea. Tamoxifen also increases the risk of cataract development. Not all women who take tamoxifen have these symptoms. Most of these side effects do not require medical attention.

Doctors carefully monitor women taking tamoxifen for any signs of more serious side effects. Among women who have not had a hysterectomy (surgery to remove the uterus), the risk of developing uterine cancer is increased for those taking tamoxifen. Women who take tamoxifen should talk with their doctor about having regular pelvic exams, and should be examined promptly if they have pelvic pain or any abnormal vaginal bleeding. Women taking tamoxifen, particularly those who are receiving chemotherapy along with tamoxifen, have a greater risk of developing a blood clot.

Aromatase inhibitors also cause hot flashes, vaginal dryness, and other symptoms of menopause. Women taking an aromatase inhibitor may also experience joint pain (arthralgia) or muscle pain (myalgia) during treatment.

Women taking aromatase inhibitors may have a higher risk of heart problems than those taking tamoxifen. Aromatase inhibitors also reduce bone density and increase the risk of bone fractures. Doctors should carefully monitor women taking aromatase inhibitors for any signs of heart damage or changes in bone density. A type of drug called a bisphosphonate can help reduce bone loss caused by aromatase inhibitors for patients at high risk of fractures.

*Trastuzumab*: Side effects from trastuzumab can include nausea, vomiting, hot flashes, and joint pain. Trastuzumab can also increase the risk of heart problems. Women receiving trastuzumab should be monitored closely by their doctors for any reduction in the heart's ability to pump blood, both during and after treatment.

*Radiation therapy*: Skin in the area treated by radiation may become red, dry, tender, and itchy, and the breast may feel heavy and tight. These problems usually go away over time. Women receiving radiation therapy may become very tired, especially in the later weeks of treatment.

Careful studies have shown that the risks of adjuvant therapy for breast cancer are outweighed by the benefit of treatment—that is, increasing the chance of long-term survival. However, it is important for women to share any concerns they may have about their treatment or side effects with their doctor or other health care provider.

## 7. What are doctors and scientists doing to learn more about adjuvant and neoadjuvant therapy for breast cancer?

Doctors and scientists are conducting research studies called clinical trials to learn how to treat breast cancer more effectively. In these studies, researchers compare two or more groups of patients who receive different treatments. Clinical trials allow researchers to examine the effectiveness of new treatments in comparison with standard ones, as well as to compare the side effects of the treatments.

Researchers are also investigating whether molecular information obtained from a woman's tumor can be used to decide if the woman would benefit from adjuvant therapy. Two large clinical trials sponsored by NCI, a part of the National Institutes of Health, are currently under way in this area of research.

The Trial Assigning Individualized Options for Treatment (TAILORx) is examining whether molecular markers that are frequently associated with risk of recurrence among women who have early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment. TAILORx is using a test called Onco*type* DX™, which calculates the risk of recurrence based on the levels of expression of 21 genes in breast tumors, in over 10,000 women recruited at 900 sites in the United States and Canada. Based on their risk of recurrence, women will be assigned to one of three different treatment groups: women with a high risk of recurrence will receive chemotherapy plus hormonal therapy; women with a low risk of recurrence will receive hormonal therapy alone; and women with an intermediate risk of recurrence will be randomly assigned to receive adjuvant hormonal therapy, with or without chemotherapy. Because the degree of benefit of chemotherapy for women with an intermediate risk of recurrence is unknown, TAILORx seeks to determine whether the Onco*type* DX test will be helpful in future treatment planning for this group.

In the Microarray In Node-negative Disease may Avoid Chemotherapy Trial (MINDACT), investigators are studying genomic profiling compared with clinical assessment to determine the need for chemotherapy in women with node-negative breast cancer (cancer that has not spread to the axillary lymph nodes). The investigators will use both a 70-gene signature test and clinical assessment to determine the women's risk of recurrence. Women eligible to receive chemotherapy who have a high risk of recurrence according to the clinical criteria and a low risk of recurrence according to the 70-gene signature, or have a low risk of recurrence according to the clinical criteria and a high risk of recurrence according to the 70-gene signature, will be randomly assigned to receive treatment based on either the genetic or clinical criteria to determine which better predicts the need for chemotherapy.

Women with breast cancer who are interested in taking part in a clinical trial should talk with their doctor. Complete listings of current clinical trials testing adjuvant and neoadjuvant therapies for female breast cancer are available from NCI's website:

- Trials of adjuvant therapy for female breast cancer
- Trials of neoadjuvant therapy for female breast cancer

Additional information about clinical trials can be found on NCI's website at http://www.cancer.gov/clinicaltrials. NCI's Cancer Information Service (CIS) can also provide information about clinical trials and help with clinical trial searches. Call the CIS at 1–800–4–CANCER (1–800–422–6237).

### Selected References


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**Related Resources**

- *Chemotherapy and You: Support for People With Cancer* (http://www.cancer.gov/cancertopics/coping/chemotherapy-and-you)
- *Radiation Therapy and You: Support for People With Cancer* (http://www.cancer.gov/cancertopics/coping/radiation-therapy-and-you)
- *Taking Part in Cancer Treatment Research Studies* (http://www.cancer.gov/clinicaltrials/learningabout/Taking-Part-in-Cancer-Treatment-Research-Studies)
- Breast Cancer Home Page (http://www.cancer.gov/cancertopics/types/breast)
- Clinical Trials Home Page (http://www.cancer.gov/clinicaltrials)