National Cancer Institute

FactSheet

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

Reviewed: 8/2/2012

Hormone Therapy for Breast Cancer

Key Points

- The hormones estrogen and progesterone can stimulate the growth of some breast cancers. Hormone therapy is used to stop or slow the growth of these tumors.
- Hormone therapy is used to treat both early and advanced breast cancer, and to prevent breast cancer in women who are at high risk of developing the disease.
- Certain medications, especially antidepressants, may reduce the potency of the hormone therapy drug tamoxifen. People who are taking antidepressants should discuss this issue with their doctor.

1. What are hormones?

Hormones are substances that function as chemical messengers in the body. They affect the actions of cells and tissues at various locations in the body, often reaching their targets through the bloodstream.

The hormones estrogen and progesterone are produced by the ovaries in premenopausal women and by some other tissues, including fat and skin, in both premenopausal and postmenopausal women. Estrogen promotes the development and maintenance of female sex characteristics and the growth of long bones. Progesterone plays a role in the menstrual cycle and pregnancy.

Estrogen and progesterone can also promote the growth of some breast cancers, which are called hormone-sensitive (or hormone-dependent) breast cancers.

2. How do hormones stimulate the growth of breast cancer?

Hormone-sensitive breast cancer cells contain proteins known as hormone receptors that become activated when hormones bind to them. The activated receptors cause changes in the expression of specific genes, which can lead to the stimulation of cell growth.

To determine whether breast cancer cells contain hormone receptors, doctors test samples of tumor tissue that have been removed by surgery. If the tumor cells contain estrogen receptors, the cancer is called estrogen receptor-positive (ER-positive), estrogen-sensitive, or estrogen-responsive. Similarly, if the tumor cells contain progesterone receptors, the cancer is called progesterone receptor-positive (PR- or PgR-positive). Approximately 70 percent of breast cancers are ER-positive. Most ER-positive breast cancers are also PR-positive (1).

Breast cancers that lack estrogen receptors are called estrogen receptor-negative (ER-negative). These tumors are estrogen-insensitive, meaning that they do not use estrogen to grow. Breast tumors that lack progesterone receptors are called progesterone receptor-negative (PR- or PgR-negative).

3. What is hormone therapy?

Hormone therapy (also called hormonal therapy, hormone treatment, or endocrine therapy) slows or stops the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones or by interfering with hormone action. Tumors that are hormone-insensitive do not respond to hormone therapy.

Hormone therapy for breast cancer is not the same as menopausal hormone therapy or female hormone replacement therapy, in which hormones are given to reduce the symptoms of menopause.

4. What types of hormone therapy are used for breast cancer?

Several strategies have been developed to treat hormone-sensitive breast cancer, including the following:

- **Blocking ovarian function**: Because the ovaries are the main source of estrogen in premenopausal women, estrogen levels in these women can be reduced by eliminating or suppressing ovarian function. Blocking ovarian function is called ovarian ablation.

  Ovarian oblation can be done surgically in an operation to remove the ovaries (called oophorectomy) or by treatment with radiation. This type of ovarian ablation is usually permanent.

  Alternatively, ovarian function can be suppressed temporarily by treatment with drugs called gonadotropin-releasing hormone (GnRH) agonists, which are also known as luteinizing hormone-releasing hormone (LH-RH) agonists. These medicines interfere with signals from the pituitary gland that stimulate the ovaries to produce estrogen.

  Examples of ovarian suppression drugs that have been approved by the U.S. Food and Drug Administration (FDA) are goserelin (Zoladex®) and leuprolide (Lupron®).

- **Blocking estrogen production**: Drugs called aromatase inhibitors can be used to block the activity of an enzyme called aromatase, which the body uses to make estrogen in the ovaries and in other tissues. Aromatase inhibitors are used primarily in postmenopausal women because the ovaries in premenopausal women produce too much aromatase for the inhibitors to block effectively. However, these drugs can be used in premenopausal women if they are given together with a drug that suppresses ovarian function.

  Examples of aromatase inhibitors approved by the FDA are anastrozole (Arimidex®) and letrozole (Femara®), both of which temporarily inactivate aromatase, and exemestane (Aromasin®), which permanently inactivates the enzyme.

- **Blocking estrogen's effects**: Several types of drugs interfere with estrogen's ability to stimulate the growth of breast cancer cells:

  - **Selective estrogen receptor modulators (SERMs)** bind to estrogen receptors, preventing estrogen from binding. Examples of SERMs approved by the FDA are tamoxifen (Nolvadex®), raloxifene (Evista®), and toremifene (Fareston®). Tamoxifen has been used for more than 30 years to treat hormone receptor-positive breast cancer.

    Because SERMs bind to estrogen receptors, they can potentially not only block estrogen activity (i.e., serve as estrogen antagonists) but also mimic estrogen effects (i.e., serve as estrogen agonists). Most SERMs behave as estrogen antagonists in some tissues and as estrogen agonists in other tissues. For example, tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone.

  - **Other antiestrogen drugs**, such as fulvestrant (Faslodex®), work in a somewhat different way to block estrogen's effects. Like SERMs, fulvestrant attaches to the estrogen receptor and functions as an estrogen antagonist. However, unlike SERMs, fulvestrant has no estrogen agonist effects. It is a pure antiestrogen. In addition, when fulvestrant binds to the estrogen receptor, the receptor is targeted for destruction.

5. How is hormone therapy used to treat breast cancer?

There are three main ways that hormone therapy is used to treat hormone-sensitive breast cancer:

- **Adjuvant therapy for early-stage breast cancer**: Research has shown that women treated for early-stage ER-positive breast cancer benefit from receiving at least 5 years of adjuvant hormone therapy (2). Adjuvant therapy is treatment given after the main treatment (surgery, in the case of early-stage breast cancer) to increase the likelihood of a cure.

Adjuvant therapy may include radiation therapy and some combination of chemotherapy, hormone therapy, and targeted therapy. Tamoxifen has been approved by the FDA for adjuvant hormone treatment of premenopausal and postmenopausal women (and men) with ER-positive early-stage breast cancer, and anastrozole and letrozole have been approved for this use in postmenopausal women.

A third aromatase inhibitor, exemestane, is approved for adjuvant treatment of early-stage breast cancer in postmenopausal women who have received tamoxifen previously.

Until recently, most women who received adjuvant hormone therapy to reduce the chance of a breast cancer recurrence took tamoxifen every day for 5 years. However, with the advent of newer hormone therapies, some of which have been compared with tamoxifen in clinical trials, additional approaches to hormone therapy have become common (3–5). For example, some women may take an aromatase inhibitor every day for 5 years, instead of tamoxifen. Other women may receive additional treatment with an aromatase inhibitor after 5 years of tamoxifen. Finally, some women may switch to an aromatase inhibitor after 2 or 3 years of tamoxifen, for a total of 5 or more years of hormone therapy.

Decisions about the type and duration of adjuvant hormone therapy must be made on an individual basis. This complicated decision-making process is best carried out by talking with an oncologist, a doctor who specializes in cancer treatment.

- **Treatment of metastatic breast cancer**: Several types of hormone therapy are approved to treat hormone-sensitive breast cancer that is metastatic (has spread to other parts of the body).

  Studies have shown that tamoxifen is effective in treating women and men with metastatic breast cancer (6). Toremifene is also approved for this use. The antiestrogen fulvestrant can be used in postmenopausal women with metastatic ER-positive breast cancer after treatment with other antiestrogens (7).

  The aromatase inhibitors anastrozole and letrozole can be given to postmenopausal women as initial therapy for metastatic hormone-sensitive breast cancer (8, 9). These two drugs, as well as the aromatase inhibitor exemestane, can also be used to treat postmenopausal women with advanced breast cancer whose disease has worsened after treatment with tamoxifen (10).

- **Neoadjuvant treatment of breast cancer**: The use of hormone therapy to treat breast cancer before surgery (neoadjuvant therapy) has been studied in clinical trials (11). The goal of neoadjuvant therapy is to reduce the size of a breast tumor to allow breast-conserving surgery. Data from randomized controlled trials have shown that neoadjuvant hormone therapies—in particular, aromatase inhibitors—can be effective in reducing the size of breast tumors in postmenopausal women. The results in premenopausal women are less clear because only a few small trials involving relatively few premenopausal women have been conducted thus far.

  No hormone therapy has yet been approved by the FDA for the neoadjuvant treatment of breast cancer.

6. Can hormone therapy be used to prevent breast cancer?

Yes. Most early breast cancers are ER-positive, and clinical trials have studied whether hormone therapy can be used to prevent breast cancer in women who are at increased risk of getting the disease.

A large NCI-sponsored randomized clinical trial called the Breast Cancer Prevention Trial found that tamoxifen, taken for 5 years, reduced the risk of developing invasive breast cancer by about 50 percent in postmenopausal women who were at increased risk of getting the disease (12). A subsequent large randomized trial, the Study of Tamoxifen and Raloxifene, which was also sponsored by NCI, found that 5 years of raloxifene reduces breast cancer risk in such women by about 38 percent (13).

As a result of these trials, both tamoxifen and raloxifene have been approved by the FDA to reduce the risk of developing breast cancer in women at high risk of the disease. Tamoxifen is approved for use regardless of menopausal status. Raloxifene is approved for use only in postmenopausal women.

The aromatase inhibitor exemestane has also been found to reduce the risk of breast cancer in postmenopausal women at increased risk of the disease. After 3 years of follow-up in another randomized trial, women who took exemestane were 65 percent less likely than those who took a placebo to develop breast cancer (14). Longer follow-up studies will be necessary to determine whether the risk reduction with

exemestane remains high over time, as well as to understand any risks of exemestane treatment. Although exemestane has been approved by the FDA for treatment of women with ER-positive breast cancer, it has not been approved for breast cancer prevention.

7. What are the side effects of hormone therapy?

The side effects of hormone therapy depend largely on the specific drug or the type of treatment (5). The benefits and risks of taking hormone therapy should be carefully weighed for each woman.

Hot flashes, night sweats, and vaginal dryness are common side effects of hormone therapy. Hormone therapy also disrupts the menstrual cycle in premenopausal women.

Less common but serious side effects of hormone therapy drugs are listed below.

Tamoxifen
- Risk of blood clots, especially in the lungs and legs (12)
- Stroke (15)
- Cataracts (16)
- Endometrial and uterine cancers (15, 17)
- Bone loss in premenopausal women
- Mood swings, depression, and loss of libido
- In men: headaches, nausea, vomiting, skin rash, impotence, and decreased sexual interest

Raloxifene
- Risk of blood clots, especially in the lungs and legs (12)
- Stroke in certain subgroups (15)

Ovarian suppression
- Bone loss
- Mood swings, depression, and loss of libido

Aromatase inhibitors
- Risk of heart attack, angina, heart failure, and hypercholesterolemia (18)
- Bone loss
- Joint pain (19–22)
- Mood swings and depression

Fulvestrant
- Gastrointestinal symptoms (23)
- Loss of strength (23)
- Pain

A common switching strategy, in which patients take tamoxifen for 2 or 3 years, followed by an aromatase inhibitor for 2 or 3 years, may yield the best balance of benefits and harms of these two types of hormone therapy (15).

8. Can other drugs interfere with hormone therapy?

Certain drugs, including several commonly prescribed antidepressants (those in the category called selective serotonin reuptake inhibitors, or SSRIs), inhibit an enzyme called CYP2D6. This enzyme plays a critical role in the use of tamoxifen by the body because it metabolizes, or breaks down, tamoxifen into molecules, or metabolites, that are much more active than tamoxifen itself.

The possibility that SSRIs might, by inhibiting CYP2D6, slow the metabolism of tamoxifen and reduce its potency is a concern given that as many as one-fourth of breast cancer patients experience clinical depression and may be treated with SSRIs. In addition, SSRIs are sometimes used to treat hot flashes caused by hormone therapy.

Researchers have found that women taking certain SSRIs together with tamoxifen have decreased blood levels of active tamoxifen metabolites. Because of this, many experts suggest that patients who are taking antidepressants along with tamoxifen should discuss treatment options with their doctors. For example,

doctors may recommend switching from an SSRI that is a potent inhibitor of CYP2D6 (such as paroxetine) to one that is a weaker inhibitor (such as sertraline) or that has no inhibitory activity (such as venlafaxine or citalopram), or they may suggest that their postmenopausal patients take an aromatase inhibitor instead of tamoxifen.

Other medications that inhibit CYP2D6 include the following:

- Quinidine, which is used to treat abnormal heart rhythms
- Diphenhydramine, which is an antihistamine
- Cimetidine, which is used to reduce stomach acid

People who are prescribed tamoxifen should discuss the use of all other medications with their doctors.

9. Where can someone find more information about drugs used in hormone therapy for breast cancer?

NCI's Drug Information Summaries provide consumer-friendly information about certain drugs that are approved by the FDA to treat cancer or conditions related to cancer. For each drug, topics covered include background information, research results, possible side effects, FDA approval information, and ongoing clinical trials. Drug Information Summaries for drugs that have been approved for breast cancer are listed at http://www.cancer.gov/cancertopics/druginfo/breastcancer.

Selected References

1. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. *Breast Cancer Research* 2007; 9(1):R6. [PubMed Abstract]

2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378(9793)771–784. [PubMed Abstract]

3. Untch M, Thomssen C. Clinical practice decisions in endocrine therapy. *Cancer Investigation* 2010; 28 Suppl 1:4–13. [PubMed Abstract]

4. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1–98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncology* 2011; 12(12):1101–1108. [PubMed Abstract]

5. Burstein HJ, Griggs JJ. Adjuvant hormonal therapy for early-stage breast cancer. *Surgical Oncology Clinics of North America* 2010; 19(3):639–647. [PubMed Abstract]

6. Sawka CA, Pritchard KI, Shelley W, et al. A randomized crossover trial of tamoxifen versus ovarian ablation for metastatic breast cancer in premenopausal women: a report of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial MA.1. *Breast Cancer Research and Treatment* 1997; 44(3):211–215. [PubMed Abstract]

7. Howell A, Pippen J, Elledge RM, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005; 104(2):236–239. [PubMed Abstract]

8. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncology* 2010; 11(12):1135–1141. [PubMed Abstract]

9. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *Journal of Clinical Oncology* 2003; 21(11):2101–2109. [PubMed Abstract]

10. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *Journal of the National Cancer Institute* 2006; 98(18):1285–1291. [PubMed Abstract]

11. Chia YH, Ellis MJ, Ma CX. Neoadjuvant endocrine therapy in primary breast cancer: indications and use as a research tool. *British Journal of Cancer* 2010; 103(6):759–764. [PubMed Abstract]

12. 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. *JAMA* 2006; 295(23):2727–2741. [PubMed Abstract]

13. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P–2 Trial: preventing breast cancer. *Cancer Prevention Research* 2010; 3(6):696–706. [PubMed Abstract]

14. Goss PE, Ingle JN, Alés-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *New England Journal of Medicine* 2011; 364(25):2381–2391. [PubMed Abstract]

15. 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. [PubMed Abstract]

16. Gorin MB, Day R, Costantino JP, et al. Long-term tamoxifen citrate use and potential ocular toxicity. *American Journal of Ophthalmology* 1998; 125(4):493–501. [PubMed Abstract]

17. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998; 351(9114):1451–1467. [PubMed Abstract]

18. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *Journal of the National Cancer Institute* 2011; 103(17):1299–1309. [PubMed Abstract]

19. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. *Journal of Clinical Oncology* 2007; 25(5):486–492. [PubMed Abstract]

20. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncology* 2008; 9(1):45–53. [PubMed Abstract]

21. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; 369(9561):559–570. Erratum in: *Lancet* 2007; 369(9565):906. [PubMed Abstract]

22. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. *Annals of Oncology* 2006; 17 Suppl 7:vii 10–4. [PubMed Abstract]

23. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *Journal of Clinical Oncology* 2002; 20(16):3386–3395. [PubMed Abstract]

Related Resources

- *Adjuvant and Neoadjuvant Therapy for Breast Cancer* (http://www.cancer.gov/cancertopics/factsheet/Therapy/adjuvant-breast)
- *Understanding Cancer Series: Estrogen Receptors/SERMs* (http://www.cancer.gov/cancertopics/understandingcancer/estrogenreceptors)

- *What You Need To Know About™ Breast Cancer* (http://www.cancer.gov/cancertopics/wyntk/breast)
- Breast Cancer Home Page (http://www.cancer.gov/cancertopics/types/breast)
- Breast Cancer Prevention (PDQ®) (http://www.cancer.gov/cancertopics/pdq/prevention/breast/Patient)
- Breast Cancer Treatment (PDQ®) (http://www.cancer.gov/cancertopics/pdq/treatment/breast/Patient)
- Agency for Healthcare Research and Quality, *Reducing the Risk of Breast Cancer With Medicine: A Guide for Women* (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=389)