NATIONAL CANCER INSTITUTE FactSheet

Menopausal Hormone Replacement Therapy Use and Cancer: Questions and Answers

Key Points

- Menopausal hormone use (sometimes referred to as hormone replacement therapy or postmenopausal hormone use) involves taking either estrogen alone or estrogen in combination with progesterone or progestin, a synthetic hormone with effects similar to those of progesterone (see Question 2).
- The most comprehensive evidence about the risks and benefits of taking menopausal hormones after menopause comes from the Women's Health Initiative Hormone Program, which was sponsored by the National Heart, Lung, and Blood Institute and the National Cancer Institute (see Questions 4–8).

1. What is menopause?

Menopause is the time in a woman's life when menstruation (having a period) ends. It is part of a biological process that begins, for most women, in their mid-thirties. During this time, the ovaries gradually produce lower levels of natural sex hormones—estrogen and progesterone. Estrogen promotes the normal development of a woman's breasts and uterus, controls the cycle of ovulation (when an ovary releases an egg into a fallopian tube), and affects many aspects of a woman's physical and emotional health. Progesterone controls menstruation and prepares the lining of the uterus to receive the fertilized egg.

"Natural menopause" occurs when a woman has her last menstrual period, or stops menstruating, and is considered complete when menstruation has stopped for 1 year. This usually occurs between ages 45 and 55, with variations in timing from woman to woman. Women who undergo surgery to remove both ovaries (an operation called bilateral oophorectomy) experience "surgical menopause"—an immediate end to menstruation caused by lack of hormones produced by the ovaries.

By the time a woman has reached natural menopause, estrogen output has decreased significantly. Even though low levels of this hormone are produced by other organs after

menopause, these levels are only about one-tenth of the level found in premenopausal women. Progesterone is nearly absent in menopausal women.

2. What are menopausal hormones and why are they used?

Doctors may recommend menopausal hormones to counter some of the problems often associated with the onset of menopause (hot flashes, night sweats, sleeplessness, and vaginal dryness) or to prevent some long-term conditions that are more common in postmenopausal women, such as osteoporosis (a condition characterized by a decrease in bone mass and density, causing bones to become fragile). Menopausal hormone use (sometimes referred to as hormone replacement therapy or postmenopausal hormone use) usually involves treatment with either estrogen alone or estrogen in combination with progesterone or progestin, a synthetic hormone with effects similar to those of progesterone. Among women who are prescribed menopausal hormones, women who have undergone a hysterectomy (surgery to remove the uterus and, sometimes, the cervix) are generally given estrogen alone. Women who have not undergone this surgery are given estrogen plus progestin, which is known to have a lower risk of causing endometrial cancer (cancer of the lining of the uterus).

3. How does medical research determine the benefits and risks of taking menopausal hormones?

Researchers commonly conduct two very different, yet important types of studies with people to examine the benefits and risks of hormone use: clinical trials and observational studies. In clinical trials, the participants are given either hormones or placebos (look-alike pills that do not contain any drug) to determine the effect of the hormones on various conditions and diseases. In observational studies, the investigators do not try to affect the outcome; they compare the health status of women taking hormones to that of women not taking hormones.

4. What has medical research found out about the risks and benefits of hormone use after menopause?

The most comprehensive evidence about the risks and benefits of taking hormones after menopause to prevent disease comes from the Women's Health Initiative (WHI) Hormone Program, which was sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), parts of the National Institutes of Health (NIH). This research program examined the effects of menopausal hormones on women's health. The WHI Hormone Program involved two studies—the use of estrogen plus progestin for women with a uterus (the Estrogen-plus-Progestin Study), and the use of estrogen alone for women without a uterus (the Estrogen-Alone Study). In both hormone therapy studies, women were randomly assigned to receive either the hormone medication being studied or the placebo.

The WHI Estrogen-plus-Progestin Study was stopped in July 2002, when investigators reported that the overall risks of estrogen plus progestin, specifically Prempro™, outweighed the benefits (1). The researchers found that use of this estrogen-plus-progestin pill increased the risk of breast cancer, heart disease, stroke, blood clots, and urinary incontinence. However, the risk of colorectal cancer and hip fractures was lower among women using estrogen plus progestin than among those taking the placebo (1). In addition, the WHI Memory Study showed that estrogen plus progestin doubled the risk for developing dementia (a decline in mental ability in which the patient can no longer function independently on a day-to-day basis) in postmenopausal women age 65 and older. The risk increased for all types of dementia, including Alzheimer's disease (2).

The WHI Estrogen-Alone Study, which involved Premarin™, was stopped in February 2004, when the researchers concluded that estrogen alone increased the risk of stroke and blood clots. In contrast with the WHI Estrogen-plus-Progestin Study, the risk of breast cancer was decreased in women using estrogen alone compared with those taking the placebo (see Question 5). Use of estrogen alone did not increase or decrease the risk of colorectal cancer (3). Similar to the results seen in the Estrogen-plus-Progestin Study, women using estrogen alone had an increased risk of urinary incontinence and a decreased risk of hip fractures.

Another large epidemiologic study, the Million Women Study, enrolled 1.3 million women in the United Kingdom. This study evaluated health outcomes in women using and not using menopausal hormones. Several analyses have been published to date, and many more are expected in the future (4, 5, 6).

5. How does menopausal hormone use affect breast cancer risk and survival?

The WHI Estrogen-plus-Progestin Study concluded that estrogen plus progestin increases the risk of invasive breast cancer. After 5 years of follow-up, women taking these hormones had a 24 percent increase in breast cancer risk compared with women taking the placebo. The increase amounted to an additional 8 cases of breast cancer for every 10,000 women taking estrogen plus progestin for 1 year compared with 10,000 women taking the placebo (7).

A detailed analysis of data from the WHI Estrogen-plus-Progestin Study showed that, among women taking estrogen plus progestin, the breast cancers were slightly larger and diagnosed at more advanced stages compared with breast cancers in women taking the placebo. Among women taking estrogen plus progestin, 25.4 percent of the cancers had spread outside the breast to nearby organs or lymph nodes compared with 16.0 percent among nonusers. Women taking estrogen plus progestin also had more abnormal mammograms (breast x-rays that require additional evaluation) than the women taking the placebo (7).

The WHI Estrogen-Alone Study concluded that taking estrogen did not increase the risk of breast cancer in women with a prior hysterectomy, at least for the 7 years of follow-up

in the study. Further analysis of data from the study indicated a 20 percent decrease in risk of breast cancer in women taking estrogen alone, although this decrease was seen mainly in the occurrence of early-stage breast cancer and ductal breast cancer (a specific type that begins in the lining of the milk ducts in the breast) (8). The observed reduction amounted to 6 fewer cases of breast cancer for every 10,000 women taking estrogen for 1 year compared with 10,000 nonusers, but this lower incidence was not statistically significant; i.e., the lower incidence could have arisen by chance rather than being related to estrogen-alone use (8). The Estrogen-Alone Study also showed a substantial increase in the frequency of abnormal mammograms (8).

A comprehensive review of data from 51 epidemiological (population) studies published in the 1980s and 1990s found a statistically significant increase in breast cancer risk among current or recent users of any hormone replacement therapy compared with the risk among nonusers. Most women in the analysis (88 percent) had used estrogen alone, and data for estrogen-plus-progestin users was not analyzed separately. Analysis of the pooled data also showed that the risk of breast cancer increased with increasing duration of hormone use, and this effect was more prominent in women with low body weight or a low body mass index. However, breast cancers in hormone users were less likely to have spread to other parts of the body compared with the breast cancers in nonusers. The increase in breast cancer risk largely, if not completely, disappeared about 5 years after cessation of hormone use (9).

As part of the Million Women Study, researchers examined six types of breast cancer among users and nonusers of menopausal hormones. The results showed that the effects of hormone use varied among breast cancer types. Overall, breast cancer risk was significantly increased among current users, although the risk was lower among women with higher body mass index (5).

6. What are the effects of hormone use on the risk of endometrial cancer?

Studies have shown that long-term exposure of the uterus to estrogen alone increases a woman's risk of endometrial cancer. The risk associated with estrogen plus progestin appears to be much less, but some data suggest that the risk is still increased compared with the risk for nonusers. The long-term effects of estrogen plus progestin on endometrial cancer risk remain uncertain (10).

The WHI Estrogen-plus-Progestin Study showed that endometrial cancer rates for women taking estrogen plus progestin daily were the same as or possibly less than those for women taking the placebo pill. Uterine bleeding, however, was a common side effect, leading to more frequent biopsies and ultrasounds for women taking estrogen plus progestin compared with those taking a placebo (11).

The Million Women Study confirmed a lower risk of endometrial cancer in women taking estrogen plus progestin in comparison with those taking estrogen only or tibolone, a synthetic steroid that is not available in the United States (6).

7. How does menopausal hormone use affect the risk of ovarian cancer?

Several observational studies have found that the use of estrogen alone is associated with a slightly increased risk of ovarian cancer for women who used this hormone for 10 or more years. One observational study that followed 44,241 menopausal women for approximately 20 years concluded that women who used estrogen alone for 10 or more years were twice as likely to develop ovarian cancer compared with women who did not use menopausal hormones (12). Another large observational study also found an association between estrogen use and death due to ovarian cancer. In this study, the increased risk appeared to be limited to women who used estrogen for 10 or more years (13).

The results from the Million Women Study showed that women currently using menopausal hormones had an increased risk of developing ovarian cancer and a 20 percent likelihood of dying from the disease compared with nonusers. However, the increased risk disappeared after hormone use stopped (4).

Data from the WHI Estrogen-plus-Progestin Study indicate that there may be an increased risk of ovarian cancer with use of estrogen plus progestin (11). After 5.6 years of follow-up, a 58 percent increased risk of ovarian cancer was reported in women using estrogen plus progestin compared with nonusers, but the increased risk was not statistically significant. One observational study suggested that regimens of estrogen plus progestin do not increase the risk of ovarian cancer if progestin is used for more than 15 days per month (14), but this study was too small to draw firm conclusions. More research is needed to clarify the relationship between menopausal hormone use, particularly for estrogen plus progestin, and the risk of ovarian cancer.

8. How does menopausal hormone use affect the risk of colorectal cancer?

After 5 years of follow-up of women taking estrogen plus progestin, the WHI Estrogen-plus-Progestin Study reported a 37 percent reduction in colorectal cancer cases compared with women taking the placebo (1). On average, the researchers found that if a group of 10,000 women takes estrogen plus progestin for a year, 6 fewer cases of colon cancer will occur than in a group of nonusers. These findings are consistent with observational studies, which have suggested that the use of postmenopausal hormones may reduce the risk of colorectal cancer (1, 15). The WHI Estrogen-Alone Study concluded that estrogen alone had no significant effect on colorectal cancer risk (3).

9. Should women with a history of cancer take menopausal hormones?

One of the roles of naturally occurring estrogen is to promote the normal growth of cells in the breast and uterus. For this reason, it is generally believed that menopausal estrogen use by women who have already been diagnosed with breast cancer may promote further tumor growth. Studies of hormone use to treat menopausal symptoms in breast cancer survivors have produced conflicting results.

In one trial, 434 breast cancer survivors receiving either estrogen alone or estrogen plus progestin were followed for 2 years before the study was stopped because researchers concluded that even short-term use of hormone replacement therapy posed an unacceptable risk of breast cancer recurrence. Among these study participants, 26 women in the group receiving hormone replacement therapy had another occurrence of breast cancer compared with 7 women in the group receiving no hormone replacement therapy (16). In another study, which included 378 women who were followed for 4 years, 11 women receiving hormone replacement therapy had another occurrence of breast cancer compared with 13 women receiving no hormone replacement therapy, so the risk of breast cancer recurrence was not increased (17). A review of 15 studies comprising a total of 1,416 breast cancer survivors and 1,998 women without a history of breast cancer found no increase in risk of cancer recurrence with hormone replacement therapy use (18).

There is limited research on the risks associated with menopausal hormone use by women who have had other cancers, particularly gynecological cancers. One review of the published research found that no firm conclusion could be drawn about the safety of hormone use in women with a history of cancer. However, survivors of gastric and bladder cancer and meningioma may be at higher risk of a recurrence. Survivors of gynecological cancers may be at higher risk because these cancers tend to be more hormone-dependent, but more studies are needed (19).

10. Does the way in which hormones are administered make a difference?

Most of the data on the long-term health effects of hormones come from studies in which hormones (estrogen alone or estrogen plus progestin) are administered orally in the form of pills. Hormones in the form of transdermal patches or gels are also used to treat menopause-related symptoms. Estrogen-containing vaginal creams and rings can be used specifically for vaginal dryness. Progesterone is also available as a pill or gel. The amount of estrogen that enters the bloodstream from estrogen-containing vaginal creams and rings depends on the types of hormones and the dose. Generally, vaginal administration of hormones results in lower levels of circulating hormones compared with an equivalent oral dose. Because the vaginal epithelium (thin layer of tissue that covers the vagina) responds to very small doses of estrogen, low-dose estrogen-containing creams or gels can be used.

11. What should women do if they are concerned about taking menopausal hormones?

Although menopausal hormones have short-term benefits such as relief from hot flashes and vaginal dryness, several health concerns are associated with their use. Women should discuss with their health care provider whether to take menopausal hormones and what alternatives may be appropriate for them. The U.S. Food and Drug Administration (FDA) currently advises women to use menopausal hormones for the shortest time and at the lowest dose possible to control symptoms. The FDA publication *Menopause & hormones* provides additional information about the risks and benefits of hormone use for

menopausal symptoms. This resource is available at http://www.fda.gov/womens/menopause/mht-FS.html on the Internet.

12. What are the alternatives for women who choose not to take menopausal hormones?

To decrease the risk of chronic disease, women can adopt a healthy lifestyle by exercising regularly, eating a healthy diet, limiting the consumption of alcohol, and not starting to smoke or, for smokers, trying to quit. Eating foods rich in calcium and vitamin D or taking dietary supplements containing these nutrients can help prevent osteoporosis. Results from the WHI showed that taking calcium and vitamin D supplements provided some benefit in preserving bone mass and preventing hip fractures, particularly in women age 60 and older. Although generally well tolerated, these supplements were associated with an increased risk of kidney stones. Other drugs, such as alendronate (Fosamax®), raloxifene (Evista®), and risedronate (Actonel®), have been shown to prevent bone loss. In addition, parathyroid hormone (Forteo®) is approved by the FDA for osteoporosis treatment.

Short-term menopause-related problems may go away on their own and frequently require no therapy at all. Local therapy for specific symptoms, such as vaginal dryness and urinary bladder conditions, is available. Some women seek relief from menopausal symptoms with nonprescription complementary and alternative therapies containing estrogen-like compounds. Some sources of these estrogen-like compounds include soy-based products, whole grain cereal, oilseeds (primarily flaxseed), legumes, and the botanical black cohosh. The benefits and risks of most of these agents have not been proven, however.

One NIH-funded study, the Herbal Alternatives (HALT) for Menopause Study, involved 351 women, some of whom were postmenopausal while others were approaching menopause. All of these women experienced hot flashes and night sweats and were given herbal supplements, menopausal hormones, or no therapy. Women in the herbal supplement groups received black cohosh alone, a multibotanical supplement (including black cohosh), or the multibotanical supplement plus counseling to increase their intake of dietary soy. Women in the herbal supplement groups had no significant reduction in the number of hot flashes and night sweats compared with women who received no therapy. The women who received menopausal hormones had significantly fewer menopausal symptoms compared with the women who received no therapy (20).

Women should talk with their doctor about the option best for them.

13. What research still needs to be done?

Unresolved questions include whether different forms of the hormones, lower doses, different hormones, or different methods of administration are safer or more effective; whether risks and/or benefits persist after women stop taking hormones; whether women might be able to take hormones safely for a short period of time; and whether certain

subgroups of women, including women with a history of cancer, might be at higher or lower risk than the general population.

The WHI continues to evaluate the longer-term effects of calcium and vitamin D supplements on preserving bone mass, preventing hip fractures, and reducing colon cancer risk, and continues long-term follow-up of women in the hormone trials.

The NIH continues to sponsor research to evaluate the effects of estrogen-like compounds on menopausal symptoms and long-term health after menopause. Several NCI-sponsored studies are evaluating the effectiveness of nonhormonal treatments, such as the botanical St. John's wort and the antidepressant drug citalopram hydrobromide, in reducing hot flashes in women with a history of breast cancer.

14. Where can people get more information about menopausal hormone use?

The following resources provide additional information about menopausal hormones and the WHI:

- **NIH Menopausal Hormone Therapy Information home page** (http://www.nih.gov/PHTindex.htm).
- **WHI Participant Web site** (http://www.whi.org).
- **NCI Menopausal Hormone Replacement Therapy (HRT) digest page** (http://www.cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use).
- **NHLBI Postmenopausal Hormone Therapy Web site** (http://www.nhlbi.nih.gov/health/women/).
- **National Center for Complementary and Alternative Medicine (NCCAM) Menopause Treatments Web page** (http://nccam.nih.gov/health/menopause.htm).

Selected References

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 2002; 288(3):321–333.

2. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *Journal of the American Medical Association* 2003; 289(20):2651–2662.

3. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 2004; 291(14):1701–1712.

4. Beral V, Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2007; 369:1703–1710.

5. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast cancer risk by histological type: A cohort study and meta-analysis. *Lancet Oncology* 2006; 7:910–918.

6. Beral V, Bull D, Reeves G, Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; 365(9470):1543–1551.

7. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative randomized trial. *Journal of the American Medical Association* 2003; 289(24):3243–3253.

8. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *Journal of the American Medical Association* 2006; 295(14):1647–1657.

9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997; 350(9084):1047–1059.

10. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: A meta-analysis. *Obstetrics and Gynecology* 1995; 85(2):304–313.

11. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The Women's Health Initiative randomized trial. *Journal of the American Medical Association* 2003; 290(13):1739–1748.

12. Lacey JV Jr., Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *Journal of the American Medical Association* 2002; 288(3):334–341.

13. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *Journal of the American Medical Association* 2001; 285(11):1460–1465.

14. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *Journal of the National Cancer Institute* 2002; 94(7):497–504.

15. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: A review and meta-analysis. *American Journal of Medicine* 1999; 106:574–582.

16. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer-is it safe?), a randomised comparison: Trial stopped. *Lancet* 2004; 363(9407):453–455.

17. von Schoultz E, Rutqvist LE. Menopausal hormone therapy after breast cancer: The Stockholm randomized trial. *Journal of the National Cancer Institute* 2005; 97(7):533–535.

18. Batur P, Blixen CE, Moore HC, Thacker HL, Xu M. Menopausal hormone therapy (HT) in patients with breast cancer. *Maturitas* 2006; 53(2):123–132.

19. Biglia N, Gadducci A, Ponzone R, Roagna R, Sismondi P. Hormone replacement therapy in cancer survivors. *Maturitas* 2004; 48(4):333–346.

20. Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: A randomized trial. *Annals of Internal Medicine* 2006; 145(12):869–879.

# # #

Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 2.11, *Clinical Trials: Questions and Answers* (http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials)
- *What You Need To Know About™ Breast Cancer* (http://www.cancer.gov/cancertopics/wyntk/breast)
- *What You Need To Know About™ Cancer of the Colon and Rectum* (http://www.cancer.gov/cancertopics/wyntk/colon-and-rectal)
- *What You Need To Know About™ Cancer of the Uterus* (http://www.cancer.gov/cancertopics/wyntk/uterus)
- *What You Need To Know About™ Ovarian Cancer* (http://www.cancer.gov/cancertopics/wyntk/ovary)
- Menopausal Hormone Replacement Therapy (HRT) Digest Page (http://www.cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use)

For more help, contact:

NCI's Cancer Information Service
Telephone (toll-free): 1–800–4–CANCER (1–800–422–6237)
TTY (toll-free): 1–800–332–8615
LiveHelp® online chat: https://cissecure.nci.nih.gov/livehelp/welcome.asp

This fact sheet was reviewed on 10/5/07