

## Menopausal Hormone Therapy and Cancer

### Key Points

- Much of the evidence about risks and benefits of menopausal hormone therapy (MHT) comes from two randomized clinical trials that were conducted as part of the Women's Health Initiative.
- Although MHT provides short-term benefits, such as relief from hot flashes and vaginal dryness, several health concerns are associated with its use, including increased risk for certain cancers.
- The U.S. Food and Drug Administration currently advises women to use MHT for the shortest time and at the lowest dose possible to control menopausal symptoms.

### 1. What is menopausal hormone therapy?

Menopausal hormone therapy (MHT) is a treatment that doctors may recommend to relieve common symptoms of menopause and to address long-term biological changes, such as bone loss, that result from declining levels of the natural hormones estrogen and progesterone in a woman's body during and after the completion of menopause. (More information is available on the MedlinePlus *Menopause* page at <http://www.nlm.nih.gov/medlineplus/menopause.html>.)

MHT usually involves treatment with estrogen alone, estrogen plus progesterone, or estrogen plus progestin, which is a synthetic hormone with effects similar to those of progesterone. Women who have had a hysterectomy are generally prescribed estrogen alone. Women who have not had this surgery are prescribed estrogen plus progestin, because estrogen alone is associated with an increased risk of endometrial cancer, whereas research has suggested that estrogen plus progestin may not be.

### 2. How do the hormones used in MHT differ from the hormones produced by a woman's body?

The hormones used in MHT come from a variety of plants and animals, or they can be made in a laboratory. The chemical structure of these hormones is similar, although usually not identical, to those of hormones produced by women's bodies.

The U.S. Food and Drug Administration (FDA) has approved many hormone products for use in MHT. FDA-approved products have undergone extensive testing and are produced under standardized conditions to ensure that every dose—whether in a pill, a skin patch, or a cream—contains the proper amount of the appropriate hormones. These FDA-approved products are available only with a doctor's prescription. The FDA has more information about MHT on its *Menopause—Medicines to Help You* page at <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118627.htm>.

Non-FDA-approved hormone products, sometimes referred to as "bio-identical hormones," are widely promoted and sold without a prescription on the Internet. Claims that these products are "safer" or more "natural" than FDA-approved hormonal products are not supported by credible scientific evidence. The FDA provides more information about these products in the *Menopausal Hormone Therapy and "Bio-identical" Hormones* section of its *Compounded Menopausal Hormone Therapy Questions and Answers* page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183088.htm#MenopausalHormoneTherapy>.



### 3. Where does evidence about risks and benefits of MHT come from?

The most comprehensive evidence about risks and benefits of MHT comes from two randomized clinical trials that were sponsored by the National Institutes of Health as part of the Women's Health Initiative (WHI) (<http://www.nhlbi.nih.gov/whi/>):

- The **WHI Estrogen-plus-Progestin Study**, in which women with a uterus were randomly assigned to receive either a hormone medication containing both estrogen and progestin (Prempro™) or a placebo.
- The **WHI Estrogen-Alone Study**, in which women without a uterus were randomly assigned to receive either a hormone medication containing estrogen alone (Premarin™) or a placebo.

More than 27,000 healthy women who were 50 to 79 years of age at the time of enrollment took part in the two trials. Although both trials were stopped early (in 2002 and 2004, respectively) when it was determined that both types of therapy were associated with specific health risks, longer-term follow-up of the participants continues to provide new information about the health effects of MHT.

### 4. What are the benefits of menopausal hormone therapy?

Research from the WHI Estrogen-plus-Progestin study has shown that women taking combined hormone therapy had the following benefits:

- One-third fewer hip and vertebral fractures than women taking the placebo. In absolute terms, this meant 10 fractures per 10,000 women per year who took hormone therapy compared with 15 fractures per 10,000 women per year who took the placebo (1).
- One-third lower risk of colorectal cancer than women taking the placebo. In absolute terms, this meant 10 cases of colorectal cancer per 10,000 women per year who took hormone therapy compared with 16 cases of colorectal cancer per 10,000 women per year who took the placebo (1).

However, a follow-up study found that neither benefit persisted after the study participants stopped taking combined hormone therapy medication (2).

Women taking estrogen alone experienced the following benefits:

- One-third lower risk for hip and vertebral fractures than women taking the placebo. In absolute terms, this meant 11 hip and 11 vertebral fractures per 10,000 women per year who took estrogen compared with 17 hip and 17 vertebral fractures per 10,000 women per year who took the placebo (3).
- A 23 percent reduced risk of breast cancer than women taking the placebo. In absolute terms, this meant 26 cases of invasive breast cancer per 10,000 women per year who took estrogen compared with 33 cases of invasive breast cancer per 10,000 women per year who took the placebo (3).

After 10.7 years of follow-up, however, the risk of hip fractures was slightly higher in the estrogen-alone group, but the risk of breast cancer remained lower than that among women who took the placebo (4).

### 5. What are the health risks of MHT?

Before the WHI studies began, it was known that MHT with estrogen alone increased the risk of endometrial cancer in women with an intact uterus. It was for this reason that, in the WHI trials, women randomly assigned to receive hormone therapy took estrogen plus progestin if they had a uterus and estrogen alone if they didn't have one.

Research from the WHI studies has shown that MHT is associated with the following harms:

- **Urinary incontinence.** Use of estrogen plus progestin increased the risk of urinary incontinence (1).
- **Dementia.** Use of estrogen plus progestin doubled the risk of developing dementia among postmenopausal women age 65 and older (5).
- **Stroke, blood clots, and heart attack.** Women who took either combined hormone therapy or estrogen alone had an increased risk of stroke, blood clots, and heart attack (1, 3). For women in both groups, however, this risk returned to normal levels after they stopped taking the medication (2, 4).

- **Breast cancer.** Women who took estrogen plus progestin were more likely to be diagnosed with breast cancer (6). The breast cancers in these women were larger and more likely to have spread to the lymph nodes by the time they were diagnosed (6). The number of breast cancers in this group of women increased with the length of time that they took the hormones and decreased after they stopped taking the hormones (7).

These studies also showed that both combination and estrogen-alone hormone use made mammography less effective for the early detection of breast cancer (6, 8). Women taking hormones had more repeat mammograms to check on abnormalities found in a screening mammogram and more breast biopsies to determine whether abnormalities detected in mammograms were cancer (6, 8).

The rate of death from breast cancer among those taking estrogen plus progestin was 2.6 per 10,000 women per year, compared with 1.3 per 10,000 women per year among those taking the placebo (9). The rate of death from any cause after a diagnosis of breast cancer was 5.3 per 10,000 women per year among women taking combined hormone therapy, compared with 3.4 per 10,000 women per year among those taking the placebo (9).

- **Lung cancer.** Women who took combined hormone therapy had the same risk of lung cancer as women who took the placebo (10). However, among those who were diagnosed with lung cancer, women who took estrogen plus progestin were more likely to die of the disease than those who took the placebo.

There were no differences in the number of cases or the number of deaths from lung cancer among women who took estrogen alone compared with those among women who took the placebo (11).

- **Colorectal cancer.** In the initial study report, women taking combined hormone therapy had a lower risk of colorectal cancer than women who took the placebo (1). However, the colorectal tumors that arose in the combined hormone therapy group were more advanced at detection than those in the placebo group. There was no difference in either the risk of colorectal cancer or the stage of disease at diagnosis between women who took estrogen alone and those who took the placebo (3).

However, a subsequent analysis of the WHI trials found no strong evidence that either estrogen alone or estrogen plus progestin had any effect on the risk of colorectal cancer, tumor stage at diagnosis, or death from colorectal cancer (12).

## 6. Does hysterectomy affect the cancer risks associated with MHT?

Women who had a hysterectomy and who are prescribed MHT generally take estrogen alone.

In 2004, when the WHI Estrogen-Alone Study was stopped early, women taking estrogen alone had a 23 percent reduced risk of breast cancer compared with those who took the placebo (4). An analysis conducted after study participants had been followed for an average of 10.7 years found that women who had taken estrogen alone still had a lower risk of breast cancer than women who had taken the placebo (4).

## 7. Do the cancer risks from MHT change over time?

Women who have had a hysterectomy and who use estrogen-alone MHT have a reduced risk of breast cancer that continues for at least 5 years after they stop taking MHT (4).

Women who take combined hormone therapy have an increased risk of breast cancer that continues after they stop taking the medication (9). In the WHI study, where women took the combined hormone therapy for an average of 5.6 years, this increased risk persisted after an average follow-up period of 11 years. Breast cancers diagnosed in this group of women were larger and more likely to have spread to the lymph nodes (a sign of more advanced disease).

Studies have documented a decline in breast cancer diagnoses in the United States after the sharp reduction in the use of MHT that followed publication of the initial results of the Estrogen-plus-Progestin Study in July 2002 (13, 14). Additional factors, such as a reduction in the use of mammography, may also have contributed to this decline (15).

**8. Is it safe for women who have had a cancer diagnosis to take MHT?**

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 MHT may promote further tumor growth in women who have already been diagnosed with breast cancer. However, studies of hormone use to treat menopausal symptoms in breast cancer survivors have produced conflicting results, with some showing an increased risk of breast cancer recurrence (16, 17) and others showing no increased risk of recurrence (18, 19).

**9. What should women do if they have menopausal symptoms but are concerned about taking MHT?**

Although MHT provides short-term benefits such as relief from hot flashes and vaginal dryness, several health concerns, described in the answer to Question 5, are associated with its use. Women should discuss whether to take MHT and what alternatives may be appropriate for them with their health care provider. The FDA currently advises women to use MHT for the shortest time and at the lowest dose possible to control menopausal symptoms. The FDA publication *Menopause and Hormones* provides additional information about the risks and benefits of MHT use for menopausal symptoms. This resource is available at <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118624.htm>.

**10. Are there alternatives for women who choose not to take menopausal hormone therapy?**

Women who are concerned about the health effects that occur naturally with the decline in hormone production that occurs during menopause can make changes in their lifestyle and diet to reduce certain risks. For example, eating foods that are rich in calcium and vitamin D or taking dietary supplements containing these nutrients may help to prevent osteoporosis. FDA-approved drugs such as alendronate (Fosamax<sup>®</sup>), raloxifene (Evista<sup>®</sup>), and risedronate (Actonel<sup>®</sup>) have been shown in randomized trials to prevent bone loss.

Medications approved by the FDA for treating depression and seizures may help to relieve menopausal symptoms such as hot flashes (20). Those that have been shown in randomized clinical trials to be effective in treating hot flashes include the following:

- Venlafaxine (Effexor<sup>®</sup>)
- Desvenlafaxine (Pristiq<sup>®</sup>)
- Paroxetine (Paxil<sup>®</sup>)
- Fluoxetine (Prozac<sup>®</sup>)
- Citalopram (Celexa<sup>®</sup>)
- Gabapentin (Neurontin<sup>®</sup>)
- Pregabalin (Lyrica<sup>®</sup>)

Some women seek relief from menopausal symptoms with over-the-counter complementary and alternative therapies. Some of these remedies contain estrogen-like compounds derived from sources such as soy products, whole-grain cereals, oilseeds (primarily flaxseed), legumes, or the plant black cohosh. To date, however, randomized clinical trials have not shown that any of these remedies is superior to a placebo in relieving hot flashes. Trials of other herbal remedies, such as evening primrose oil, ginseng, and wild yam, have also not shown that they effectively reduce menopausal symptoms (19).

The National Institute on Aging (NIA), which is part of the National Institutes of Health (NIH), has more information about how to manage the symptoms of menopause on the *Menopause AgePage* at <http://www.nia.nih.gov/HealthInformation/Publications/menopause.htm>.

**11. What questions remain in this area of research?**

The WHI trials were landmark studies that have transformed our understanding of the health effects of MHT. Follow-up studies have expanded and refined the original findings of these two trials. Many questions, however, remain to be answered, such as the following:

- Are different forms of hormones, lower doses, different hormones, or different methods of administration safer or more effective than those tested in the WHI trials?
- Does hormone use present different risks and benefits for women younger than those studied in the WHI trials?
- Is there an optimal age at which to initiate MHT or an optimal duration of therapy that maximizes benefits and minimizes risks?

It's important to note that women who were enrolled in the WHI trials were, on average, 63 years old, although about 5,000 of them were under age 60, so the results of the study may also apply to younger women. However, women in the study were not using MHT to relieve menopausal symptoms. In addition, the WHI trials tested single-dose strengths of one estrogen-only medication (Premarin) and one estrogen-plus-progestin medication (Prempro).

NIA is sponsoring the Early Versus Late Intervention Trial With Estradiol (ELITE) (<http://clinicaltrials.gov/ct2/show/NCT00114517>) to try to answer some of these remaining questions. This clinical trial is comparing the effects of estrogen in a group of women who are within 6 years of menopause and another group of women who are at least 10 years past menopause. Women are randomly assigned to take either estradiol (Estrace®) or a placebo for 5 years. Women with a uterus will also use a progesterone gel or a placebo gel for the last 10 days of each month. This trial has enrolled 643 women and is expected to be completed in the summer of 2013.

NCI is supporting a range of MHT-related research, including studies aimed at understanding the genetic factors that affect women's response to MHT and the role of chronic use of female hormones in the initiation of breast cancer, as well as developing more effective nonhormonal therapies for treating hot flashes.

## 12. Where can people get more information about MHT?

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

- NIH Menopausal Hormone Therapy Information home page (<http://www.nih.gov/PHIndex.htm>)
- WHI Participant website (<http://www.whi.org>)
- National Heart, Lung, and Blood Institute Postmenopausal Hormone Therapy website (<http://www.nhlbi.nih.gov/health/women/>)
- National Center for Complementary and Alternative Medicine Menopausal Symptoms and CAM website (<http://nccam.nih.gov/health/menopause/menopausesymptoms.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. *JAMA* 2002; 288(3):321–333. [[PubMed Abstract](#)]
2. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008; 299(9):1036–1045. [[PubMed Abstract](#)]
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. *JAMA* 2004; 291(14):1701–1712. [[PubMed Abstract](#)]
4. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011; 305(13):1305–1314. [[PubMed Abstract](#)]
5. 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. *JAMA* 2003; 289(20):2651–2662. [[PubMed Abstract](#)]
6. Chlebowski RT, Anderson G, Pettinger M, et al. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. *Archives of Internal Medicine* 2008; 168(4):370–377. [[PubMed Abstract](#)]
7. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *New England Journal of Medicine* 2009; 360(6):573–587. [[PubMed Abstract](#)]

8. Chlebowski RT, Anderson G, Manson JE, et al. Estrogen alone in postmenopausal women and breast cancer detection by means of mammography and breast biopsy. *Journal of Clinical Oncology* 2010; 28(16): 2690–2697. [[PubMed Abstract](#)]
9. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010; 304(15):1684–1692. [[PubMed Abstract](#)]
10. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009; 374(9697):1243–1251. [[PubMed Abstract](#)]
11. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *Journal of the National Cancer Institute* 2010; 102(18):1413–1421. [[PubMed Abstract](#)]
12. Prentice RL, Pettinger M, Beresford SA, et al. Colorectal cancer in relation to postmenopausal estrogen and estrogen plus progestin in the Women's Health Initiative clinical trial and observational study. *Cancer Epidemiology, Biomarkers and Prevention* 2009; 18(5):1531–1537. [[PubMed Abstract](#)]
13. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *New England Journal of Medicine* 2007; 356(16):1670–1674. [[PubMed Abstract](#)]
14. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Research* 2007; 9(3):R28. [[PubMed Abstract](#)]
15. Sprague BL, Trentham-Dietz A, Remington PL. The contribution of postmenopausal hormone use cessation to the declining incidence of breast cancer. *Cancer Causes and Control* 2011; 22(1):125–134. [[PubMed Abstract](#)]
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. [[PubMed Abstract](#)]
17. Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *Journal of the National Cancer Institute* 2008; 100(7):475–482. [[PubMed Abstract](#)]
18. 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. [[PubMed Abstract](#)]
19. 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. [[PubMed Abstract](#)]
20. Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: current treatment options, challenges and future directions. *International Journal of Women's Health* 2010; 2: 123–135. [[PubMed Abstract](#)]

## Related Resources

- *Cancer Clinical Trials*  
(<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 Home Page  
(<http://www.cancer.gov/cancertopics/menopausal-hormone-use>)

## How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- **Call** NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237)
- **Visit** us at <http://www.cancer.gov> or <http://www.cancer.gov/espanol>
- **Chat** using LiveHelp, NCI's instant messaging service, at <http://www.cancer.gov/livehelp>
- **E-mail** us at [cancergovstaff@mail.nih.gov](mailto:cancergovstaff@mail.nih.gov)
- **Order** publications at <http://www.cancer.gov/publications> or by calling 1-800-4-CANCER
- **Get help** with quitting smoking at 1-877-44U-QUIT (1-877-448-7848)