CANCER FACTS

National Cancer Institute • National Institutes of Health
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Menopausal Hormone Use: 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).
- Estrogen is prescribed to treat some of the problems often associated with menopause, such as hot flashes, night sweats, sleeplessness, and vaginal dryness. Doctors may also recommend hormones to prevent long-term conditions more common in postmenopausal women, such as osteoporosis (see Question 2).
- A recent large clinical trial showed that the health risks associated with estrogen plus progestin use were greater than the benefits (see Questions 4–11).
- The overall health effects of estrogen alone in postmenopausal women are less clear. The best evidence will come from a large ongoing clinical trial involving women taking estrogen alone, which is expected to end in 2005 (see Questions 4–11).

1. What is menopause?

Menopause is the time in a woman's life when menstruation 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 sex hormones—estrogen and progesterone. Estrogen promotes the 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 (having a period) and prepares the lining of the uterus to receive the fertilized egg.

"Natural menopause" begins when a woman has her last 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 hormone production and menstruation.

During menopause, a woman may experience problems such as hot flashes, night sweats, sleeplessness, and vaginal dryness. In addition, some long-term conditions, such as osteoporosis and coronary heart disease, are more common in women in the decades after menopause.

By the time the menopause transition is complete, hormone output has decreased significantly. Even though low levels of estrogen are produced by the adrenal glands and fat cells after menopause, they 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?

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.

Estrogen usage, with or without progestin, approximately doubles the estrogen level of a menopausal woman; however, even with hormone treatment, the estrogen and progesterone levels do not reach the natural levels of a premenopausal woman.

Doctors may recommend using hormones to counter some of the problems often associated with 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. Data from a 1997 national survey showed that 45 percent of U.S. women born between 1897 and 1950 used menopausal hormones for at least 1 month, and 20 percent continued use for 5 or more years (1).

3. How do scientists determine the health outcomes associated with hormone use?

In order to study the benefits and risks of hormone use, researchers commonly conduct two types of human studies: 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, there is no intervention by the investigators; they compare the health status of women taking hormones to women not taking the hormones. The strongest evidence for proving an association between menopausal hormones and a disease or condition comes from clinical trials.

4. Do the benefits of hormone use after menopause outweigh the risks?

The best evidence for the risks and benefits of postmenopausal hormone use comes from the Women's Health Initiative (WHI), a large randomized clinical trial of over 16,000 healthy women ages 50 through 79, in which half of the participants took hormones and the other half took a placebo pill (which does not contain any drug). The trial, sponsored by the National Institutes of Health (NIH), was halted early when, in July 2002, investigators reported that the overall risks of estrogen plus progestin, specifically Prempro™, outweighed the benefits (2). The WHI found that use of this estrogen plus progestin pill increases the risk of breast cancer, heart disease, stroke, and blood clots. The study also found that there were fewer cases of hip fractures and colon cancer among women using estrogen plus progestin than in those taking a placebo (2).

Findings from the WHI Memory Study (WHIMS), reported in May 2003, showed that in older women, age 65 and above, use of estrogen plus progestin doubled the risk of developing dementia (3). These same women also did more poorly on cognitive function tests compared with those taking placebo (4).

Additionally, an analysis of the quality of life of a subgroup of WHI participants ages 50 through 79 found no change in general health, vitality, mental health, depressive symptoms, or sexual satisfaction associated with use of estrogen plus progestin (5).

The risks and benefits of estrogen alone are less clear. The study of women in the WHI taking estrogen alone is scheduled to continue until 2005, and the results of this trial will provide evidence for the associated health effects.

5. What are the effects of hormone use on the uterus?

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

For example, some observational reports show that the risk of endometrial cancer for women taking estrogen plus progestin is nearly the same as for women not using estrogen (6), as long as progestin is used for 10 or more days per month (7, 8). However, another observational study showed that, compared to women who had never used hormones, women who used estrogen plus progestin with progestin for fewer than 10 days per month and women who used estrogen plus progestin daily were twice as likely to develop endometrial cancer. The same study showed that women who used estrogen plus progestin with progestin used 10–21 days per month were not at increased risk of developing endometrial cancer compared to nonusers (9).

The WHI randomized trial showed that endometrial cancer rates for women taking estrogen plus progestin daily were the same as for those taking the placebo pill. Uterine

bleeding, however, was a common side effect, leading to more frequent biopsies and ultrasounds for women taking combined hormones compared to those taking a placebo pill (10).

Among women who use menopausal hormones, women who have undergone hysterectomy (surgical removal of the uterus) are generally given estrogen alone, whereas women who have not undergone this procedure are given estrogen plus progestin.

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

In 2002, the estrogen plus progestin component of the WHI concluded that combined estrogen and progestin increases the risk of invasive breast cancer. After an average of 5.2 years of followup, the study found a 26-percent increase in breast cancer risk among women taking the hormones as compared with women taking the placebo. The increase amounted to an additional 8 cases of breast cancer for every 10,000 women treated for 1 year compared to 10,000 nonusers (2).

After an average followup of 5.6 years, a more detailed analysis of the WHI results showed that, among women taking estrogen plus progestin, the breast cancers were slightly larger (1.7 versus 1.5 centimeters) and at more advanced stages compared with cancers in women taking the placebo. Among the women taking hormones, 25.4 percent of the cancers had spread outside the breast to nearby organs or lymph nodes compared with 16.0 percent among nonusers (11). The component of the WHI study that includes 11,000 trial participants taking estrogen alone is expected to end in 2005, and will provide evidence on the effects of this hormone on breast cancer risk.

Observational studies also indicate an increase in breast cancer risk among hormone users. A 1997 analysis of over 90 percent of breast cancer studies throughout the world showed an increased risk of breast cancer for women who used menopausal hormones for 5 or more years. Most of the women included in these studies used estrogen alone; however, the women who used estrogen plus progestin appeared have a somewhat higher risk than those using estrogen alone (12). The increase in risk was seen not only in current users, but also in women who had stopped therapy some time in the previous 4 years. No increased risk was seen in women who had stopped therapy more than 4 years earlier.

Additional observational studies support the conclusion that hormone use is associated with an increased risk of breast cancer, with the greatest risk among women using estrogen plus progestin (13, 14, 15). In the Million Women Study, British researchers found that current use of estrogen, estrogen plus progestin, or other hormone preparations (including varied delivery mechanisms) significantly increased the risk of developing breast cancer in women ages 50 to 64. Women using estrogen plus progestin were at greater risk than those using other hormone preparations. Current hormone users were also more likely to die from breast cancer than women who did not use them. Within about 5 years of stopping use, increased risk largely disappeared (13).

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 modest increased risk of developing ovarian cancer. One 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 (16). Another recent, 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 estrogens for 10 or more years (17).

The most direct evidence about the risk of ovarian cancer in women who use estrogen plus progestin comes from the randomized WHI study (10). These data suggest that there may be an increased ovarian cancer risk with combined hormone use. After 5.6 years of followup, a 58-percent increased risk of ovarian cancer was reported in the women using estrogen plus progestin compared to the nonusers, but the increased risk was not statistically significant. One observational study suggested that combined estrogen-progestin regimens do not increase the risk of ovarian cancer if progestin is used for more than 15 days per month (18), but this study was too small to draw firm conclusions. More research is needed to clarify the relationship between menopausal hormone use, particularly for combined therapy, and the risk of ovarian cancer.

8. What are the effects of menopausal hormones on heart disease?

WHI researchers have found that estrogen plus progestin does not protect but may increase the risk of heart disease among generally healthy postmenopausal women. The greatest increased risk occurred in the first year (2). The most recent analysis of WHI results showed that estrogen plus progestin use was associated with a 24-percent overall increase in the risk of heart disease, with an 81-percent increased risk in the first year of use (19).

Another randomized trial, the Heart and Estrogen/Progestin Replacement Study (HERS), concluded that estrogen combined with progestin has no beneficial effects on the heart in women with a history of heart disease. After 6.8 years of followup, there was no reduction in the risk of heart attacks or deaths from heart disease (20).

The Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), a randomized study looking at the effects of estrogen alone and estrogen plus progestin on women with coronary artery disease found that neither hormone treatment had any significant effect on the progression of the disease (21).

Some observational studies in which women reported whether they were using menopausal hormones have found evidence that estrogen alone may protect a woman against coronary heart disease (22). Most of the participants in these studies were healthy women at low risk for developing heart disease. The WHI is continuing to investigate the

effects of estrogen alone on the heart in a randomized clinical trial that is expected to conclude in 2005.

9. What are the effects of menopausal hormones on bone health?

Osteoporosis is the loss of bone mass and density, which causes bones to become fragile and increases the chance of bone fractures. Low levels of estrogen have been linked to osteoporosis in women.

Estrogen alone and estrogen combined with progestin have been shown to protect against osteoporosis. Results from the WHI showed that estrogen plus progestin can prevent fractures of the hip, vertebrae, and other bones (2). On average, for example, the researchers found that if a group of 10,000 women takes estrogen plus progestin for a year, 5 fewer cases of hip fractures will occur than in 10,000 nonusers.

A more detailed analysis of the WHI study (23) found a decreased risk of fracture in all subgroups of women regardless of age, smoking, fall and fracture history, past use of hormones, parental fracture history, or years since menopause. Use of estrogen and progestin also had a consistent positive effect on bone mineral density.

However, some studies have shown that the benefits on bone health disappear after short-term hormone use is discontinued. Use of estrogen for 3 to 5 years to relieve symptoms of menopause did very little to prevent fractures from osteoporosis in women when they reached ages 75 to 80 (24, 25). These studies suggested that women who take estrogen to maintain bone density must continue taking estrogen to benefit from its effects on bone health.

10. What are the effects of postmenopausal hormone use on quality of life and cognitive functions, specifically memory and learning?

Quality of life

Estrogen is prescribed to treat problems associated with menopause such as hot flashes, night sweats, and vaginal dryness. Menopausal hormones have also been thought to improve mood and psychological well-being in women who have hot flashes and sleeplessness during menopause.

However, a recent report from the WHI that focused on the quality of life of women ages 50 through 79 who took estrogen plus progestin indicated no significant effects on their general health, vitality, mental health, depressive symptoms, or sexual satisfaction. Although hormone use was associated with a small benefit in terms of sleep disturbance, physical functioning, and bodily pain after 1 year of use, the effect was too small to be considered clinically significant. At 3 years, there were no benefits in any quality of life issues (4).

The WHI results may not be relevant for women with severe menopausal symptoms, however. Participants in the WHI study were randomly assigned to receive either

hormones or placebo, and those women who had menopausal symptoms reported relief from symptoms with hormone use. Women who felt that they needed menopausal hormones to treat severe symptoms may not have been willing to take the chance of not receiving hormones and may, therefore, have been underrepresented in the study.

A smaller study of women using estrogen plus progestin found that the effects on quality of life depended on whether or not a woman had menopausal symptoms. Among women experiencing hot flashes, estrogen plus progestin use improved mental health and depressive symptoms. Among those who did not experience hot flashes, however, no emotional benefits were associated with hormone use, and physical functioning (ranging from the ability to dress and bathe to the ability to participate in strenuous sports) was somewhat worse (26).

Memory and learning

Results from 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 (3). A separate study also showed that estrogen plus progestin adversely affected cognitive function when women on the combination therapy were compared with women age 65 and older on placebo. Generally, the women in the WHI Memory Study age 65 and older did well on cognitive tests during the study, but the women on combination therapy did not do as well (5).

11. Are there other benefits or risks associated with menopausal hormone use?

Colon cancer

After 5 years of followup of women taking estrogen plus progestin, the WHI study reported a 37-percent reduction in colorectal cancer cases compared with women taking a placebo (2). 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 nonusers.

The WHI trial of estrogen alone will provide information on whether estrogen has a similar effect.

Blood clots

Data from the WHI study showed that women who use estrogen plus progestin have double the combined rate of blood clots in the lungs and legs (2). On average, the researchers found that if a group of 10,000 women takes estrogen plus progestin for a year, 18 more cases of blood clots will occur than in nonusers. Other studies have consistently reported increased risks of blood clots in the lung (pulmonary embolisms) and deep veins in the legs with hormone use (27, 28, 29).

Stroke

Data from the WHI study showed a 41-percent increase in the incidence of stroke for women using estrogen plus progestin compared with the women not using hormones (2). A longer followup for the same women reported a 31-percent increase in stroke, amounting to 7 additional cases of stroke for every 10,000 women for each year of treatment compared with 10,000 nonusers (30). Previous observational studies have reported conflicting results regarding stroke risk, but two smaller randomized trials showed no significant effect on stroke for women taking either estrogen alone (31) or estrogen plus progestin (32).

Gallbladder disease

Previous studies have consistently shown that women who use estrogen plus progestin are at increased risk for gallbladder disease (28, 33, 34).

12. What are the risks of menopausal hormones for women who have a history of cancer?

One of the roles of naturally occurring estrogen is to promote the normal growth of cells in the breast and uterus. For this reason, there is concern that menopausal estrogen use by women who have had cancer may promote further tumor growth. The effect of menopausal estrogen use after endometrial and breast cancer remains uncertain (35). Little research has been done on the risks associated with menopausal hormone use by women who have had endometrial cancer. A few small studies have found no evidence that hormone use has a negative effect on survival and/or recurrence of the disease in these women (36). However, no large, long-term studies have compared the potential benefits, such as protection against osteoporosis, with the potential cancer risks.

One observational study of breast cancer patients, most of whom were using estrogen alone, reported no increase in recurrence or mortality among women who continued hormone use after their diagnosis (37). Another study of breast cancer patients showed that users of estrogen had lower mortality rates from breast cancer than patients who did not use estrogen. Most of these patients stopped using estrogen at the time of diagnosis. However, the benefit of prior estrogen use diminished with time (38).

13. Does the route of administration of hormones make a difference?

Most of the data on the long-term health effects of hormones come from studies where hormones (estrogen alone or estrogen in combination with progesterone or progestin) are administered orally in the form of pills. Other ways hormones are given include transdermal patches, gels, and vaginal creams and rings. These forms of estrogen are all equally effective methods of treating symptoms of menopause, such as hot flashes and vaginal dryness. In addition, progesterone is available as a pill or gel.

Several studies have found that the benefit of transdermal products on bone density and bone metabolism is comparable to that of oral therapy (39, 40, 41). It is not known

whether transdermal estrogen and progestin will have different effects than pills on the heart and blood vessels.

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 can be used to correct some effects of menopause on the vagina. Vaginal estrogen therapy does not appear to protect against bone loss (39, 40).

14. Are there any alternatives for women who choose not to take menopausal hormones?

Although menopausal hormones can have short-term benefits, several health concerns are associated with their use, and many women feel that hormones are not a good choice for them. Women should discuss with their health care provider whether to take menopausal hormones and what alternatives may be appropriate for them.

All women can adopt a healthy lifestyle by not smoking, exercising regularly, and eating a healthy diet. A healthy lifestyle helps to decrease a woman's risk of bone loss. Health professionals also recommend calcium and vitamin D supplements to prevent osteoporosis (42). Another part of the WHI, due to be finished in 2005, is testing the effect of calcium and vitamin D supplements on hip and other fractures as well as the effect on colon cancer. Other drugs, such as alendronate (Fosamax®), raloxifene (Evista®), and risedronate (Actonel®) have been shown to prevent bone loss, and are increasingly becoming the treatment of choice for osteoporosis in many menopausal women (43). Parathyroid hormone (Forteo®) has recently been approved by the Food and Drug Administration for osteoporosis treatment. Tibolone is being studied in clinical trials to prevent osteoporosis.

Although short-term menopause-related problems may go away on their own and frequently require no therapy at all, some women seek relief from these symptoms with nonprescription remedies, such as estrogen-containing foods (soy products, whole-grain cereal, seeds, and certain fruits and vegetables) and creams; herbs such as black cohosh; and vitamin E and vitamin B complexes. The benefits and risks of most of these agents are unproven, but remain an active area of research. Researchers are studying the safety and efficacy of these therapies (42). Local therapy is also available for vaginal dryness and urinary bladder conditions.

15. What research still needs to be done?

Questions remain about the adverse health effects associated with the use of estrogen alone in postmenopausal women. Additional unresolved issues are whether different forms of the hormones, lower doses, different hormones, or different routes 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 might be at higher or lower risk than the general population.

The WHI continues to do research that focuses on ways to prevent heart disease, breast and colorectal cancer, and osteoporosis in menopausal women (44). Parts of the WHI will evaluate the effect of a diet low in fats and high in fruits, vegetables, and grains on the prevention of breast cancer, colorectal cancer, and heart disease, as well as the effect of calcium and vitamin D supplements on the prevention of osteoporosis-related fractures.

Several studies to evaluate the association between menopausal hormones and the occurrence of colorectal cancer are currently under way (45). Other research projects are described at various Government Web sites (46, 47).

16. Where can someone get additional information about menopausal hormone use?

Additional information about menopausal hormones and WHI is available on the NIH's Menopausal Hormone Therapy Homepage at http://www.nih.gov/PHTindex.htm on the Internet.

Additional information about the WHI study is available on the Women's Health Initiative Participant Web site at http://www.whi.org on the Internet.

Also, visit NCI's hormone digest page at http://cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use, and the online journal for reporters, *BenchMarks*, at http://cancer.gov/BenchMarks/archives/2002_08/index.html on the Internet.

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47. http://clinicaltrials.gov

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Publications (available at http://www.cancer.gov/publications)

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- Cancer Facts 4.19, *The Study of Tamoxifen and Raloxifene (STAR): Questions and Answers*
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Use http://www.cancer.gov to reach the NCI's Web site.

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