

A special update for the Women's Health Gathering

Hormone Therapy

UVa Update 2004

The Secret to Good Health? Science Confirms Exercise.

I Inside this booklet, UVa Health System experts will answer your questions about hormone therapy (HT), including:

**What are the risks and benefits of HT?
Should I take HT and for how long?
Should I stop or restart?**

No matter what you decide about menopausal hormone therapy, science confirms that *exercise* is the key component to good health as you age.

UVa medical experts who contributed to this information booklet, include JoAnn V. Pinkerton, M.D., national expert on women's midlife health, Dearing Johns, M.D., David Brenin, M.D., Karen Johnston, M.D., Jennifer Harvey, M.D., Elizabeth Mandell, M.D., John Schmitt, M.D., Christine Peterson, M.D., and Richard Santen, M.D. Reviewed by Rebecca Kightlinger, DO, Sue Woodson, CNP, Patricia Dougherty, CNP.



July 2002: Medical experts at the University of Virginia Health System gathered with 600 women in a public forum in Charlottesville to discuss the recently stopped Women's Health Initiative (WHI) study and its surprising findings about hormone therapy (HT). The 2002 Hormone Therapy information update was developed in response to this transformative moment in women's health: the abrupt halting of a major WHI study that revealed a link between daily use of the HT Prempro and rare, but serious side effects, including breast cancer, heart attack and stroke.

May 2004: As a part of UVa's 2004 Women's Health Gathering, our medical experts have updated this information to continue to inform women about the risks and benefits of postmenopausal hormone therapy from new data still coming out of the WHI and another major study published in 2003 known as the Million Women Study (MWS).

Take heart: UVa's medical experts have some very good news to share. The WHI and other studies confirm that it's never too late to reap numerous health benefits from exercise, including significantly reducing your chances of getting breast cancer. If you haven't already, make this a transformative time in your life by looking to an active lifestyle (whether or not you need medication) - for the secret to good health as you age.

Important Terms at a Glance

WHI	Women's Health Initiative, a federally funded series of clinical trial studies involving 160,000 women to determine health effects of postmenopausal hormone therapy
HT	Hormone Therapy
E+PT	an HT that combines estrogen and progesterone
ET	an HT that has only estrogen

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Q. What is the Women's Health Initiative (WHI)?

A. The WHI is a series of randomized clinical trials involving more than 160,000 women ages 50 to 79 to determine how hormone therapy impacts women's health. One trial studied life style adjustments and the use of calcium and vitamin D, another looked at the use of estrogen plus progesterone therapy (E+PT) and a third study looked at estrogen-only therapy (ET). The E+PT trial that was stopped in 2002 was looking at whether taking a specific combined dose of hormones prevented heart disease. The study looked at the most popular E+PT at the time - Prempro, a daily dose of conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg). In 2004, the estrogen-only study was stopped.

Q. What were the early WHI findings released in 2002 about this form of E+PT?

A. The main findings show that compared to women taking placebo (sugar) pills:

- The number of women who developed breast cancer was higher in women taking E+PT.
- The number of women who developed heart attacks, strokes or blood clots in the lungs and legs was higher in women taking E+PT.
- The number of women who had hip and other fractures or colorectal cancer was lower in women taking E+PT.
- There were no differences in the number of women who had endometrial cancer, which is cancer of the uterus. (There is a known increase in the risk of endometrial cancer among women with a uterus who take estrogen-only therapy).

Q. What do we know in 2004 about this form of E+PT?

A.

- Women over age 65 taking E+PT had twice the rate of developing probable dementia as women who didn't take the drug and it provided no protection against cognitive decline. Alzheimer's was not increased.
- Women taking E+PT had slightly larger (1/10 inch) breast cancer tumors and more advanced local disease (lymph node spread) upon diagnosis compared to women not taking it.
- Women taking E+PT did not have an improvement in overall quality of life measured by energy and fatigue, body pain, emotional health and social functioning. Younger women in the study, however, did show an improvement in quality of sleep and 77 percent who had mild to moderate hot flushes (also known as hot flashes) said their flushes improved. (Women with severe hot flushes were not included in the study.)

Q. What do we know in 2004 about ET, based on WHI's preliminary findings

A. This trial was stopped after women were on ET therapy for an average of seven years. The first published paper is expected around May 2004, but preliminary findings show:

- There was a small increase in strokes (don't yet know in whom or when)
- There was a small increase in probable dementia
- There was no increase or decrease in coronary heart disease (CHD) or heart events
- There was a decreased risk of hip fracture
- There was no increase in breast cancer (Many believe that because there were fewer women enrolled in this trial, it may not have had enough women to show the smaller increase risk of breast cancer as found in the Million Women Study with taking estrogen only.)

Q. What is the Million Women Study (MWS) that was in the news in 2003?

A. This observational study had findings very similar to the WHI. It involved over 1 million women, ages 50 to 64, who were initially breast-cancer free and followed from 1996 to 2001 in a national screening program. It looked at many different kinds of hormone products (unlike the WHI that looked at just one kind of E+PT.)

Q. What did we learn about HT from this study?

A.

- This study suggests that ET also increases the risk of breast cancer, but not by as much as E+PT.
- Users of E+PT and ET had an increased risk of breast cancer and increased risk of dying from breast cancer. E+PT had the highest risk (an additional 19 breast cancers per 1,000 women who take E+PT for 10 years compared to an additional 5 breast cancers per 1,000 women who take ET for 10 years.)
- The risk of breast cancer increases in relationship to the number of years it is taken. For example, taking E+PT for five years was associated with an increase in 7 new cases of breast cancer but at 10 years, 19 cases. The reason for this is that both the risk increases each year and the number of women getting breast cancer as they age increases. Taking E+PT for 20 years is estimated to increase the number to 100 extra cases. This finding is one of the reasons that the recommendation is to use HT for five years or less.
- The risk of breast cancer decreased with time after last use and within five years reached the same level as non-hormone therapy users.
- No significant differences were found among different hormone therapy products, or with different routes or administration with the exception that local vaginal estrogen products, which are used to relieve vaginal dryness showed no increase risk in breast cancer.

Q. What should I do with all this information?

A. If you don't already, think of good health as something you can improve rather than depend on medication to help you maintain.

Exercise and a healthful diet can go a long way in keeping you healthy.

- Definitely don't take E+PT to try and protect against heart disease or Alzheimer's disease (a form of dementia.) Talk to your doctor about whether alternative medications might be a better choice than HT for you to protect your bones.
- Take the lowest dose of HT for the shortest possible time to help alleviate difficult menopausal symptoms such as hot flashes, night sweats, insomnia and irritability.
- Perform monthly breast self-exams, have a doctor examine your breasts at least once a year and get annual mammograms. A digital mammogram may be better able to detect cancer in dense breast tissue (which is difficult to see through on mammography). Denser breasts on mammography are a common side effect of HT.)
- If menopausal symptoms are affecting your quality of life, talk to your doctor and weigh the possibility that the small increased risk of breast cancer caused by the use of estrogen or estrogen plus progesterone therapy may be justified if you are having significant menopausal symptoms, particularly if you are undergoing an early menopause, having had an early surgical menopause or are highly symptomatic (have greater than 7 hot flashes per day, 60 hot flashes per week or soaking night sweats disrupting your sleep).
- If you have a uterus it is important to recognize that estrogen-only therapy increases your risk of uterine cancer.

Q. What are the increased risks for women taking E+PT in real numbers?

A. It's important to remember only 2.5 percent of the women in the WHI study had a serious health problem related to hormone use. With that said, women taking E+PT had slightly larger breast cancer tumors and more likely to have cancer spread to lymph nodes (25.9 percent compared to 15.8 percent among women taking a placebo.)

For every 10,000 women taking E+PT pills, the study showed:

- 38 developed breast cancer each year compared to 30 breast cancers for every 10,000 women taking placebo pills each year (an extra 8/10,000)
- 37 developed a heart attack compared to 30 out of every 10,000 women taking placebo pills (an extra 7/10,000)
- 29 had a stroke each year, compared to 21 out of every 10,000 women taking placebo pills (an extra 8/10,000)
- 34 had blood clots in the lungs or legs, compared to 16 women out of every 10,000 women taking placebo pills (an extra 18/10,000)
- 45 had dementia compared with 23 out of every 10,000 women taking placebo pills (an extra 22/10,000).

Q. What health benefits does E+PT have?

A. E+PT offers some protection against colon cancer and bone fractures caused by osteoporosis. For every 10,000 women taking E+PT pills the study showed:

- 10 had a hip fracture each year, compared to 15 out of every 10,000 women taking placebo pills each year (an extra 5/10,000 fewer fractures, including hip fractures)
- 10 developed colon cancer each year, compared to 16 out of every 10,000 women taking placebo pills (an extra 6/10,000 fewer cases colon cancer)
- 77 percent of 2,000 women taking HT said their hot flushes improved. (Although 52 percent taking a placebo said their hot flushes improved.)
- In most randomized placebo controlled trials, ET or E+PT reduces hot flushes 90% of the time compared to placebo at 25 to 30 percent.
- HT is considered “gold standard” and the only FDA approved method for relief of hot flushes and night sweats.

Q. How long can I safely take E+PT before my risk for breast cancer goes up?

A. The WHI study showed there was no statistically significant difference in the development of breast cancer during the first 4 years between women taking E+PT and those taking placebo pills. After that time, the numbers began to increase. After an average of 5.2 years, there was an increased risk of breast cancer in women taking E+PT compared to those taking placebo pills. The Million Women Study showed that the risk, although slight, can increase by as early as one year after starting ET or E+PT.

Q. Is there an increased risk of breast cancer in women taking estrogen only?

A. The WHI did not show an increased risk of breast cancer from estrogen only. The Million Women Study, however, did show a slight increase in breast cancer among women taking estrogen-only therapy. From these two studies, we can conclude that the risk from taking estrogen only is small and much less than from E+PT.

Q. What about the risk of ovarian cancer and hormone use?

A. In October 2003, a study from the WHI found that postmenopausal women who took E+PT were more likely to develop ovarian cancer than those taking a placebo. However, researchers note that the number of overall cases was so low that the higher number could be a fluke. In a separate study, researchers from the National Cancer Institute found that postmenopausal women who use estrogen-only therapy for 10 years or more have an increased risk for ovarian cancer. Risk increased with length of estrogen use. So far, the studies suggesting possible increase in ovarian cancer risk are observational. We need more data.

Q. What are breast specialists saying about the WHI and MWS results?

A. With the data we have from this study, it means the medical risk/benefit ratio for taking hormones has become too high for many women. If you are healthy and taking hormones only to prevent hot flashes and other symptoms, HT may make sense for you. Discuss your goals for therapy carefully with your doctor. Taking HT is a very individual decision that each woman needs to make. Breast experts also note that taking E+PT increases breast tissue density, which makes it harder to read mammograms accurately. When women stop taking the hormones, the dense white tissue on the mammogram goes away within a few weeks.

Q. What do heart experts say about the WHI? Will taking the combined hormones damage my heart?

A. The WHI studies show E+PT failed to protect the heart and blood vessels. They do not show definite damage in the heart from taking this combination. There are probably many menopausal women who could take hormones safely and benefit, but there is no way to know for sure which women will benefit. Estrogen therapy alone also did not show any protection against heart disease, although it also did not show an increased risk of heart disease. That said, you should definitely stop hormone therapy if you have had a heart attack, stroke or stroke-like symptoms, or if you have developed a vein clot. You probably should also stop hormone therapy if you need to be immobilized because of a broken bone or major surgery. Being immobilized increases your chances of forming a blood clot.

Q. What is the biggest danger of taking these hormones together, with regard to my heart and blood vessels?

A. There is an increase in vein clotting early in the course of therapy. In the first one to two years of this combination therapy, clotting in veins is likely to increase. Clotting in veins is different from clotting in arteries that go to the heart. There are still questions about whether there is a significant increase in the risk of heart attack if you are taking E+PT. Reanalysis of data did NOT confirm an increased risk of a heart attack.

Q. Do you have recommendations about other hormone alternatives (lower-dose estrogens, micronized progesterone, natural hormones)?

A. There are still no definitive answers on how long to safely take hormone therapy or the health effects of other types and doses of HT now becoming available. Transdermal hormones including patches, creams or gels avoid the first-pass liver effect and have less risk of blood clots. Theoretically lower doses appearing on the market should be safer but we lack long-term trials to prove this.

The Million Women study showed that the health risks between different doses and types of E+PT and ET therapy did not differ with regards to breast cancer risk. No difference was seen among different types of dosages of HT including oral versus patch. Local vaginal estrogen did NOT increase risk of breast cancer.

Without more data, it is not possible to make specific recommendations about other hormone medications, including compounded “natural” products. Without scientific clinical trial data, one cannot assume that alternative estrogen plus progesterone treatments have the same risks or are any safer than those studied in WHI.

Q. I am taking prescription hormones, what should I do?

A. Do not panic or abruptly discontinue your hormones. Many women did this in 2002 and later went back on hormones after their debilitating menopausal symptoms returned. We recommend that you talk with your health care provider about your individual health risk profile and the hormones you are currently taking. Stopping abruptly may cause a recurrence of menopausal symptoms (even if you did not have them before going on hormones). If you would like to stop taking the hormones, it may be better to taper off gradually. It is also possible that benefits could exceed risks for you or that there are alternative lifestyle changes or medications that you can take to lower your health risks. Therefore discussion with your health care provider is important.

Q. How much of a difference can lifestyle changes make?

A. Researchers reported back from analyzing data from the WHI study that exercise at any age will help reduce the risk of breast cancer, no matter when a woman begins exercising. Since age is a factor of increased risk, this is really good news for postmenopausal women.

Science confirms that exercise is the secret to good health. A healthy diet also can go far toward preserving your good health. Don't smoke and quit if you do smoke. There are several good clinical studies that show that controlling high blood pressure and normalizing your cholesterol levels lead to robust benefits to your heart and blood vessels. Those are the most important things you can do for your health before you need medications. Some studies show that if you're a postmenopausal woman who exercises aerobically (heartbeat more rapid, building a sweat) four hours a week, you can decrease your breast cancer risk by 15-20 percent. If you only exercise one hour a week, you can decrease your risk by 7 percent. The exercising benefits were even greater for premenopausal women. If you need more evidence, a study published in 2003 based on WHI data found that postmenopausal women can reduce their breast cancer risk by 18 percent with brisk walking 2 1/2 hours a week. Women who kept their body mass index (BMI) below 24 received the greatest health benefits.

The bottom line is that exercise is important for preventing breast cancer as well as for preventing strokes, heart attacks and clots. Eat a healthy diet, including calcium every day, and eat less saturated fat (solid at room temperature) and more olive and fish oils. Avoiding alcohol can help you reduce your risk of breast cancer and prevent hot flushes. Avoiding drinks with caffeine also can help you prevent hot flushes.

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Q. I'm still worried about cardiovascular disease, which I've heard is the #1 killer of American women. Are there other drugs that can protect my heart and blood vessels?

A. Raloxifene is being studied to learn how well it might prevent heart disease. We know that in a large trial of women with osteoporosis, there were fewer breast cancer cases and women at highest risk of heart disease had less heart disease than expected. The study has been going for eight years and has not been stopped yet for any negative findings. It is also being tested in women at high risk of heart disease (Ruth trial) and those at high risk for breast cancer (Start trial). To slow bone loss, strength training in older women has been shown to increase bone density about 1%.

Another trial evaluated men and women who had heart or blood vessel disease or diabetes plus a risk factor to learn the effects of statins. The cardiac protective effect of this drug was greater than the effects seen in the WHI. Ask your doctor about all of the options for your heart, including lifestyle options. Statins have been shown to lower cholesterol and to decrease heart events in both women and men with and without heart disease.

Q. What can I do if I want to keep taking hormones for bone protection?

A. You have to look closely at your personal history and risk factors. If you have a high risk of osteoporosis or colon cancer for example, you might choose to continue taking E+PT pills to prevent a broken hip and colon cancer. We still don't know the safest or lowest preparation that will give us these protective effects, however. You should also explore with your doctor other medicines that could also protect your bones, such as the bisphosphonate family of drugs, known as Fosamax or Actonel. Miacalcin, which helps protect the backbone, usually is used by women who can't take bisphosphonates. Raloxifene is a different type of drug that appears to decrease stimulation to breast (compared with estrogen) while it helps protect bone. Don't forget, also, that your body needs calcium before, during and after menopause. You'll probably need to supplement your diet with calcium, and as you age, you'll need Vitamin D to aid with absorption. If you have had severe bone loss, magnesium supplements may help you absorb calcium better. Exercise against resistance and strength training are also important.

Q. What did we learn from WHI about the effect of hormones on our brains?

A. A WHI study showed that women who started taking E+PT after age 65 were more likely than women that age not taking E+PT to develop probable dementia. This counters a long-held belief that hormones protected women against cognitive decline associated with aging. There are many observational studies which suggest a protective effect of estrogen on the brain. Research is ongoing to see if there is a positive effect of estrogen on the brain if given at the time of menopause. However, women should not start HT solely for possible effects on the brain.

Q. What should I do if I do not want to take HT and I have severe hot flashes?

A. Nonmedical options include layered clothing, paced respiration, exercise without perspiration. Vitamin E at 800 IU, soy products in your diet or black cohosh sold as remifenin 20 mg twice a day may be helpful, but usually only for mild hot flashes. There are several options now that are helpful for hot flashes but have not been well tested in highly symptomatic women and are not FDA approved for the relief of hot flashes. These include the low dose anti-depression drugs like Effexor, Prozac, and Paxil. Others probably also work. Neurontin has recently been shown to help and Clonidine (anti-hypertensive) sometimes helps. For vaginal dryness, you can use vaginal moisturizers and lubricants. If this is not helpful, then you can use a very low dose of local estrogen which can be helpful without much absorption into the body. For depression, which sometimes is benefited by estrogen, you can take one of the SSRI drugs if your health care provider believes that this will be helpful for you. For heart disease prevention, a statin drug is beneficial but HT is not. For prevention of fractures and osteoporosis, a group of drugs called bisphosphonates is effective. These include Fosamax and Actonel. Two additional medications for treatment of osteoporosis include the nasal spray miacalcitonin and the daily injection, Forteo. Miacalcitonin is used primarily in women who can't tolerate other medications as there are very few side effects with it, but also milder effects on bone density. Forteo is a new bone building medicine which is used primarily in women with severe osteoporosis or who fail other treatments. It is only approved by the FDA for 18 months of use. There is also one selective estrogen receptor modulator (SERM) on the market known as Evista. It prevents bone loss and fractures as well as showing a 75% decrease in breast cancer in women with osteoporosis. Effects of Evista on prevention of breast cancer in women at high risk of breast cancer and prevention of heart disease in women at high risk of heart disease are currently being studied. Additional SERMS will be on the market within the next two years.

Stay Tuned. There's more to come.

There are dozens of yet-to-be published research papers looking at data collected during WHI and other studies. WHI did not look at the effects of HT on symptomatic menopausal women. More research is needed and experts warn against applying findings to this group of women, who often suffer the most from menopausal symptoms.

If you're dealing with the debilitating effects of menopausal symptoms, don't rule out HT. Talk to your doctor about your individual risks and try to minimize them with an active lifestyle.

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WHI's Estrogen Plus Progesterone Study Findings At a Glance

CONDITION	FOR EACH YEAR		
	If you are post-menopausal and are taking no hormones , your risks are:	If you are taking estrogen 0.625 mg and progesterone 2.5 mg daily , your risks are:	The increase (or decrease) in risk due to this particular form of HT is:
Coronary heart disease	30 per 10,000	37 per 10,000	7 extra per 10,000
Stroke	21 per 10,000	29 per 10,000	8 extra per 10,000
Pulmonary embolism	8 per 10,000	16 per 10,000	8 extra per 10,000
Invasive breast cancer	30 per 10,000	38 per 10,000	8 extra per 10,000
Dementia	23 per 10,000	45 per 10,000	22 extra per 10,000
Colorectal cancer	16 per 10,000	10 per 10,000	6 fewer per 10,000

WHI's Estrogen-Only Study Preliminary Findings At a Glance

Outcomes	Reported Changes vs Placebo After Nearly 7 Years
Coronary Heart Disease	No Increased or Decreased Overall Risk
Breast Cancer	No Increased Risk
Stroke	Increased Risk
Hip Fractures	Decreased Risk
Probable Dementia and Mild Cognitive Impairment	Trend Toward Increased Risk

