



# NIH NEWS RELEASE

NATIONAL INSTITUTES OF HEALTH

[National Heart, Lung, and Blood Institute](#)

EMBARGOED FOR RELEASE

Tuesday, July 9, 2002

9:30 a.m. Eastern Time

Contact:

NHLBI Communications Office: (301) 496-4236

NCI Press Office: (301) 496-6641

## **NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit**

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has stopped early a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer. The large multi-center trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years.

Participants in this component of WHI, like most women with a uterus who take hormone therapy, were given progestin in combination with estrogen. This practice is known to prevent endometrial cancer. A separate WHI study of estrogen alone in women who had a hysterectomy before joining the WHI hormone program continues unchanged because, at this point, the balance of risks and benefits of estrogen alone is still uncertain.

The report from the WHI investigators on the estrogen plus progestin study findings will be published in the July 17 issue of *The Journal of the American Medical Association (JAMA)*; because of the importance of the information, the study is being released early on Tuesday, July 9, as an expedited article on the *JAMA* Web site. (Full text version available to all at [jama.com](http://jama.com).)

"We have long sought the answer to the question: Does postmenopausal hormone therapy prevent heart disease and, if it does, what are the risks? The bottom-line answer from WHI is that this combined form of hormone therapy is unlikely to benefit the heart. The cardiovascular and cancer risks of estrogen plus progestin outweigh any benefits--and a 26 percent increase in breast cancer risk is too high a price to pay, even if there were a heart benefit. Similarly, the risks outweigh the benefits of fewer hip fractures," said NHLBI Director Claude Lenfant, M.D.

"Menopausal women who might have been candidates for estrogen plus progestin should now focus on well-proven treatments to reduce the risk of cardiovascular disease, including measures to prevent and control high blood pressure, high blood cholesterol, and obesity. This effort could not be more important: heart disease remains the number one killer of American women," added Lenfant.

The estrogen plus progestin trial of the WHI involved 16,608 women ages 50 to 79 years with an intact uterus. An important objective of the trial was to examine the effect of estrogen plus progestin on the prevention of heart disease and hip fractures, and any associated change in risk for breast and colon cancer. The study did not address the short-term risks and benefits of hormones for the treatment of menopausal symptoms.

About 6 million women in the U.S. are taking estrogen plus progestin for a variety of reasons, including symptom relief, because their doctors advised it, or for long-term health.

"Women with a uterus who are currently taking estrogen plus progestin should have a serious talk with their doctor to see if they should continue it. If they are taking this hormone combination for short-term relief of symptoms, it may be reasonable to continue since the benefits are likely to outweigh the risks. Longer term use or use for disease prevention must be re-evaluated given the multiple adverse effects noted in WHI," said Jacques Rossouw, M.D., acting director of the WHI.

According to Rossouw, the adverse effects of estrogen plus progestin applied to all women, irrespective of age, ethnicity, or prior disease status.

"When the estrogen-only trial is completed, a comparison of the results of these two trials may provide a better idea of the roles of estrogen, compared to estrogen plus progestin, in health and disease," said Marcia Stefanick, Ph.D., chair of the WHI Steering Committee and Associate Professor of Medicine, Stanford University, Palo Alto, California.

Women enrolled in the estrogen plus progestin study were randomly assigned to a daily dose of estrogen plus progestin (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) or to a placebo. Participants were enrolled in the study between 1993 and 1998 at over 40 clinical sites across the country.

In 2000 and again in 2001, WHI investigators complied with a recommendation from the study's Data and Safety Monitoring Board (DSMB) to inform participants of a small increase in heart attacks, strokes, and blood clots in women taking hormones. The DSMB, an independent advisory committee charged with reviewing results and ensuring participant safety, found that the actual number of women having any one of these events was small and it did not cross the statistical boundary established to ensure participant safety. Therefore, the group recommended continuing the trial due to the still uncertain balance of risks and benefits.

Then, at the DSMB's regularly scheduled meeting on May 31, 2002, the data review revealed for the first time that the number of cases of invasive breast cancer in the estrogen plus progestin group had crossed the boundary established as a signal of increased risk.

"In designing the trial and following the results, the safety of the patients was of the utmost importance," said Garnet Anderson, Ph.D., a biostatistician who led the analysis at the Fred Hutchinson Cancer Research Center, Seattle, Washington. "Because breast cancer is so serious an event, we set the bar lower to monitor for it. We pre-specified that the change in cancer rates did not have to be that large to warrant stopping the trial. And the trial was stopped at the first clear indication of increased risk," she added. She also noted that, at that point, there was no indication of increased risk for breast cancer in the estrogen-only group.

The DSMB's May 31 recommendation to stop the trial was based on the finding of increased breast cancer risk, supported by the evidence of overall health risks exceeding any benefits. Following the NHLBI's decision to stop the study, the Institute and the investigators have worked intensively to develop information materials for participants. On July 8, participants started receiving letters informing them about the results and telling them that they should stop study medications. Participants will be contacted by their clinical centers for further counseling and will continue to have clinic visits so that their health outcomes can be followed.

All WHI participants, including those in the other study components, are also receiving a newsletter with a summary of the findings and an explanation of risks and benefits.

Dr. Rossouw stressed the importance of understanding how the risk to an individual woman can be low, but the risk to the population at large can be great.

"The WHI results tell us that during 1 year, among 10,000 postmenopausal women with a uterus who are taking estrogen plus progestin, 8 more will have invasive breast cancer, 7 more will have a heart attack, 8 more will have a stroke, and 18 more will have blood clots, including 8 with blood clots in the lungs, than will a similar group of 10,000 women not taking these hormones. This is a relatively small annual increase in risk for an individual woman. Individual women who have participated in the trial and women in the population who have been on estrogen and progestin should not be unduly alarmed. However, even small individual risks over time, and on a population-wide basis, add up to tens of thousands of these serious adverse health events," explained Rossouw.

The National Cancer Institute (NCI) re-emphasized the recommendation that all women in their forties and older get screened for breast cancer with mammography every 1 to 2 years.

"Women in the WHI, women taking hormones for any reason, and any woman over 40 should remain committed to their regular program of breast cancer screening to allow the earliest possible detection of breast cancer," said Leslie Ford, M.D., associate director for clinical

research in NCI's Division of Cancer Prevention.

"The reduction in colorectal cancer risk in the WHI is intriguing, but the balance of harm versus benefit does not justify any woman beginning or continuing to take estrogen plus progestin for this purpose. NCI has a number of clinical trials under way investigating new methods to detect and prevent both colorectal cancer and breast cancer that will provide critical information to help women make important health decisions," added Ford.

Specific study findings for the estrogen plus progestin group compared to placebo include:

- A 41 percent increase in strokes
- A 29 percent increase in heart attacks
- A doubling of rates of venous thromboembolism (blood clots)
- A 22 percent increase in total cardiovascular disease
- A 26 percent increase in breast cancer
- A 37 percent reduction in cases of colorectal cancer
- A one-third reduction in hip fracture rates
- A 24 percent reduction in total fractures
- No difference in total mortality (of all causes)

The WHI involves over 161,000 women who are participating in a set of clinical trials or an observational study. The clinical trials are designed to test promising but unproven preventive measures for heart disease, breast and colorectal cancer, and osteoporosis. In addition to the trials of estrogen alone and estrogen plus progestin, other trials are studying a low-fat eating pattern and calcium/Vitamin D supplementation. WHI is sponsored by NHLBI in collaboration with four other components of the NIH-- the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, and the Office of Research on Women's Health. Note: Wyeth-Ayerst Research provided the medication (active hormones and placebo) for the estrogen plus progestin study.

The complete media kit from the July 9, 2002, news conference is available at <http://www.nhlbi.nih.gov/health/women/kit.htm>. General information about the WHI -- including additional research results -- is available on the NHLBI Web site at <http://www.nhlbi.nih.gov/whi> and at [www.whi.org](http://www.whi.org) (for study participants). More information on breast cancer, including prevention and early detection, is available from the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) and at [www.cancer.gov](http://www.cancer.gov).

---

*Please send us your feedback, comments, and questions*

by using the appropriate link on the page, [Contact the NHLBI](#).

Note to users of screen readers and other assistive technologies:

[Please report any accessibility problems here.](#)