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WHI Updated Analysis: No Increased Risk of Breast Cancer with Estrogen-Alone

Estrogen-alone hormone therapy does not increase the risk of breast cancer in postmenopausal women, according to an updated analysis of the breast cancer findings of the Women's Health Initiative (WHI) Estrogen-Alone Trial.

The results contrast with the previously reported WHI Estrogen plus Progestin Trial, which found an increase in breast cancer over about 5 years among those taking combined hormone therapy.

The WHI is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. The new analysis is published in the April 12 issue of the *Journal of the American Medical Association.*

Over an average of about 7 years of follow-up, study participants taking estrogen had fewer breast cancer tumors than those in the placebo group. Women in the estrogen group were diagnosed with breast cancer at a rate of 28 per 10,000 participants per year versus a rate of 34 per 10,000 participants per year in the placebo group. The difference in rates of breast cancer (6 per 10,000) between the groups was not statistically significant, meaning it could have occurred by chance.

The new analysis also found that participants taking estrogen had 50 percent more abnormal mammograms that required follow-up and underwent 33 percent (747 compared to 549) more breast biopsies. An abnormal mammogram does not necessarily signal cancer – as shown in this study's results.

"Longer follow-up is needed to fully explain the reduced number of breast cancers in women taking estrogen. However, this new analysis does not alter the overall conclusion

from the WHI that hormones, including estrogen-alone and estrogen plus progestin, should not be used for the prevention of chronic disease," said NHLBI Director and WHI Director Elizabeth G. Nabel, M.D. "The findings still support current recommendations that hormone therapy should only be used to treat menopausal symptoms and should be used at the smallest effective dose for the shortest possible time."

The WHI Estrogen-Alone Trial was stopped at the end of February 2004 because of an increased risk of stroke and no significant effect on heart disease. The trial also found that estrogen increased the risk of blood clots in the legs, reduced the risk of hip fractures and had no significant effect on colorectal cancer. A separate report on the WHI memory study found estrogen increased memory problems. The WHI Estrogen Plus Progestin study was stopped in 2002 because of an increased risk of breast cancer and because, overall, risks from use of the hormones outweighed the benefits. The combination therapy increased the risk for heart attack, stroke, and blood clots but also reduced the risk for hip and other fractures, and colorectal cancer.

When the WHI Estrogen-Alone Trial findings were published in April 2004, the effect on invasive breast cancer was uncertain. At that time, 218 cases of breast cancer had been reported among all estrogen study participants and there was no in-depth analysis yet of the cancers. The new report provides a more detailed analysis of 237 invasive breast cancers and of the mammograms in the two study groups.

The Estrogen-Alone Trial involved 40 clinical centers and 10,739 generally healthy postmenopausal women ages 50-79 who did not have a uterus. Estrogen-alone (without progestin) is only recommended for women without a uterus; women with a uterus who take estrogen have an increased risk of endometrial cancer, so they are now advised to take estrogen combined with progestin. Participants were enrolled in the study between 1993 and 1998 with 5,310 women assigned to active estrogen (0.625 mg/day of conjugated equine estrogens) and 5,429 assigned to placebo. About 35 percent of the women had used hormone therapy prior to the study and about 13 percent were using hormones at the time they enrolled, but they had to be off of hormones for at least 3 months prior to starting the trial.

Subgroup analyses found that women who had a low risk of breast cancer – no family history, no benign breast disease, etc. – had fewer breast cancers on estrogen, while those with higher risk had more breast cancers on estrogen compared to placebo.

"This finding underscores the need to individualize treatment for menopause symptoms based on a woman's medical history and her risk profile," said WHI Project Officer Jacques Rossouw, M.D.

Women in the estrogen group tended to have larger tumors that were likely to have spread

to lymph nodes, a finding that suggests estrogen might reduce the risk of smaller tumors but not larger ones, or that smaller tumors are not diagnosed early due to changes in breast tissue. Another subgroup analysis suggested that for participants taking estrogen, ductal carcinomas that occur in the milk ducts of the breast were reduced to a greater extent than lobular carcinomas, which form in the glands where breast milk is made. It is unknown whether any effects on breast tumors will persist over time.

According to Stanford University's Marcia Stefanick, Ph.D., the study's lead author and chair of the WHI Steering Committee, the study improves understanding of the role of estrogen therapy in breast cancer, though more research is needed to explain the subgroup findings. "What is clear now is that, overall, postmenopausal women without a uterus who choose to take estrogen-alone do not have an increased breast cancer risk, at least over the first 7 years of treatment. This is clinically relevant, but women who are taking estrogen should also be aware that they will likely need more repeat mammograms and more breast biopsies," she said.

Rossouw said more research is needed on the role of progestin. Participants in the Estrogen-Alone and Estrogen Plus Progestin trials began at the same level of risk for breast cancer. According to Rossouw, the increased risk of breast cancer found in women taking combined hormones may be due to the effects of progestin – when it is combined with estrogen.

To interview an NHLBI spokesperson, contact the NHLBI Communications Office at (301) 496-4236; to interview Dr. Stefanick, call Susan Ipaktchian, Office of Communications & Public Affairs at Stanford University School of Medicine at (650) 725-5375. To interview a cancer expert, call the National Cancer Institute Media Relations Branch at (301) 496-6641.

Part of the National Institutes of Health, the National Heart, Lung, and Blood Institute (NHLBI) plans, conducts, and supports research related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, and blood diseases; and sleep disorders. The Institute also administers national health education campaigns on women and heart disease, healthy weight for children, and other topics. NHLBI press releases and other materials are available online at: www.nhlbi.nih.gov.

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