

Estrogen Alone Does Not Increase Risk of Breast Cancer

STANFORD, Calif., April 11 - Post menopausal women who took estrogen alone for more than seven years did not have an increased risk of breast cancer, according to a study of more than 10,000 women ages 50 to 79.

Moreover, women taking 0.625 mg/day of Premarin (conjugated equine estrogen) had fewer breast cancers than women randomized to placebo, Marcia L. Stefanick, Ph.D., a professor of medicine and obstetrics and gynecology at Stanford, wrote in the April 12 issue of the *Journal of the American Medical Association*.

These Premarin data emerged from the Women's Health Initiative (WHI) estrogen-only trial, which enrolled 10,737 women who had surgical menopause due to hysterectomy.

The study of unopposed estrogen reported today was run in parallel with a WHI trial of estrogen plus progestin. That study found an increase in breast cancer over about five years among those taking combined hormone therapy.

In July 2002 the National Institutes of Health announced that it was stopping the Prempro WHI trial because that combination was associated with a significant increase in the relative risk of breast cancer as well as significant increases in the relative risk of heart attack, stroke and venous thrombosis.

"This is very different from what we observed among women randomized to estrogen plus progestin (Prempro)," Dr. Stefanick said in an interview. "And it once again illustrates the need to recognize that the Women's Health Initiative was actually two separate trials, with different findings."

The first WHI trial recruited 16,602 post menopausal women and randomized 8,506 of them to Prempro 2.5 mg daily and the rest (8,102 women) to placebo. In that study women randomized to Prempro had

an increased risk of breast cancer.

As Dr. Stefanick pointed out, the Premarin-only study had entirely different results.

But while there was no increase in breast cancer among women taking Premarin, "the proportions of mammograms with abnormalities requiring follow-up was significantly increased in the [Premarin] group in the first year and in each year thereafter."

After one year of treatment 9.2% of the women in Premarin arm had abnormal findings on mammograms versus 5.5% of women in the placebo group ($P < 0.001$). After seven years, the cumulative percentage of abnormal mammography was 36.2% in the Premarin arm versus 28.1% in placebo ($P < 0.001$). However, this increase was seen only for recommended short-interval follow-up mammograms in the estrogen-alone trial, whereas it applied also to those with suspicious abnormality or highly suggestive of malignancy in the estrogen-progesterone trial.

Dr. Stefanick said most of these represented women who had calcifications on mammography. Although "we don't know exactly what the means," it did not increase the risk of malignancy.

Dr. Stefanick acknowledged that the conflicting results from the parallel WHI studies can be confusing to both patients and physicians. "But we are not flip-flopping," she said. "These are two distinct different trials."

Among the findings:

After a mean follow-up of 7.1 years, the hazard ratio for invasive breast cancer was 0.80 (95% CI, 0.62-1.04; $P=0.09$) among women taking Premarin versus placebo.

The annualized rate of breast cancer was 0.28% in the Premarin arm versus 0.34% in the placebo arm.

There were 104 cases of breast cancer in the Premarin arm versus 133 in the placebo arm.

Additional analysis found "fewer breast cancers with localized disease were diagnosed in the [Pramarin] group than in the placebo group (HR, 0.69; 95% CI, 0.51-0.95), while the incidence of cancers of more advanced stage was comparable in the groups. A similar reduction was found for ductal carcinoma (HR, 0.71%; 95 CI, 0.52-0.99) but not for lobular disease."

There were significant interactions between treatment assignment and five-year risk of breast cancer ($P=0.01$), history of benign breast disease ($P=0.005$) and number of first degree relatives with breast cancer ($P=0.01$). In all three circumstances, there was "an apparent protective effect of [Pramarin]", the authors wrote.

The WHI was funded by the National Heart, Lung and Blood Institute (NHLBI), which issued a statement in response to these latest findings.

Elizabeth G. Nabel, M.D., who is director of the NHLBI and director of WHI, said, "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.

"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 American College of Obstetricians and Gynecologists also commented on the new WHI data.

"This should be reassuring to women who have had hysterectomies and want to use hormone therapy for menopausal symptoms but have been wary because they are afraid estrogen will increase their risk of breast cancer," said Isaac Schiff, M.D., who chairs ACOG's Task Force on Hormone Therapy.

"Some previous studies have associated estrogen with increased breast cancer incidence, and when the estrogen-plus-progestin arm of the WHI was halted, many suspected that it was the estrogen that led to the increased breast cancer risk. These new findings appear to show otherwise."

Dr. Stefanick and colleagues concluded that initiation of estrogen therapy in women after hysterectomy "should continue to be based on careful consideration of potential risks and benefits for a given individual."

Action Points

Explain to patients who ask that estrogen therapy has been linked to increased risk of stroke, DVT, and cardiovascular disease.

Explain to patients who ask that current recommendations suggest that hormone therapy should be initiated at low doses for a limited period (two to three years).