

# Hormone Replacement Therapy Increases Breast Density on Mammography

McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst* 2005;97:1366–76.

## Study Overview

**Objective.** To assess the effect of estrogen/progestin on mammographic density.

**Design.** Observational cohort study.

**Setting and participants.** The Women's Health Initiative (WHI) was a prospective, randomized trial comparing conjugated estrogen plus medroxyprogesterone acetate with placebo in 16,608 postmenopausal women to assess whether hormones would reduce cardiovascular events. The trial was stopped early because of increased risks for breast cancer and chronic disease. As part of an ancillary analysis on mammographic breast density, a stratified random sample of patients enrolled in the WHI were selected. Participants had a baseline mammogram and breast examination within 6 months prior to randomization and received annual breast examinations and screening mammograms. Mammograms were digitized and breast density was calculated using a validated computer-assisted technique. Two trained observers performed density measurements.

**Main outcome measures.** The effect of estrogen/progestin on mammographic density and abnormal findings at 1 and 2 years as compared with baseline density.

**Main results.** 413 women were included, and baseline characteristics, including mammographic percent densities, were well balanced between cohorts. Compared with baseline, mean mammographic percent density increased by 6.0% at year 1 in the estrogen/progestin group but decreased by 0.9% in the placebo group (difference, 6.9% [95% confidence interval (CI), 5.3%–8.5%];  $P < 0.001$ ). At 2-year follow-up, the mean changes in mammographic density persisted but were attenuated slightly, with an absolute increase of 4.9% in the estrogen/progestin group and a decrease of 0.8% in the placebo group (difference, 5.7% [95% CI, 4.3%–7.3%];  $P < 0.001$ ). These effects were consistent across racial/ethnic groups but were higher among women aged 70 to 79 years in the estrogen/progestin group (mean increase at year 1, 11.6%) than in the placebo group (mean decrease at year 1, 0.1%) (difference,

11.7% [95% CI, 8.2%–15.4%];  $P < 0.001$  across age-groups). Compared with placebo, use of estrogen/progestin was associated with an increased risk of having an abnormal mammogram at year 1 (relative risk, 3.9 [95% CI, 1.5–10.2];  $P = 0.003$ ) that was not explained by an increase in density.

**Conclusion.** Use of estrogen/progestin for up to 2 years was associated with increases in mammographic density.

## Commentary

Screening mammography reduces breast cancer-related mortality [1]; however, factors such as breast density influence the sensitivity of mammography. Density is based on relative amounts of glandular and fatty tissue within the breast. As glandular tissue becomes replaced by fat with age, the sensitivity of mammography improves because the breast is less dense. In a breast cancer screening program, women with dense breasts were 6 times more likely to develop breast cancer after a "negative" screening mammogram than women with fatty breasts [2]. The fact that breast density is affected after menopause suggests that declining hormonal levels may be responsible.

In the current analysis, McTiernan et al assessed whether hormone replacement therapy (HRT) in postmenopausal women reduced breast density on mammography. Although this was a substudy of a trial designed with a different primary objective (ie, whether HRT reduces cardiovascular outcomes), this analysis appears to have been designed a priori and included a population of women selected from a large randomized sample. Additional strengths of this analysis include the fact that radiologists were blinded to treatment cohorts and that this was a placebo-controlled comparison. The authors concluded that HRT significantly increased breast density for at least as long as women were taking supplements. However, the authors could not address whether increased density contributed to false-negative mammography readings or ultimately increased breast cancer-related mortality. It is important to consider that only 2 radiologists reviewed the images using a schema that may not be widely used. Therefore, it is difficult to know how generalizable these findings are to the community at large. As well, there were slight

imbalances between the women selected for this substudy and the overall WHI population (they were older, of a higher socioeconomic status, and more likely to be non-Hispanic white), which could potentially account for density disparities that may not apply to all women included in the WHI. Nonetheless, these findings are provocative and concur with what is known about HRT and breast density. The real question is whether density changes related to HRT directly result in negative outcomes for women.

### **Applications for Clinical Practice**

Breast density can affect the sensitivity of mammography.

HRT increases breast density.

*—Review by David R. Spiegel, MD*

### **References**

1. Fletcher SW, Black W, Harris R, et al. Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst* 1993;85:1644–56.
2. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000; 92:1081–7.

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