Estrogen-Plus-Progestin Use and Mammographic Density in Postmenopausal Women: Women's Health Initiative Randomized Trial

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Background: **Increased mammographic density reduces the sensitivity of screening mammography, is associated with increased breast cancer risk, and may be hormone related. We assessed the effect of estrogen-plus-progestin therapy on mammographic density.** ***Methods:*** **In a racially and ethnically diverse ancillary study of the Women's Health Initiative, we examined data from 413 postmenopausal women who had been randomly assigned to receive daily combined conjugated equine estrogens (0.625 mg) plus medroxyprogesterone acetate (i.e., progestin; 2.5 mg) (n = 202) or daily placebo (n = 211). We assessed the effect of estrogen plus progestin on measured mammographic percent density and abnormal findings over a 1-year and 2-year period. All tests of statistical significance were two-sided and were based on *F* tests or *t* tests from mixed-effects models.** ***Results:*** **Mean mammographic percent density increased by 6.0% at year 1, compared with baseline, in the estrogen-plus-progestin group but decreased by 0.9% in the placebo group (difference = 6.9%, 95% confidence interval [CI] = 5.3% to 8.5%; *P*<.001). The mean changes in mammographic density persisted but were attenuated slightly after 2 years, with an absolute increase of 4.9% in the estrogen-plus-progestin group and a decrease of 0.8% in the placebo group (difference = 5.7%, 95% CI = 4.3% to 7.3%; *P*<.001). These effects were consistent across racial/ethnic groups but were higher among women aged 70–79 years in the estrogen-plus-progestin group (mean increase at year 1 = 11.6%) than in the placebo group (mean decrease at year 1 = 0.1%) (difference of the means = 11.7%, 95% CI = 8.2% to 15.4%; *P*<.001, comparing across age groups). At year 1, women who were adherent to treatment in the estrogen-plus-progestin group had a mean increase in density of 7.7% (95% CI = 5.9% to 9.5%), and women in the placebo group had a mean decrease in density of 1.1% (95% CI = 0.3% to 1.9%). Use of estrogen plus progestin was associated with an increased risk of having an abnormal mammogram at year 1 (relative risk = 3.9, 95% CI = 1.5 to 10.2; *P* = .003), compared with placebo, that was not explained by an increase in density.** ***Conclusions:*** **Use of up to 2 years of estrogen plus progestin was associated with increases in mammographic density. [J Natl Cancer Inst 2005;97:1366–76]**

Mammographic density refers to the relative proportion of white-appearing areas (presumptive connective and epithelial tissues) to dark-appearing areas (presumptive fatty tissue) in a mammogram. Increased density reduces the sensitivity of screening mammography *(1–3)*. Women with the highest level of mammographic density have a four to six times higher risk of developing breast cancer than women with the lowest levels *(4–7)*. Recent data indicate that risks of both estrogen receptor–positive and –negative breast cancer are higher in women with moderate or high mammographic density than in women with low mammographic density *(8)*.

Mammographic density declines after menopause *(9)*, suggesting a hormonal etiology to breast density. Observational studies have reported higher mean density levels among current users of menopausal hormone therapy than among nonusers *(10,11)*. A small number of clinical trials conducted primarily in non-Hispanic white women have reported a change toward increased density after initiation of various menopausal hormone regimens *(12,13)*.

Between 1993 and 1998, the Women's Health Initiative (WHI) randomly assigned 16 608 postmenopausal women to receive combined estrogen plus progestin (the estrogen-plus-progestin group) or to receive placebo (the placebo group). More women in the estrogen-plus-progestin group than in the placebo group were diagnosed with breast cancer, and the cancers were at more advanced stages at diagnosis *(14)*. In addition, the frequency of abnormal mammograms in the estrogen-plus-progestin group was higher than that in the placebo group, indicating that increased breast density may be associated with abnormal mammograms and with delaying the diagnosis of breast cancer. The association between estrogen-plus-progestin use and mammographic density and associations among estrogen-and-progestin use, mammographic density, and abnormal mammogram

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See "Notes" following "References."

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frequency have not been previously investigated in the WHI trial. In addition, the association between estrogen-plus-progestin use and mammographic density in minority racial/ethnic groups has not been previously described in a randomized clinical trial setting.

In the Mammogram Density Ancillary Study, we evaluated the association between estrogen-plus-progestin use and mammographic density over 2 years in a randomly identified subsample of WHI estrogen-plus-progestin clinical trial participants, and we oversampled for minority race/ethnicity inclusion. The cohort for our study was a stratified random sample of participants in the WHI estrogen-plus-progestin trial that was selected to include equal numbers of women from four racial/ethnic groups: non-Hispanic white, African American, Hispanic, and Asian American. We tested the hypotheses that estrogen-plus-progestin use increases mammographic density and that this effect is similar across racial/ethnic groups. In an exploratory analysis, we also assessed whether the association between estrogen-plus-progestin use and mammographic density could explain the observed increase in frequency of abnormal mammograms among women using estrogen plus progestin in the full WHI clinical trial *(14)*.

Patients and Methods

WHI Study Design

The WHI estrogen-plus-progestin randomized clinical trial enrolled 16 608 postmenopausal women with no prior hysterectomy from 1993 through 1998 at 40 clinical centers by following a previously described design *(15,16)*. The study was approved by the human subjects committees at each participating institution. In brief, women recruited by mass mailings and media were eligible if they were between 50 years and 79 years at entry, were postmenopausal, and provided written informed consent. Women with prior hysterectomy or breast cancer or those with medical conditions likely to result in death within 3 years were excluded. Prior menopausal hormone use required a 3-month washout period before baseline testing; mammogram density has been shown to decrease within a few weeks after menopausal hormone use is stopped *(17)*. All women had a baseline mammogram and clinical breast examination within 6 months before randomization. Women with abnormal findings on baseline mammograms were required to have a workup showing absence of breast cancer before being randomly assigned to a group. Women were randomly assigned to combined hormones (i.e., daily conjugated equine estrogens at 0.625 mg and medroxyprogesterone acetate at 2.5 mg in a single tablet [Prempro, Wyeth Ayerst, Philadelphia, PA]) or to an identical-appearing placebo. Participants had follow-up clinic visits every 6 months, at which time their pill adherence was assessed on the basis of pill counts, potential adverse effects were determined, and exposure covariates were updated *(14)*. During follow-up, women received annual clinical breast examinations and screening mammograms. Only a qualitative classification of mammographic density was provided on the reports on these screening mammograms [e.g., Breast Imaging Reporting and Data System (BI-RADS) *(18)*]. Hence, for women who consented to participate in this ancillary study, we requested the women's mammograms from their mammographers, digitized them, and calculated mammographic percent density.

Estrogen-Plus-Progestin Trial Result

The WHI estrogen-plus-progestin trial was designed to assess whether use of these hormones would reduce cardiovascular events in postmenopausal women *(16)*. For monitoring purposes, a global index of benefit and risk was developed that included first occurrence of coronary heart disease, stroke, colorectal cancer, endometrial cancer, pulmonary embolus, hip fracture, and death due to other causes, as well as to invasive breast cancer. After 5.6 ± 1.3 years (mean ± standard deviation [SD]) of follow-up, the trial was stopped early on the basis of an increased breast cancer risk and overall risks of chronic disease that exceeded benefits as measured by the global index *(15)*.

Mammogram Density Ancillary Study

Seventeen of 40 WHI clinical centers initially agreed to participate in the Mammogram Density Ancillary Study, which was a separately funded study with a different administration from that of WHI. The clinical coordinating center identified a stratified random sample of women in the estrogen-plus-progestin trial to be approached for ancillary study participation, with the goal of sampling 150 women within each of four racial/ethnic groups (African American, Asian/Pacific Islander, Hispanic, and non-Hispanic white). A 10% oversample was selected to allow for women who elect not to participate in the ancillary sample (i.e., nonrespondents). The a priori decision was to oversample other racial/ethnic groups if one or more groups were underrecruited. Inclusion criteria included availability of a prerandomization (baseline) mammogram and at least one follow-up mammogram after 1 or 2 years. The sample size was determined on the basis of an estimated percent density difference of 8% ± 10% (mean ± SD) between the hormone therapy and placebo groups after 1 year of treatment, with the assumption of 33% losses due to loss to follow-up and nonadherence. One a priori aim of the study was to determine whether a treatment effect (estrogen-plus-progestin versus placebo) exists within different racial/ethnic groups. Two years of follow-up was chosen to determine the longer-term effects of hormone therapy on mammographic density.

The WHI clinics referred women to one or more mammographers or to the women's own health care providers for mammographic screening. Mammograms, therefore, were not the property of the WHI clinic and had to be requested after a woman gave consent to participate in this ancillary study. After the participants provided written informed consent, mammograms were requested from the mammogram facility, retrieved, and forwarded to the ancillary study office at the University of North Carolina for digitizing and mammographic density measurement.

Films were digitized on a Lumisys 85 laser digitizer with a maximum resolution of approximately 50 μm and 12-bit depth. The digitizer was recalibrated before each digitizing session. The resulting raw image files were converted to bitmap format suitable for display and density measurement on a personal computer monitor by standard data-averaging methods. Recorded on each film were a unique serial number, date, laterality, and view.

Mammographic Density Measurement

Mammographic density was assessed by use of a previously validated *(19)* computer-assisted interactive thresholding

technique that used software from the Imaging Research Program (Sunnybrook Health Science Centre, Toronto, Ontario, Canada). Digitized mammograms were displayed on a computer monitor to allow the observer to select appropriate threshold values of pixel brightness to identify the breast edge and all noncontiguous areas of mammographic density. Thresholding was interactive, so that, as the observer moved a sliding control on-screen with a pointing device (mouse), the threshold pixel value changed and overlaid a colored line on the image corresponding to the selected pixel value. This operation dynamically measured the areas of interest that resulted from the selected pixel value. The breast edge was defined first and then the areas of mammographic density, which need not be contiguous, were defined. Extraneous features such as pectoralis muscles and film anomalies were first excluded from the calculations by an on-screen outlining process that restricted calculations to the regions of interest.

After identifying the thresholds, the software first calculated the total area of the breast and the total combined area of mammographic density in pixels and then, from these data, calculated the percent mammographic density. The latter was the ratio of measured dense area to the total breast area, with a potential range of 0%–100%. Ideally, only the craniocaudal view of the right breast was measured. If this view was unavailable, the left craniocaudal view was used.

Measurements were done in batches of 30–40 films selected without respect to sequence (e.g., whether they were prerandomization or follow-up films) and sorted in random order. Baseline and follow-up films from the same participant were not necessarily included in the same batch, and batches for each observer were generated independently.

Two trained observers (CM and JP) performed density measurements on all films. Before beginning the measurements for this study, these observers demonstrated high reliability for measuring percent density with this technique (i.e., intraclass correlation coefficients of >.92). Repeat measures were included in each batch at random to allow assessment of change in intraobserver reliability over the course of the study. The observers were blinded to time sequence (baseline versus follow-up), to the other observer's results, to measurements already completed on other films from that same participant, and to treatment status. Five percent of films were randomly selected for assessment of American College of Radiology mammographic quality scores by a radiologist (EP) to determine whether observer reliability was affected by film quality. We calculated percent density for each film as the mean measurement from both observers for that film.

Classification of Mammogram Clinical Recommendations

Mammogram reports were obtained from the performance sites and were coded for recommendation (negative; benign findings—negative; short-interval follow-up suggested; suspicious abnormality; and highly suggestive of malignancy) *(20)*. Abnormal mammograms were defined as those with recommendations for short-interval follow-up and those suspicious or highly suggestive of malignancy.

Statistical Methods

All primary analyses focused on changes in the mean percent density measured at year 1 and year 2, compared with baseline, in relation to estrogen-plus-progestin randomization assignment. Mixed-effects (i.e., repeated measures) models with log-transformed percent density values were used to test whether treatment affected longitudinal density change, whether this relationship depended on ethnicity, mammographic sequence (baseline or follow-up), or baseline characteristics. Baseline characteristics included age (50–59, 60–69, or 70–79 years), race/ethnicity (African American, Asian/Pacific Islander, Hispanic, or non-Hispanic white), education (high school diploma or less, education after high school, or college degree or higher), annual household income (<$35 000 or ≥$35 000), years since menopause (<5, 5–9.9, 10–14.9, or ≥15 years), age at menarche (≤12 or >12 years), number of term pregnancies (none, 1–2, 3–4, or ≥5), prior exogenous hormone use, family history of breast cancer (any first- or second-degree relatives), body mass index (weight in kilograms/[height in meters]^2), ovarian status (history of bilateral oophorectomy), smoking (never, past, or current), alcohol use (grams/day), physical activity [metabolic equivalent tasks (MET)-hours/week *(21)*], and baseline percent mammographic density (<10%, 10–<25%, or ≥25%). For consistency across literature, the cutpoints that we chose were similar to those used by Cuzick et al. *(22)*, based on the Boyd breast cancer risk classification scale *(19)*. Because of sparse data, we collapsed the categories 0% and 1%–10% into the category <10%, and we collapsed the categories 26%–50%, 51%–75%, and 76%–100% into the category ≥25%. We also examined weight change and change in physical activity at each annual follow-up interval. These covariates were chosen because of their possible associations with mammographic density. An F test or t test that was based on the type III sums of squares or estimated parameters from the mixed-effects model was used to determine whether there was a statistically significant treatment effect during follow-up or there was a statistically significant treatment effect at any particular year, respectively. Statistical significance of interactions between treatment assignment and ethnicity/baseline characteristics during follow-up was based on an F test from mixed-effects models and judged by a Bonferroni-corrected α value of .003 to account for 17 tests (.05/17 = .003). Confidence intervals (CIs), which were based on the t distribution, were presented for changes in percent density. Comparisons of baseline characteristics by randomization assignment were made by chi-squared tests of association. All primary analyses were based on the intention-to-treat principle, and all statistical tests were two-sided.

In a related analysis, we investigated whether the increased risk of abnormal mammograms with estrogen-plus-progestin use *(14)* was due to increased mammographic density. We fit longitudinal models with abnormal mammogram at baseline and follow-up as the binary response variable (negative and benign findings—negative were coded as a 0, and short interval follow-up suggested, suspicious abnormality, and highly suggestive of malignancy were coded as a 1), and adjusted for treatment assignment, mammographic density at baseline and change in density at follow-up, and baseline characteristics (age, body mass index, and race/ethnicity).

Results

Demographics

After the Mammogram Density Ancillary Study began, two clinical centers declined to participate; these centers had very

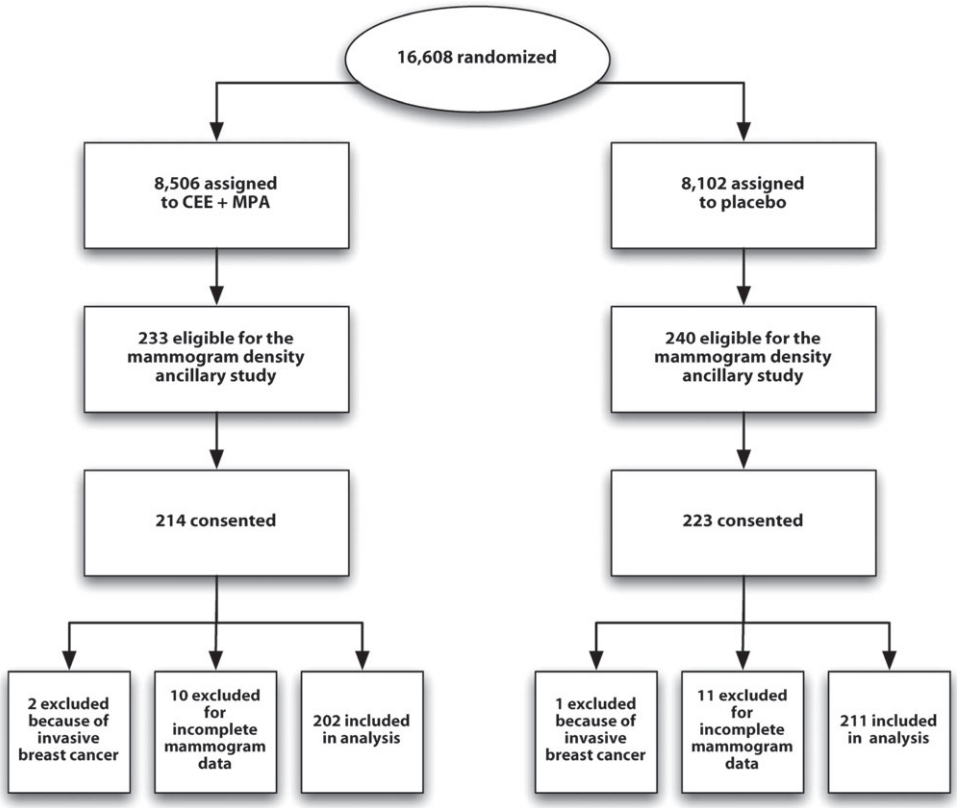

Fig. 1. Mammogram Density Ancillary Study of the estrogen-plus-progestin clinical trial of the Women's Health Initiative Study. CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate.

high proportions of minority participants. We approached 233 women assigned to estrogen-plus-progestin use and 240 women assigned to placebo and asked them to join the mammogram density ancillary study (Fig. 1). Of these women, 214 in the estrogen-plus-progestin group and 223 in the placebo group consented to participate. Ten participants in the estrogen-plus-progestin group and 11 in the placebo group did not have a baseline plus at least one follow-up film that could be retrieved, digitized, and compared, and we excluded three women who had invasive breast cancer, leaving a final total number of 413 women: 202 in the estrogen-plus-progestin group and 211 in the placebo group.

Women in this ancillary study were older ($P = .002$), more likely to be non-Hispanic white ($P<.001$) and better educated ($P<.001$), and to have a higher income ($P = .004$) than women who were eligible but not enrolled; they were also less likely to have used menopausal hormone therapy in the year before enrollment ($P<.001$) (data not shown). They were equally likely to be in the estrogen-plus-progestin group or the placebo group of the trial, however. Baseline mammograms were taken within 6 months before randomization, except for four women, for whom the most recent prior screening mammograms were used (with a mean of 9 months before randomization and no prior menopausal hormone use). There were no substantive differences in baseline characteristics between participants by treatment group (Table 1). The age of participants was 62.2 ± 7.9 years (mean ± SD). The participants had been postmenopausal for 12.5 ± 9.0 years at baseline, and more than one-third had been postmenopausal for more than 15 years. Women were distributed among ethnic/racial groups as follows: 43% were non-Hispanic white, 35% were African American, approximately 16% were Hispanic, and 6% were Asian/Pacific Islander.

Twenty percent of the participants had used menopausal hormone therapy at any time before randomization, and among these women, most had used hormones in excess of 1 year, with only 4% of the whole sample being current users at the time of mammographic screening (a 3-month "washout" period was required before randomization). Fewer than one-third were normal weight or less (body mass index < 25.0), approximately one-third were overweight (body mass index = 25.0–29.9 kg/m^2), and almost 40% were obese (body mass index ≥ 30 kg/m^2). Approximately 12% had at least one first- or second-degree relative with breast cancer. More than half had never smoked, and 14% were current smokers.

Compared with the rest of the WHI estrogen-plus-progestin trial participants, participants in the Mammogram Density Ancillary Study were slightly younger, were more likely to be of a minority racial/ethnic group (by design), were less likely to be current or past menopausal hormone therapy users, were more likely to be obese, were less likely to have a family history of breast cancer, and were of similar parity *(15)*. All participants had at least one follow-up mammogram, and 93% had two follow-up mammograms. The mean time between the baseline and the first follow-up mammogram was 1.2 ± 0.3 years and between the first and second follow-up mammograms was 1.1 ± 0.2 years.

Baseline Percent Density

Baseline mammographic percent density ranged from 0% to 54.8% (Fig. 2), with a mean of 8.0% ± 10.2% and similar distributions within each treatment group (mean = 7.7% among women randomly assigned to the estrogen-plus-progestin group, and mean = 8.2% among women randomly assigned to the

Table 1. Baseline characteristics of the 413 women in the Women's Health Initiative (WHI) Mammogram Density Ancillary Study, Estrogen-Plus-Progestin Trial Subsample, by randomization assignment*

Characteristic	Estrogen plus progestin, No. (%)	Placebo, No. (%)
Age group at screening		
50–59 y	92 (45.5)	85 (40.3)
60–69 y	66 (32.7)	81 (38.4)
70–79 y	44 (21.8)	45 (21.3)
Race/Ethnicity		
Non-Hispanic white	84 (41.6)	92 (43.6)
African American	67 (33.2)	80 (37.9)
Hispanic	36 (17.8)	30 (14.2)
Asian/Pacific Islander	15 (7.4)	9 (4.3)
Education		
High school diploma/GED or less	59 (29.4)	62 (29.8)
School after high school	90 (44.8)	80 (38.5)
College or higher	52 (25.9)	66 (31.7)
Income		
<$35 000	102 (54.0)	114 (58.2)
≥$35 000	87 (46.0)	82 (41.8)
Time since menopause		
<5 y	51 (27.9)	37 (19.6)
5–<10 y	30 (16.4)	40 (21.2)
10–<15 y	30 (16.4)	40 (21.2)
≥15 y	72 (39.3)	72 (38.1)
Age at menarche		
≤12 y	87 (43.1)	91 (43.5)
>12 y	115 (56.9)	118 (56.5)
No. of term (>6 mo) pregnancies		
Never pregnant	17 (8.5)	28 (13.4)
1–2	64 (32.0)	52 (24.9)
3–4	79 (39.5)	80 (38.3)
≥5	40 (20.0)	49 (23.4)
Oral contraceptive use duration		
Never used	112 (55.4)	105 (49.8)
<5 y	56 (27.7)	59 (28.0)
5–<10 y	17 (8.4)	22 (10.4)
≥10 y	17 (8.4)	25 (11.8)
Lifetime menopausal hormone therapy duration		
Never used	162 (80.6)	170 (80.6)
<5 y	31 (15.4)	28 (13.3)
≥5 y	8 (4.0)	13 (6.2)
Years since last used menopausal hormones		
Never used menopausal hormones	162 (80.6)	170 (80.6)
≤1 y	15 (7.5)	14 (6.6)
>1 y	24 (11.9)	27 (12.8)
Female 1st or 2nd degree relative had breast cancer	24 (12.3)	27 (13.4)
Bilateral oophorectomy	1 (0.5)	1 (0.5)
BMI		
Normal (<25.0 kg/m^2)	58 (28.9)	45 (21.3)
Overweight (25.0–29.9 kg/m^2)	66 (32.8)	79 (37.4)
Obese (≥30.0 kg/m^2)	77 (38.3)	87 (41.2)
Physical activity†		
0–≤3.75 MET-hours/week	83 (44.4)	78 (39.6)
3.75–≤14 MET-hours/week	51 (27.3)	61 (31.0)
>14 MET-hours/week	53 (28.3)	58 (29.4)
Alcohol†		
Nondrinkers	107 (55.4)	108 (53.7)
≤2.7 g/day	38 (19.7)	43 (21.4)
>2.7 g/day	48 (24.9)	50 (24.9)
Smoking		
Never smoked	102 (50.7)	112 (53.3)
Past smoker	71 (35.3)	66 (31.4)
Current smoker	28 (13.9)	32 (15.2)

*There were no statistically significant differences between treatment arms. GED = General Equivalency Diploma; BMI = body mass index; MET = Metabolic Equivalent Tasks.

†Categories chosen based on distribution of the variable in the entire WHI dataset.

placebo group; $P = .46$) (Table 2). Body mass index was inversely related to baseline percent mammographic density, with overweight women having lower baseline percent density ($P<.001$, data not shown). Age and years since menopause had modest inverse relationships with percent density ($P = .01$, data not shown). Baseline percent density also differed among the four ethnic groups ($P = .001$). Mean percent density was highest for the 24 Asian American women (18.6%), whereas the mean percent density values for the 66 Hispanics (8.1%), 176 non-Hispanic whites (6.9%), and 147 African Americans (7.4%) were lower and were

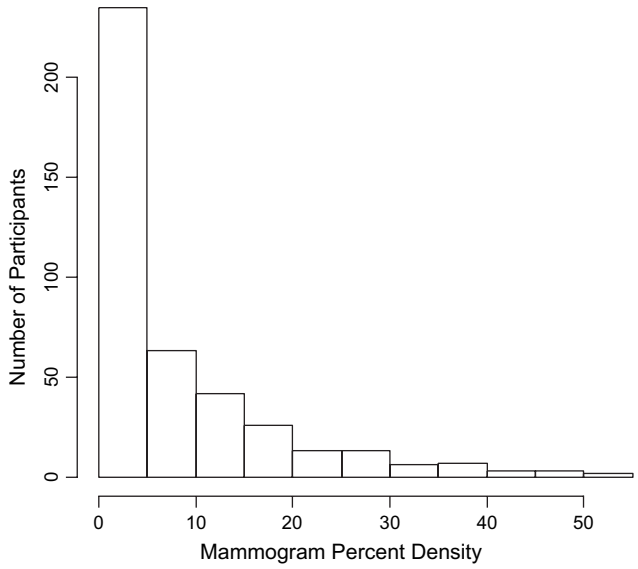

Fig. 2. Distribution of mammographic percent density at baseline.

comparable to each other. After adjusting for age and body mass index, the difference in the mean percent density between Asian Americans and non-Hispanic whites was statistically significant ($P = .002$), whereas that among African American, Hispanic, and non-Hispanic white women was not statistically significantly different.

Estrogen-Plus-Progestin Use and Mammographic Percent Density

Mean mammographic percent density was increased by 6.0% at year 1 in the estrogen-plus-progestin group but was decreased by 0.9% in the placebo group (difference = 6.9%, 95% CI = 5.3% to 8.5%; $P<.001$), both compared with baseline values (Table 2). After 2 years, the mean changes in mammographic density persisted but were attenuated slightly, with an absolute increase of 4.9% in the estrogen-plus-progestin group and a decrease of 0.8% in placebo group (difference between groups = 5.7%, 95% CI = 4.3% to 7.3%, $P<.001$, from a repeated-measures model), both compared with baseline. The slight decrease in percent density from year 1 to year 2 among women in the estrogen-plus-progestin group was not statistically significant ($P = .53$). However, we found a change in the percent density by treatment assignment for year 1 minus baseline and for year 2 minus baseline (Fig. 3). We also observed that 75% of the participants in the estrogen-plus-progestin group experienced an increase in percent density (Fig. 3). Conditions that may affect endogenous hormone levels, such as ovarian status or change in weight or physical activity, could affect mammographic density. Two participants reported bilateral oophorectomies at baseline. Excluding these participants did not change results of these analyses. Change from baseline in either weight or physical activity was not associated with change in percent density (data not shown).

These effects of combined hormone use on breast density were consistent across racial/ethnic groups, with women of any racial/ethnic group who were randomly assigned to the estrogen-plus-progestin group having an increase in breast density compared with those assigned to the placebo group ($P = .46$ for test of heterogeneity) (Table 3). In a comparison stratified by age, the greatest increase in percent density with estrogen-plus-progestin use was observed in 70- to 79-year-olds (with a mean increase in the estrogen-plus-progestin group of 11.6% and a mean decrease in the placebo group of 0.1%; difference = 11.7%, 95% CI = 8.2% to 15.4%; $P<.001$) (Table 4), and the test for interaction between estrogen-plus-progestin use and age was statistically significant ($P<.001$). The greatest increase in percent density with estrogen-plus-progestin use was observed in the group with lowest baseline breast density (Table 5), and the test for interaction of estrogen-plus-progestin use with baseline percent density was of borderline statistical significance at the Bonferroni-corrected level ($P = .004$). None of the other baseline characteristics were statistically significant modifiers of the estrogen-plus-progestin effect (at the Bonferroni-adjusted .003 level or the unadjusted .05 level). The interaction of treatment with baseline smoking status was of borderline statistical significance (unadjusted $P = .052$), and the greatest effect of estrogen plus progestin use on increased mammographic density was observed in nonsmokers (data not shown).

Adherence

To adjust outcomes for study medication adherence, participants' percent density measurements at follow-up were censored when a participant became nonadherent (e.g., stopped taking study drugs, used <80% of study drugs, or, if in the placebo group, started menopausal hormone therapy). The compliance effect of estrogen-plus-progestin use was stronger than that observed in the intention-to-treat analyses. At year 1, women who were adherent to treatment had a mean 7.7% (95% CI = 5.9% to 9.5%) increase in mammographic density in the

Table 2. Mammographic percent density (MPD) at baseline, year 1, and year 2 by treatment assignment

	Estrogen plus progestin			Placebo				
Measurement	No.	Median	Mean (95% CI)	No.	Median	Mean (95% CI)	P*	P†
Baseline	202	3.9	7.7 (6.4 to 9.1)	211	3.6	8.2 (6.7 to 9.6)	.46	
Year 1	202	9.6	13.8 (12.0 to 15.5)	211	3.0	7.3 (5.9 to 8.6)		
Year 2	188	10.1	12.8 (11.1 to 14.4)	198	3.1	7.3 (5.8 to 8.8)		
Year 1–baseline	202	2.2	6.0 (4.6 to 7.5)	211	−0.2	−0.9 (−1.5 to −0.2)	<.001	<.001
Year 2–baseline	188	2.1	4.9 (3.6 to 6.3)	198	−0.2	−0.8 (−1.6 to −0.1)	<.001	

*P value of main effect of estrogen plus progestin, by visit, is based on a two-sided t test from a repeated-measures model with log(percent density + 0.001) as the response. All statistical tests were two-sided. CI = confidence interval.

†P value of overall main effect of estrogen plus progestin at follow-up is based on a two-sided F test from a repeated-measures model with log(percent density + 0.001) as the response.

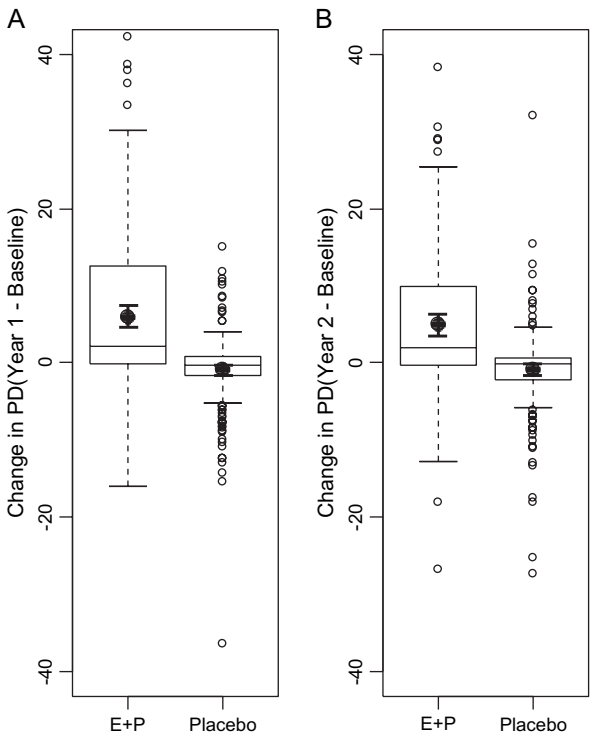

Fig. 3. Estrogen plus progestin and mammographic percent density after 1 and 2 years of therapy. Box plots of change in percent density by treatment assignment for year 1 minus baseline (**A**) and year 2 minus baseline (**B**) are presented. Lower and upper bounds of the box represent the interquartile range of the data. The **horizontal line** within each box represents the median. **Whiskers** extend to the most extreme value, which is no further than 1.5 times the interquartile range away from the box. The **solid dot and dash** within each box plot represent the mean change and 95% confidence interval, respectively. PD = percent density; E+P = estrogen plus progestin.

estrogen-plus-progestin group compared with baseline and a 1.1% (95% CI = 0.3% to 1.9%) decrease in the placebo group compared with baseline (Table 6).

Abnormal Mammograms

A total of 24 women (19 in the estrogen-plus-progestin group and five in the placebo group) had a mammogram classified as abnormal at year 1 and an additional 16 (10 in the estrogen-plus-progestin group and six in the placebo group) had a mammogram classified as abnormal at year 2 of follow-up. Use of estrogen plus progestin nearly quadrupled the risk of having an abnormal mammogram after 1 year of follow-up (RR = 3.9, 95% CI = 1.5 to 10.2; P = .003). Even after excluding participants with an abnormal mammogram at year 1, use of estrogen plus progestin nearly doubled the risk of an abnormal mammogram after 2 years of follow-up, but the increase was not statistically significant (RR = 1.8, 95% CI = 0.68 to 4.9; P = .31).

The increased risk of having an abnormal mammogram among participants assigned to the estrogen-plus-progestin group could not be explained by the increase in percent breast density as a mediating variable. Change in mammographic percent density at year 1 was not predictive of abnormal mammograms (P>.25), after adjusting for treatment assignment, mammographic density at baseline, and baseline characteristics (e.g., age, body mass index, and ethnicity). In a posthoc analysis, we limited the model to only those participants using estrogen plus progestin and found a weak relationship (P = .11) between change in mammographic density and abnormal mammograms. For example, for every 6% increase in mammographic percent density, the odds of an abnormal mammogram increased 1.26 (95% CI = 0.95 to 1.68) times.

Table 3. Mammographic percent density (MPD) at baseline, year 1, and year 2 by race/ethnicity and treatment assignment*

Group	Estrogen plus progestin			Placebo		
	No.	Median MPD	Mean MPD (95 % CI)	No.	Median MPD	Mean MPD (95 % CI)
Non-Hispanic white						
Baseline	84	3.7	6.3 (4.5 to 8.0)	92	2.8	7.5 (5.4 to 9.7)
Year 1	84	11.3	13.7 (11.1 to 16.4)	92	2.5	6.7 (4.6 to 8.7)
Year 2	79	10.3	13.0 (10.4 to 15.6)	91	1.9	7.0 (4.8 to 9.2)
Year 1–baseline	84	4.1	7.5 (5.2 to 9.7)	92	−0.3	−0.9 (−1.7 to −0.1)
Year 2–baseline	79	3.4	6.5 (4.3 to 8.8)	91	−0.1	−0.3 (−1.2 to 0.6)
African American						
Baseline	67	3.2	7.7 (5.0 to 10.4)	80	3.7	7.2 (5.4 to 9.0)
Year 1	67	7.7	12.6 (9.7 to 15.5)	80	3.3	6.8 (5.0 to 8.5)
Year 2	65	8.6	10.6 (8.2 to 13.0)	74	3.2	6.4 (4.6 to 8.3)
Year 1–baseline	67	1.3	4.9 (2.4 to 7.4)	80	0.0	−0.4 (−1.7 to 0.9)
Year 2–baseline	65	1.3	3.1 (0.9 to 5.3)	74	−0.3	−1.1 (−2.5 to 0.3)
Hispanic						
Baseline	36	5.5	6.9 (4.5 to 9.3)	30	4.7	9.4 (4.8 to 14.0)
Year 1	36	7.3	11.5 (7.8 to 15.2)	30	3.3	8.1 (3.9 to 12.3)
Year 2	30	8.9	11.2 (7.3 to 15.0)	24	4.1	7.2 (2.8 to 11.6)
Year 1–baseline	36	1.2	4.6 (1.4 to 7.8)	30	−0.4	−1.3 (−2.7 to 0.1)
Year 2–baseline	30	1.5	4.3 (1.0 to 7.7)	24	−0.4	−1.9 (−4.2 to 0.3)
Asian/Pacific Islander						
Baseline	15	13.1	18.0 (10.4 to 25.6)	9	14.4	19.6 (4.8 to 34.3)
Year 1	15	24.9	24.5 (14.5 to 34.4)	9	13.9	15.7 (3.1 to 28.2)
Year 2	14	26.6	25.2 (16.7 to 33.6)	9	12.8	18.3 (2.5 to 34.0)
Year 1–baseline	15	0.1	6.5 (−1.7 to 14.6)	9	−2.1	−3.9 (−8.6 to 0.8)
Year 2–baseline	14	2.2	5.9 (1.0 to 10.8)	9	−0.1	−1.3 (−9.6 to 6.9)

*P = .46, for interaction between estrogen plus progestin and race/ethnicity is based on a two-sided F test from a repeated-measures model with log(percent density + 0.001) as the response. CI = confidence interval.

Table 4. Mammographic percent density (MPD) at baseline, year 1, and year 2 by treatment assignment and age*

Group	Estrogen plus progestin			Placebo		
	No.	Median MPD	Mean MPD (95% CI)	No.	Median MPD	Mean MPD (95% CI)
50–59 y						
Baseline	92	4.0	9.6 (7.2 to 12.0)	85	4.5	9.0 (6.7 to 11.2)
Year 1	92	7.5	12.6 (9.9 to 15.3)	85	3.3	7.7 (5.6 to 9.8)
Year 2	85	9.3	11.0 (8.7 to 13.2)	79	3.9	7.6 (5.3 to 9.9)
Year 1–baseline	92	0.8	3.0 (1.1 to 4.8)	85	−0.2	−1.3 (−2.4 to −0.1)
Year 2–baseline	85	1.0	1.3 (−0.3 to 2.9)	79	−0.3	−1.3 (−2.8 to 0.3)
60–69 y						
Baseline	66	4.6	6.0 (4.3 to 7.7)	81	2.9	8.0 (5.5 to 10.5)
Year 1	66	9.0	12.5 (9.7 to 15.4)	81	2.6	7.1 (4.8 to 9.4)
Year 2	60	10.1	12.6 (9.7 to 15.6)	77	2.1	6.9 (4.4 to 9.4)
Year 1–baseline	66	3.0	6.5 (4.0 to 9.1)	81	−0.3	−0.9 (−2.0 to 0.1)
Year 2–baseline	60	2.9	6.4 (4.2 to 8.6)	77	−0.1	−0.9 (−1.9 to 0.0)
70–79 y						
Baseline	44	2.3	6.4 (3.8 to 9.1)	45	4.3	7.1 (4.2 to 9.9)
Year 1	44	17.0	18.1 (14.0 to 22.1)	45	2.6	6.9 (3.8 to 10.0)
Year 2	43	15.8	16.5 (12.5 to 20.6)	42	3.0	7.6 (4.2 to 11.0)
Year 1–baseline	44	10.7	11.6 (8.2 to 15.1)	45	−0.0	−0.1 (−1.4 to 1.1)
Year 2–baseline	43	8.4	10.0 (6.5 to 13.4)	42	−0.0	0.1 (−1.3 to 1.5)

*P<.001 for interaction between estrogen plus progestin and age is based on a two-sided F test from a repeated-measures model with log(percent density + 0.001) as the response. CI = confidence interval.

Discussion

We found a statistically significant absolute mean 6.0% increase from baseline in mammographic percent density after 1 year among women assigned to the estrogen-plus-progestin group compared with a 0.9% decrease from baseline in the placebo group. The increase in density with estrogen-plus-progestin use persisted but was attenuated slightly by year 2, with an absolute mean percent density increase of 4.9% from baseline compared with a mean decrease of 0.8% from baseline in the placebo group. These results, suggesting that a combined hormone effect on density is maintained but is not progressive, extend the findings of Greendale et al. *(13)*, who reported that 1 year of the same combined hormone intervention increased mammographic density by 4.6% compared with nonuse. Whether these changes persist for longer than 2 years will require further study.

Approximately 75% of the women assigned to estrogen-plus-progestin use in our study experienced an increase in mammographic percent density. This value is higher than those in some previous reports *(23)*, perhaps because of differences between method of classifying mammogram density. In one report *(24)*, for example, initiation of combined hormone therapy use increased mammographic density in 73% of subjects, although it increased the Wolfe classification, a categorical classification, in only 24% of subjects.

At baseline, mammographic density was somewhat greater in Asian/Pacific Islanders than in non-Hispanic whites, blacks, and Hispanics, all of whom had similar breast densities. Unlike a prior report of substantially lower mammographic density in

Table 5. Mammographic percent density (MPD) at baseline, year 1, and year 2 by treatment assignment and percent density at baseline*

Group	Estrogen plus progestin			Placebo		
	No.	Median MPD	Mean MPD (95% CI)	No.	Median MPD	Mean MPD (95% CI)
Low MPD (<10%)						
Baseline	152	2.2	3.2 (2.7 to 3.6)	146	1.3	2.5 (2.1 to 2.9)
Year 1	152	6.7	10.4 (8.8 to 12.1)	146	1.5	2.5 (2.0 to 3.0)
Year 2	140	6.5	9.4 (7.9 to 10.9)	137	1.4	2.5 (1.9 to 3.1)
Year 1–baseline	152	2.9	7.3 (5.7 to 8.9)	146	−0.1	0.0 (−0.3 to 0.4)
Year 2–baseline	140	3.2	6.2 (4.8 to 7.6)	137	−0.1	0.0 (−0.6 to 0.6)
Medium MPD (10–<25%)						
Baseline	32	14.0	14.8 (13.6 to 16.0)	49	15.0	16.0 (14.8 to 17.2)
Year 1	32	14.9	18.6 (14.4 to 22.7)	49	12.9	14.3 (12.2 to 16.3)
Year 2	32	14.7	18.6 (14.6 to 22.6)	46	13.3	13.5 (11.4 to 15.7)
Year 1–baseline	32	1.0	3.8 (−0.4 to 8.0)	49	−2.2	−1.7 (−3.5 to 0.1)
Year 2–baseline	32	0.9	3.8 (−0.2 to 7.9)	46	−3.1	−2.3 (−4.2 to −0.3)
High MPD (≥25%)						
Baseline	18	31.2	34.0 (30.4 to 37.6)	16	35.4	36.4 (31.5 to 41.4)
Year 1	18	31.0	33.3 (27.4 to 39.2)	16	26.0	29.8 (21.9 to 37.6)
Year 2	16	30.3	30.8 (24.6 to 37.0)	15	28.7	32.4 (23.6 to 41.1)
Year 1–baseline	18	−0.1	−0.7 (−6.2 to 4.9)	16	−5.5	−6.7 (−12.2 to −1.2)
Year 2–baseline	16	−1.9	−3.8 (−9.2 to 1.5)	15	1.1	−4.2 (−10.9 to 2.5)

*P = .004, for the interaction between estrogen plus progestin and baseline percent density is based on a two-sided F test from a repeated-measures model with log(percent density + 0.001) as the response. CI = confidence interval.

Table 6. Mammographic percent density (MPD) at baseline, year 1, and year 2 by treatment assignment adjusted for adherence*

Group	Estrogen plus progestin			Placebo				
	No.	Median MPD	Mean MPD (95% CI)	No.	Median MPD	Mean MPD (95% CI)	P†	P‡
Baseline	202	3.9	7.7 (6.4 to 9.1)	211	3.6	8.2 (6.7 to 9.6)	.46	
Year 1	151	13.4	15.7 (13.5 to 17.8)	165	2.6	7.3 (5.6 to 8.9)		
Year 2	119	12.4	14.6 (12.4 to 16.8)	134	2.1	6.6 (5.0 to 8.3)		
Year 1–baseline	151	4.7	7.7 (5.9 to 9.5)	165	−0.3	−1.1 (−1.9 to −0.3)	<.001	<.001
Year 2–baseline	119	3.8	6.8 (5.0 to 8.6)	134	−0.2	−1.1 (−2.0 to −0.3)	<.001	

*CI = confidence interval.

†*P* value of main effect of estrogen plus progestin, by visit, is based on a two-sided *t* test from a repeated-measures model with log(percent density + 0.001) as the response.

‡*P* value of overall main effect of estrogen plus progestin at follow-up is based on a two-sided *F* test from a repeated-measures model with log(percent density + 0.001) as the response.

African American women *(25)*, mammographic density was not lower in African Americans relative to Hispanic and non-Hispanic whites in this population. The association between estrogen-plus-progestin use and increased mammographic density was consistent across racial/ethnic groups.

A prior observational study *(7)* estimated that breast cancer risk increases by approximately 15% with each 10% increase in percent density. However, too few cases of breast cancer (n = 6) occurred within the current study population of 413 women to assess the relationship between hormone-associated percent density change and breast cancer risk. A substantially larger study would be required to determine whether an increase in mammographic density is a useful clinical marker of breast cancer risk or simply a biologically interesting group effect. If we assume that the latter is the case, interventions that change mammogram density may still help to identify agents with influence on breast cancer risk but may not add to breast cancer risk assessment in individual women.

There may be individual variation in response to estrogen-plus-progestin therapy, including variability in genes controlling production or metabolism of estrogens and progesterone. In 232 postmenopausal women participants in two double-blind placebo-controlled trials *(26)*, the magnitude of increase in mammographic density in women using combined estrogen-and-progestin therapy was greater in those with genetically determined lower activity of enzymes that metabolize estrogen and progesterone. In particular, both the ValVal and LeuVal genotypes of the AKR1C4 (aldo-keto reductase 1C4) gene were statistically significantly associated with mammogram density compared with the LeuLeu genotype (both $P<.001$). There was also an association between the cytochrome P450 1B1 gene polymorphism (Val432Leu); women with the LeuLeu genotype compared with the ValVal genotype had increased mammogram density with estrogen-plus-progestin use ($P = .03$). Data from the Postmenopausal Estrogen and Progestin Interventions trial indicate that an increase in serum estrone levels is a strong predictor of change in mammogram density in women randomly assigned to either estrogen alone or estrogen-plus-progestin therapy, which suggests that the metabolism of these hormones is key to their effect on mammogram density *(27)*.

Increased mammographic density decreases sensitivity of mammographic screening *(3)*. In a study of more than 460 000 screening mammograms *(3)*, sensitivity was 88% in the "almost entirely fatty" category but was 82% in the "scattered fibroglandular tissue" category of BI-RAD mammogram density classifications. Our finding of a mean 6.0% increase in percent density could, therefore, mean that estrogen-plus-progestin use could cause a breast density increase in some women that was large enough to adversely affect screening sensitivity.

Despite the appeal of a hypothesis relating increased mammographic density to increased frequency of abnormal mammograms, neither mammographic density nor change in density was statistically significantly associated with abnormal mammogram findings. Although mammograms with greater density are more difficult to interpret and although estrogen-plus-progestin use statistically significantly and independently increased both percent density and the frequency of abnormal mammograms, our results indicate that the modest, albeit statistically significant, increase in mammographic density associated with estrogen-plus-progestin use may not necessarily mediate the increase in abnormal mammograms. The statistical power to evaluate this relationship was limited by the sample size and by our decision to analyze only the cross-sectional relationship between density and abnormal mammography at a single time point. Definitive assessment of these relationships, therefore, requires further evaluation in larger populations. The causes of increased abnormal mammograms with hormone therapy use are certainly of interest, given the potentially large numbers of women affected *(14,28)*.

Strengths of this report include the double-blind randomized design, which is unlikely to be influenced by selection factors or misclassifications of exposure and covariates that can potentially influence observational studies. The 2-year follow-up period provides new information on duration and cumulative nature of effects. The methods used to measure percent density are well established and have excellent observer reliability. Finally, the study was conducted as an ancillary study to a randomized clinical trial where reliable estimates of clinical endpoints and screening mammographic clinical recommendation categories were available. Study limitations include the evaluation of a single formulation and dose of hormones, a single schedule of hormone use, and the relatively small number of abnormal mammograms and breast cancers observed.

Despite the increased breast cancer risks associated with estrogen-plus-progestin use, many women continue to choose this therapy. In light of the current findings that estrogen-plus-progestin use increases mammographic density, a factor associated with increased breast cancer risk and reduced mammogram screening efficacy, health professionals may want to consider

mammographic density change as part of regular mammographic measurement and as part of risk–benefit assessment when helping women choose whether or not to begin or continue this therapy. It may also be useful for women to be given their mammogram density level. The BI-RADS guidelines for radiographic interpretation *(18)* indicate that there should be a one-sentence description of breast density in every mammography report, although it is not clear whether this information is currently a routine part of clinical mammogram reports or whether it is given to patients.

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