Effects of Estrogen and Estrogen–Progestin on Mammographic Parenchymal Density

Gail A. Greendale, MD; Beth A. Reboussin, PhD; Angela Sie, MD; H. Rosy Singh, MD; Linda K. Olson, MD; Olga Gatewood, MD; Lawrence W. Bassett, MD; Carol Wasilauskas, RN, MS; Trudy Bush, PhD; and Elizabeth Barrett-Connor, MD, for the Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators*

Background: In longitudinal studies, greater mammographic density is associated with an increased risk for breast cancer.

Objective: To assess differences between placebo, estrogen, and three estrogen–progestin regimens on change in mammographic density.

Design: Subset analysis of a 3-year, multicenter, double-blind, randomized, placebo-controlled trial.

Setting: Seven ambulatory study centers.

Participants: 307 of the 875 women in the Postmenopausal Estrogen/Progestin Interventions Trial. Participants had a baseline mammogram and at least one follow-up mammogram available, adhered to treatment, had not taken estrogen for at least 5 years before baseline, and did not have breast implants.

Intervention: Treatments were placebo, conjugated equine estrogens (CEE), CEE plus cyclic medroxyprogesterone acetate (MPA), CEE plus daily MPA, and CEE plus cyclic micronized progesterone (MP).

Measurements: Change in radiographic density (according to American College of Radiology Breast Imaging Reporting and Data System grades) on mammography.

Results: Almost all increases in mammographic density occurred within the first year. At 12 months, the percentage of women with density grade increases was 0% (95% CI, 0.0% to 4.6%) in the placebo group, 3.5% (CI, 1.0% to 12.0%) in the CEE group, 23.5% (CI, 11.9% to 35.1%) in the CEE plus cyclic MPA group, 19.4% (CI, 9.9% to 28.9%) in the CEE plus daily MPA group, and 16.4% (CI, 6.6% to 26.2%) in the CEE plus cyclic MP group. At 12 months, the odds of an increase in mammographic density were 13.1 (95% CI, 2.4 to 73.3) with CEE plus cyclic MPA, 9.0 (CI, 1.6 to 50.1) with CEE plus daily MPA, and 7.2 (CI, 1.3 to 40.0) with CEE plus cyclic micronized progesterone compared with CEE alone.

Conclusions: Further study of the magnitude and meaning of increased mammographic density due to use of estrogen and estrogen–progestins is warranted because mammographic density may be a marker for risk for breast cancer.

*For a partial list of the PEPI Investigators, see Appendix.

This paper is also available at http://www.acponline.org.

Ann Intern Med. 1999;130:262-269.

For author affiliations and current author addresses, see end of text.

The density of the breast on radiography is determined by the tissue's relative proportions of fat, connective tissue, and epithelial tissue. Fat is lucent, or dark, on the image; connective and epithelial tissues are dense, or white. Several methods for classifying mammographic parenchymal density are available, including the use of Wolfe patterns (a visual parenchymal method), estimations of the percentage of the breast area that is dense (the percentage-density method), and assessments of absolute density (the degree of density in dense areas of the breast) (1–4).

Regardless of the method used to classify it, mammographic density seems to be a strong, independent risk factor for the development of breast cancer (5–7). Further, the increased risk associated with greater mammographic density persists for up to 9 years after screening (8); this argues strongly against detection bias ("masking") as the sole cause of the observed increase in cancer (9).

Previous studies (10–16) have examined the association between postmenopausal hormone use and mammographic density, but these were observational studies, convenience samples, or uncontrolled clinical trials. To date, the association between postmenopausal hormone use and mammographic density has not been studied in a long-term, placebo-controlled, randomized, double-blind trial of hormone replacement therapy. We describe the effects on mammographic density of placebo, conjugated equine estrogens (CEE), and CEE combined with one of three progestin regimens in 307 women from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial.

Methods

Participants

Between December 1989 and February 1991, the PEPI Trial enrolled 875 postmenopausal women at seven clinical centers in the United States (Appendix). The PEPI Trial was a randomized, double-blind, placebo-controlled trial of the effects of CEE or CEE plus one of three progestin regimens on selected cardiac risk factors and other health out-

comes. Data on study design, recruitment, eligibility, exclusion criteria, and the baseline characteristics of the entire PEPI sample are reported in detail elsewhere (17). In brief, participants were required to be between 45 and 64 years of age, to be naturally or surgically menopausal, to have not taken estrogen or progestin for at least 2 months before screening, to be at least 1 year but not more than 10 years past menopause (if naturally menopausal), and to have no major contraindications to estrogen therapy. Treatments were 1) placebo; 2) CEE, 0.625 mg/d; 3) CEE plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 days per month; 4) CEE plus daily MPA, 2.5 mg/d; or 5) CEE plus micronized progesterone, 200 mg/d for 12 days per month. The PEPI Trial was conducted with the approval of the institutional review boards at each participating center.

Eligibility for the Mammographic Study

This analysis was done with data from all 307 participants who met the eligibility criteria for the mammographic density study. To be eligible for the mammographic density study, participants had to 1) have a baseline mammogram (done before randomization) and at least one follow-up mammogram (done at 12, 24, or 36 months) available for review, 2) adhere to treatment (taking ≥80% of assigned medication), 3) not have taken estrogen for at least 5 years before baseline, and 4) not have breast implants (implants obscure density readings).

Data Collection

A self-administered questionnaire was used at baseline and then annually to collect demographic, behavioral, medical, and gynecologic data and information on history of use of noncontraceptive estrogen. Height and weight were obtained at baseline and annually while participants were wearing lightweight clothing and no shoes. Body mass index was calculated as body weight in kilograms divided by height in meters squared.

Mammogram Review

Three expert mammography radiologists from three of the seven participating clinical centers independently rated each set of participants' mammograms. Before the ratings were done, standardized procedures for film evaluation were established and an in-person training session was held to ensure uniform implementation and recording of rating criteria. Radiologists were unaware of treatment assignments, but they did know the dates and sequences of mammograms. Each set of mammograms

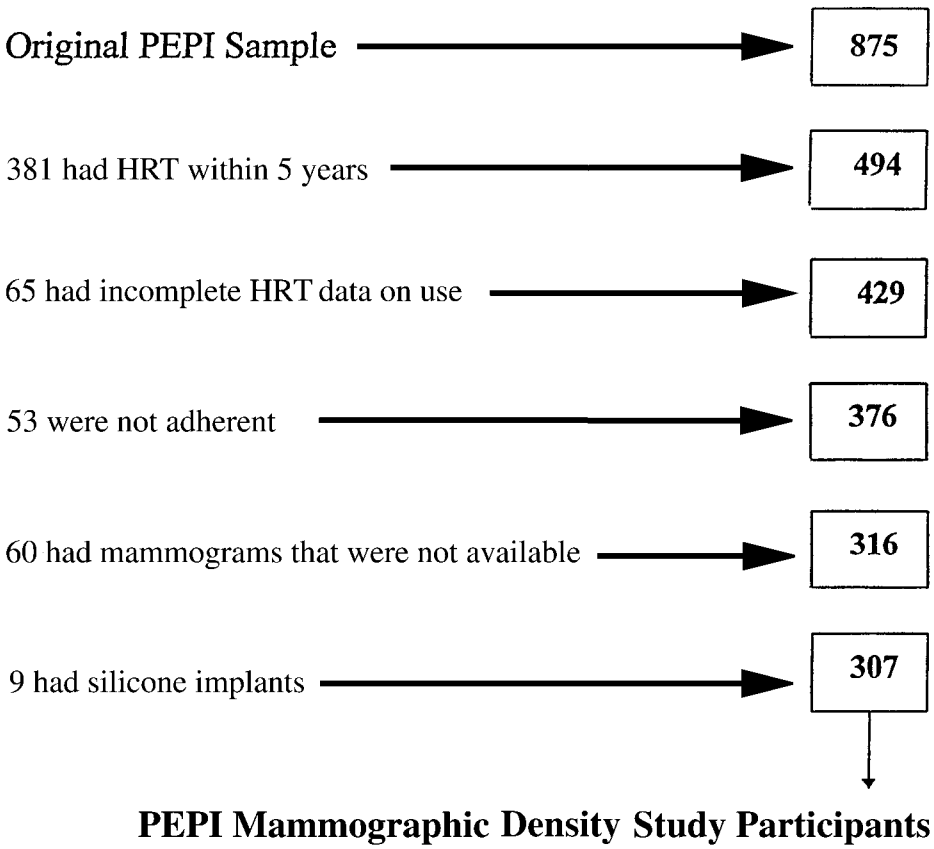

Figure. Diagram of the Postmenopausal Estrogen/Progestin Interventions (*PEPI*) Trial mammographic density study showing numbers of and reasons for exclusions. HRT = hormone replacement therapy.

was viewed as a whole; left and right breasts were rated separately. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) was used (18). The BI-RADS categories are 1) entirely fatty, 2) fatty with scattered fibroglandular tissue, 3) heterogeneously dense, and 4) extremely dense. In practice, these classifications are used to alert clinicians that the ability to detect small cancers in the dense breast is reduced.

Statistical Analysis

The interrater reliability of BI-RADS was assessed by using weighted κ statistics (19) for ordered categories. The BI-RADS grade for each breast at each time point was the value (1, 2, 3, or 4) assigned by two or more radiologists. There was complete agreement for all left and right readings with the exception of a discrepancy between breasts for one 12-month examination and one 36-month examination. Results are given for the right breast only because of high concurrence between effects in the right and left breasts (this high degree of between-breast agreement is consistent with that in previous reports [20]). The percentage of women with an increase in BI-RADS grade is presented by study visit and treatment group.

Logistic regression models were used to examine the effect of treatment on mammographic density. Increase in BI-RADS grade was the outcome variable. We considered changes between baseline and 12 months on BI-RADS because of the low prevalence of change after 12 months. The initial model was adjusted for blocking variables (clinic and uterus status). Potential confounding factors considered for inclusion in the multivariable model were baseline BI-RADS grade, age, cigarette smoking, alcohol use, parity, and body mass index. Values for covariates were those obtained at baseline.

Our final model included treatment assignment, clinic site, uterus status, baseline BI-RADS grade, age, cigarette smoking, and alcohol use (parity and body mass index had no significant effects). Pairwise comparisons between treatment groups were made by using two-sided *t*-tests. Interaction terms were then added to examine factors that might modify the effects of hormone treatment on mammographic density after adjustment for potential confounders. Because none of the 49 women in whom the BI-RADS grade for baseline mammograms was 3 had an increase in density at 12 months, these women were deleted from the multivariable modeling (this deletion did not affect the results because the cases were uninformative). We assessed the presence of an interaction between treatment and 1) baseline BI-RADS grade, 2) age, 3) smoking status (1 = current smoker, 0 = former or never smoker), or 4) any alcohol consumption (yes/no). The statistical significance of the interaction terms was tested with likelihood ratio chi-square tests (21).

Industry Role

Hormones were contributed by pharmaceutical companies, but these companies had no role in the conduct of the trial or the interpretation of its results.

Results

Of the 875 PEPI Trial participants, 307 were eligible for the mammographic density study. The

Table 1. Selected Characteristics of Participants in the PEPI Mammographic Density Study Compared with All Other PEPI Trial Participants*

Characteristic	Mammographic Study Participants (n = 307)	All Other PEPI Trial Participants (n = 568)	P Value†
Chronologic age ± SD, *y*	59.2 ± 4.2 (301)	59.0 ± 4.3 (546)	>0.2
Age at natural menopause ± SD, *y*	50.6 ± 3.0 (238)	50.7 ± 3.1 (363)	>0.2
Body mass index ± SD, kg/m^2	27.1 ± 4.9 (301)	26.2 ± 4.5 (546)	0.009
Current alcohol use, %	61.8 (301)	64.8 (545)	>0.2
Current smoking, %	15.3 (301)	8.3 (545)	0.002
Breast pain, %			
Baseline	3.6 (307)	4.6 (568)	>0.2
1 year	13.1 (305)	13.4 (544)	>0.2
3 years	9.0 (301)	12.5 (543)	0.118
Parity, %			
0	12.7 (307)	12.5 (568)	
1 or 2	27.7 (307)	30.5 (568)	
>3	59.6 (307)	59.6 (568)	
Previous oral contraceptive use, %	60.3 (307)	60.6 (568)	>0.2
Hormone replacement therapy			
Ever	9.8 (307)	80.4 (556)	0.001
Never	90.2 (307)	19.6 (556)	
Nonwhite, %	11.4 (307)	11.4 (568)	>0.2

* All characteristics are those measured at baseline, except for breast pain. Numbers given in parentheses are the sample sizes, which vary because of missing data. PEPI = Postmenopausal Estrogen/Progestin Interventions Trial.

† According to *t*-test (continuous variables) or chi-square test (categorical variables) for comparison of the mean values for mammographic density study participants with those of the remaining PEPI Trial participants.

Table 2. Baseline BI-RADS Density Grades by Study Radiologist*

Variable	BI-RADS Grade at Baseline											
	Radiologist 1 (n = 305)†				Radiologist 2 (n = 305)†				Radiologist 3 (n = 307)†			
	1	2	3	4	1	2	3	4	1	2	3	4
Mammograms, *n (%)*‡	64 (21)	166 (54)	69 (23)	6 (2)	57 (19)	191 (63)	54 (18)	3 (1)	27 (9)	204 (66)	71 (23)	5 (2)

* Only data for right breasts are included. The κ statistics are 0.72 for radiologist 1 compared with radiologist 2, 0.58 for radiologist 1 compared with radiologist 3, and 0.60 for radiologist 2 compared with radiologist 3. In BI-RADS, 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, and 4 = extremely dense. BI-RADS = American College of Radiology Breast Imaging Reporting and Data System.
† The sample size for each radiologist differs slightly because each radiologist did not read all mammograms.
‡ Percentage total exceeds 100% because of rounding.

most common reason for ineligibility was having taken estrogen within 5 years of baseline (381 women [44%]). The number of women excluded from the mammographic density study for each exclusion criterion is shown in the **Figure**.

The characteristics of the 307 participants included in the mammographic density study are compared with those of the other PEPI Trial participants in **Table 1**. Because women who had used estrogen replacement therapy within 5 years of baseline were excluded from the mammographic density study, mammographic density study participants were much less likely to have ever used estrogen ($P = 0.001$). They were also heavier ($P = 0.009$) and were more likely to be current smokers ($P = 0.002$). Other characteristics, including breast pain symptoms, were similar in the two groups.

The baseline distribution of BI-RADS grades for each reader is shown in **Table 2**. Overall, most mammograms were classified as grade 1 or grade 2. Extremely dense mammograms (grade 4) were rare. The interrater reliability of mammographic density readings at all time points was high for the three radiologists. The κ statistics were 0.58 to 0.72 at baseline, 0.59 to 0.74 at year 1, 0.61 to 0.75 at year 2, and 0.58 to 0.70 at year 3.

Table 3 shows the percentages of women whose mammographic density increased by at least one BI-RADS grade for each treatment group over time. Women who had baseline BI-RADS grades of 4 ($n = 3$) and women who began a 1-year follow-up period with a BI-RADS grade of 4 ($n = 4$ at 12 months and $n = 3$ at 24 months) could not have further increases in density. Therefore, they are excluded from the analysis in **Table 3**. In general, combination treatment was associated with the greatest number of density increases—five to seven times more across the progestin-containing treatment groups compared with the estrogen-only group. Density increases for all active treatment groups were concentrated in the first year of the study. No increases in density were seen in the placebo group at 12 or 24 months, and only 2.0% of the women in this group had density increases between 24 and 36 months.

From baseline to 12 months, 36 of 295 women (12.2%) had an increase in BI-RADS grade (**Table 4**). Increases were confined to those women who had grade 1 or grade 2 mammograms at baseline (**Table 4**). No density grade decreases were seen among women with grade 3 mammograms at baseline. By definition, women with grade 4 mammograms could not have further density increases. All density increases were increases of one grade level.

The adjusted effect of hormone treatment on mammographic density between baseline and 12 months is shown in **Table 5**. The final model was adjusted for baseline BI-RADS grade, age, cigarette smoking, alcohol use, clinical site, and uterus status. Parity and body mass index were not statistically significant covariates. Because no density increases were seen in the placebo group (**Table 3**), the logistic regression model shown in **Table 5** compares the effect of each estrogen–progestin treatment with that of CEE only. The relative odds of a density increase in the combination treatment groups were 13.1 for CEE plus cyclic MPA, 9.0 for CEE plus daily MPA, and 7.2 for CEE plus micronized progesterone compared with CEE only ($P < 0.024$ for all comparisons). No significant differences were seen between any of the estrogen–progestin treatments ($P > 0.2$ for each between-group comparison).

No statistically significant interaction was found between treatment effects and any of the following: BI-RADS grade at baseline, age, cigarette smoking, or alcohol use. However, age ($P = 0.001$) and alcohol use ($P = 0.011$) had statistically significant independent (main) effects on increases in mammographic density. For each 5-year increment in age, the odds of having an increase in mammographic density were 2.4 times (95% CI, 1.1 to 4.3 times) greater. Women who drank any alcohol were 3.6 times (CI, 1.3 to 10.4 times) more likely to have an increase than were women who drank no alcohol. No evidence for a graded effect of alcohol within the range of consumption of the PEPI participants

(7.08 ± 14.18 g/d) was seen (data not shown). In the multivariable model, the independent effect of smoking was of marginal statistical significance ($P = 0.056$). The odds of an increase in mammographic density were 0.2 times (CI, 0.02 to 1.5 times) less in current smokers than in nonsmokers.

Discussion

The PEPI Trial is the first randomized, placebo-controlled study to assess the long-term effects of CEE alone and CEE combined with three progestin regimens on mammographic parenchymal density in postmenopausal women. Over 3 years of follow-up, we found that approximately 8% of estrogen users and 19% to 24% of estrogen–progestin users had an increase in mammographic density, most often in the first year; increases in density were rare in the placebo group (2%). Compared with women treated with CEE only, estrogen–progestin users had a 7-fold to 13-fold increased risk for developing denser breasts on mammography, and this increased risk did not differ significantly by progestin regimen.

Since mammographic parenchymal density patterns were originally described as a risk factor for breast cancer (1, 22), numerous investigators have explored the relation between mammographic density and risk for breast cancer (4–7). Mammographic density has been classified in several ways, including a visual parenchymal method (Wolfe patterns); assessment of the percentage of the breast that is dense (the percentage-density method); and assessment of the absolute density (1–4). The Wolfe patterns are N1 (lowest risk, parenchyma primarily fat, no ducts visible), P1 (low risk, parenchyma chiefly fat with prominent ducts anteriorly making up as much as one fourth of breast volume), P2 (high risk, prominent duct pattern in more than one fourth of breast volume), and DY (highest risk, extensive density often obscures underlying ductal pattern). The more recently developed percentage-density method calculates the percentage of the breast that is dense (the dense area of the breast divided by the entire breast area). This may be done manually or with computer-assisted techniques (2–4). Absolute density assesses the degree of density within the dense areas of the breast.

Regardless of the classification method used, consistent evidence indicates that greater mammographic density increases risk for breast cancer (5–7) and that this increased risk exceeds that which can be ascribed to poorer detection ("masking") alone (8, 9). Although the epidemiologic linkage between mammographic density and future breast cancer is strong, the mechanisms by which density confers this increased risk remain uncertain. Epithelial hyperplasia and concomitant increases in growth factors have been suggested (6); several biopsy studies have shown that high-density areas are associated with epithelial hyperplasia (23–26).

Most previous work suggests that hormones increase mammographic density and that combination hormone regimens do so more often than estrogen-only regimens, but study designs and small sample sizes have precluded definitive conclusions. Using data from a population-based screening study, Bergkvist and colleagues (27) found no change in Wolfe patterns in women who began estrogen replacement therapy between two mammography screening visits. However, these authors categorized density into only two groups (N1–P1 and P1–P2), and this may have diminished the study's ability to discriminate change. In a nested case–control analysis, Bland and colleagues (11) found no association between estrogen replacement therapy and parenchymal density readings. In contrast, several small pre–post studies reported increases in density with hormone use (12–15). In a clinical sample of postmenopausal women, Kaufman and colleagues (14)

Table 3. Readings Showing an Increase in BI-RADS Density Grade, by Treatment and Study Visit*

Variable	Placebo Group	CEE Group†	CEE + Cyclic Group‡	CEE + Daily MPA Group§	CEE + MP Group‖
Baseline to 12 months¶					
Readings (95% CI), %	0.0 (0.0–4.6)	3.5 (1.0–12.0)	23.5 (11.9–35.1)	19.4 (9.9–28.9)	16.4 (6.6–26.2)
Sample size, *n*	64	58	51	67	55
12 to 24 months**					
Readings (95% CI), %	0.0 (0.0–5.4)	4.8 (1.5–16.0)	0.0 (0.0–6.6)	3.3 (1.0–11.5)	2.3 (0.5–12.0)
Sample size, *n*	54	42	44	61	44
24 to 36 months††					
Readings (95% CI), %	2.0 (0.5–10.5)	0.0 (0.0–8.9)	0.0 (0.0–7.0)	0.0 (0.0–5.2)	0.0 (0.0–6.3)
Sample size, *n*	51	32	41	56	46

* An increase is defined as having occurred if at least two readers scored a film as denser than the previous film. BI-RADS = American College of Radiology Breast Imaging Reporting and Data Systems; CEE = conjugated equine estrogens; MP = micronized progesterone; MPA = medroxyprogesterone acetate.
† CEE: 0.625 mg/d orally.
‡ CEE + cyclic MPA: CEE, 0.625 mg/d orally; MPA, 10 mg/d orally on days 1 through 12.
§ CEE + continuous MPA: CEE, 0.625 mg/d orally; MPA, 2.5 mg/d orally.
‖ CEE + MP: CEE, 0.625 mg/d orally; MP, 200 mg/d orally on days 1 through 12.
¶ Does not include women with grade 4 mammograms at baseline ($n = 3$).
** Does not include women with grade 4 mammograms at 12 months ($n = 4$).
†† Does not include women with grade 4 mammograms at 24 months ($n = 3$).

Table 4. BI-RADS Density Grade at 12 Months by Baseline BI-RADS Density Grade*

Baseline Grade	Grade at 12 Months			
	1	2	3	4
	← *n (%)* →			
1	38 (12.8)	10 (3.4)	0	0
2	0	161 (54.6)	26 (8.7)	0
3	0	0	60 (20.3)	0
4	0	0	0	0

* Sample size = 295. In BI-RADS, 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, and 4 = extremely dense. BI-RADS = American College of Radiology Breast Imaging Reporting and Data System.

reported that women taking hormone replacement therapy for 5 or more years did not experience the usual decreases in density seen with aging. No details of the hormone replacement therapy regimens were given. In another sample of 64 women (13), 9 of 33 hormone replacement therapy users (who were using six different regimens) developed increased density compared with none of 31 nonusers. Berkowitz and coworkers (12) noted that mammographic density did not increase in 14 women using estrogen only but did increase in 5 of 16 women using combined therapy. Finally, in an uncontrolled, 1-year clinical trial of CEE with either 2.5 or 5.0 mg of MPA, 30 of 41 women developed increased density (15). Our study adds substantially to this body of work because the randomized design and the duration of the PEPI Trial gave us a unique opportunity to characterize the relative effects on mammographic density of estrogen or estrogen–progestin compared with placebo, to distinguish between the effects of each regimen used, and to determine the temporal pattern of mammographic density change related to hormone use.

Do the mammographic density increases seen in the PEPI Trial translate into an increased risk for breast cancer? The risk for breast cancer associated with greater mammographic density is graded and continuous; there is no evidence for a "threshold" of density above which risk increases. This graded relation was illustrated in a large follow-up study by Saftlas and colleagues (4), who categorized baseline percentage-density into quintiles and found that successive quintiles had increasingly higher relative risks for future breast cancer; these risks were 1.7, 2.5, 3.8, and 4.3 ($P < 0.001$). A similarly strong, graded risk for breast cancer development was reported by Boyd and colleagues (28): For women 50 to 59 years of age, relative risks for cancer increased from 1.9 to 7.1 as baseline percentage-density increased from 25% to 75% or more. In addition, we found that estrogen–progestin had a strikingly greater effect on parenchymal density compared with estrogen only. This is concordant with two lines of evidence that previously suggested a role for progestins in the cause of breast cancer. First, some (29, 30) but not all (31) cohort studies have reported that risk for breast cancer is greater in postmenopausal women who use estrogen–progestin than in those who use estrogen only. Second, progestins are more potent mitogens for breast tissue than are estrogens (32).

We explored several factors that might be independent predictors of mammographic density or that might confound or modify the effects of hormone replacement therapy on breast tissue. These included BI-RADS grade, age, cigarette smoking, alcohol use, parity, and body mass index (6, 33, 34). Independent of treatment, older age was significantly associated with a lower likelihood of density increases. We used age (rather than years since menopause) in our models because in women with hysterectomy but intact ovaries (21% of the sample), years since menopause cannot be accurately estimated. However, age and years since menopause are highly related in the PEPI sample (35). We hypothesized that an interaction would exist between treatment and smoking—that is, that cigarette use would decrease the effect of hormone replacement therapy on mammographic density, possibly because of increased hormone metabolism (33). Our data, however, did not uphold this interaction hypothesis. The results of the PEPI Trial agree with previous reports showing that alcohol has a positive, independent effect on mammographic density (6). On the basis of alcohol's property of increasing estrogen levels (34), we expected that it would also enhance the effects of hormone replacement therapy on mammographic density, but this interaction hypothesis was not supported.

The PEPI Trial used BI-RADS for classification of mammographic parenchymal density because this is the standard system used in clinical radiology

Table 5. Adjusted Odds Ratios for an Increase in BI-RADS Density Grade at 12 Months*

Comparison†	Odds Ratios (95% CI)	*P* Value‡
CEE + cyclic MPA vs. CEE	13.1 (2.4–73.3)	0.003
CEE + daily MPA vs. CEE	9.0 (1.6–50.1)	0.012
CEE + MP vs. CEE	7.2 (1.3–40.0)	0.024
CEE + daily MPA vs. CEE + cyclic MPA	0.7 (0.2–2.1)	>0.2
CEE + MP vs. CEE + cyclic MPA	0.5 (0.2–1.8)	>0.2
CEE + MP vs. CEE + daily MPA	0.8 (0.8–2.5)	>0.2

* The placebo group is not included in this model because density did not increase in this group. Models do not include women receiving active treatment ($n = 52$) with grade 3 or 4 mammograms at baseline. (These women did not show any density increases; thus, their data are uninformative for modeling.) Models adjusted for baseline BI-RADS density, grade, age, cigarette smoking, alcohol use, clinic site, and uterus status. BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; CEE = conjugated equine estrogens; MP = micronized progesterone; MPA = medroxyprogesterone acetate.

† CEE = CEE, 0.625 mg/d orally ($n = 50$); CEE + cyclic MPA = CEE, 0.625 mg/d orally, and MPA, 10 mg/d orally on days 1 through 12 ($n = 42$); CEE + daily MPA = CEE, 0.625 mg/d orally, and MPA, 2.5 mg/d orally ($n = 51$); and CEE + MP = CEE, 0.625 mg/d orally, and MP, 200 mg/d orally on days 1 through 12 ($n = 42$).

‡ Based on two-sided *t*-test that the odds ratio equals 1.

practice in the United States (18). The advantage of BI-RADS is that it is used by practicing radiologists. The BI-RADS readings were highly reliable, with between-radiologist agreement ranging from 70% to 90%; this compares favorably with reports of reliability for other methods used to rate mammographic density (6, 36, 37). The disadvantages of BI-RADS should also be noted. The system uses broad categories and thus is suboptimal for assessing change in density. For example, the "distance" between category 2 (scattered fibroglandular densities) and category 3 (heterogeneously dense) is large. Therefore, a woman who has a grade 2 mammogram at baseline could develop a substantial increase in density yet not have a grade 3 mammogram. Previous studies that have assessed risk for breast cancer on the basis of mammographic density have used the percentage-density method (4, 28). The exact relation between BI-RADS grades and percentage-density readings has not been assessed. Percentage-density is a continuous value, a more refined measure than that provided by the four-category BI-RADS. But—and this is of central importance to interpretation of the significance of our findings—an ordered correspondence exists between BI-RADS and percentage-density (that is, a higher BI-RADS grade corresponds to a higher percentage-density).

The limitations of our study must be acknowledged. We restricted our analysis to women who adhered to therapy to evaluate the effect of hormones on change in mammographic density. To the extent that noncompliance with hormone therapy could be related to stronger or weaker increases in density, it is plausible that this analysis underestimates or overestimates the effect of hormones on mammographic density. We compared the substudy participants with the remainder of the PEPI sample with respect to self-reported breast tenderness (which may be a marker for greater breast stimulation). No difference was seen between adherent and nonadherent women in the percentage of women reporting breast tenderness during the 3 years of follow up. Although the radiologists were blinded to treatment assignments, they were aware of the dates and sequences of mammograms; this could have influenced their readings. However, the presence of a placebo group should have controlled for the possible tendency to read "increases." Finally, the predictive implications of change in mammographic density due to hormone replacement therapy may not be equivalent to the implications of naturally occurring greater density.

Epidemiologic studies have found that increased mammographic density is an independent risk factor for breast cancer; thus, mammographic density may be a surrogate end point for the development of this disease. If the risk for breast cancer associated with mammographic density is linear and continuous, and if the effects of exogenous hormones can be equated to the risks seen with naturally occurring increases in density, then the increases in density found in the PEPI Trial may confer some as yet unquantifiable increase in risk. The estrogen–progestin combinations used in the PEPI Trial affected mammographic density equally, and they affected it to a much greater degree than did CEE alone. In summary, increasing mammographic density might serve as a marker for women whose risk for breast cancer is increased by hormone replacement therapy. Further study of this potentially important risk stratifier is warranted.

Appendix: An Abridged List of the PEPI Investigators

George Washington University, Washington, D.C.—Principal Investigator: Vanessa Barnabei, MD, PhD (formerly Valery T. Miller, MD, and John LaRosa, MD); Co-Investigator: Craig Kessler, MD.

The Johns Hopkins University, Baltimore, MD—Principal Investigator: Trudy Bush, PhD; Co-Investigators: Howard Zacur, MD, PhD, David Foster, MD, and Roger Sherwin, MD.

Stanford University, Stanford, California—Principal Investigator: Marcia L. Stefanick, PhD (formerly Peter D. Wood, DSc); Co-Investigators: Robert Marcus, MD, Katherine O'Hanlan, MD, Melissa Ruyle, and Mary Sheehan, MS.

The University of California, Los Angeles, California—Principal Investigator: Howard L. Judd, MD; Co-Investigator: Gail A. Greendale, MD.

The University of California, San Diego, California—Principal Investigator: Elizabeth Barrett-Connor, MD; Co-Investigator: Robert Langer, MD.

The University of Iowa, Ames, Iowa—Principal Investigator: Susan R. Johnson, MD (formerly Helmut G. Schrott, MD).

The University of Texas Health Science Center, San Antonio, Texas—Principal Investigator: Carl Pauerstein, MD; Co-Investigator: José Trabal, MD.

Wake Forest University School of Medicine, Winston-Salem, North Carolina (Coordinating Center)—Principal Investigator: Mark Espeland, PhD (formerly H. Bradley Wells, PhD); Co-Investigators: George Howard, DrPH; Robert Byington, PhD; Claudine Legault, PhD; Beth A. Reboussin, PhD; and Sally Shumaker, PhD.

From University of California, Los Angeles, School of Medicine, Los Angeles, California; Wake Forest School of Medicine, Winston-Salem, North Carolina; Johns Hopkins University and University of Maryland Medical School, Baltimore, Maryland; and University of California at San Diego, San Diego, California.

Grant Support: The PEPI Trial is supported by cooperative agreement research grants U01-HL40154, U01-HL40185, UL-HL40195, U01-HL40205, U01-HL40207, U01-HL40231, U01-HL40232, and U01-HL40273 from the National Heart, Lung, and Blood Institute; the National Institute of Child Health and Human Development; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute on Aging. Packaged medication and placebos were provided by Wyeth-Ayerst Laboratories, the Schering-Plough Research Institute, and the Upjohn Company. For this work, Dr. Greendale was supported by the Iris Cantor–UCLA Women's Center and the UCLA Center of Excellence in Women's Health (PHS 282-97-0025).

Requests for Reprints: Gail A. Greendale, MD, Division of Geriatrics, University of California, Los Angeles, School of Medicine, 10945 Le Conte Avenue, Suite 2339, Los Angeles, CA 90095-1687.

Current Author Addresses: Dr. Greendale: Division of Geriatrics, University of California, Los Angeles, School of Medicine, 10945 Le Conte Avenue, Suite 2339, Los Angeles, CA 90095-1687.
Dr. Reboussin and Ms. Wasilauskas: Department of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1063.
Dr. Sie: Radia Medical Imaging, 1632 116th Avenue, NE, Suite D, Bellevue, WA 98004-3035.
Dr. Singh: Advanced Radiology, 7253 Ambassador Road, Baltimore, MD 21244-2714.
Dr. Olson: Radiology Department, University of California, San Diego, Medical Center-Hillcrest, 200 West Arbor Drive, San Diego, CA 92103-8756.
Dr. Gatewood: Radiology and Radiological Science, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287-5999.
Dr. Bassett: Radiological Sciences, University of California, Los Angeles, BL-428 CHS, Box 951721, Los Angeles, CA 90095-1721.
Dr. Bush: Department of Epidemiology and Preventive Medicine, University of Maryland Medical School, Howard Hall, Room 133, 660 West Redwood Street, Baltimore, MD 21201-1596.
Dr. Barrett-Connor: Department of Family and Preventive Medicine, University of California, San Diego, Clinical Science Building, Room 347, 0628, 9500 Gilman Drive, La Jolla, CA 92093-0628.

References

1. **Wolfe JN.** Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol. 1976;126:1130-7.
2. **Brisson J, Sadowsky NL, Twaddle JA, Morrison AS, Cole P, Merletti F.** The relation of mammographic features of the breast to breast cancer risk factors. Am J Epidemiol. 1982;115:438-43.
3. **Wolfe JN, Saftlas AF, Salane M.** Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. AJR Am J Roentgenol. 1987;148:1087-92.
4. **Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, Salane M, et al.** Mammographic densities and risk of breast cancer. Cancer. 1991;67: 2833-8.
5. **Saftlas AF, Szklo M.** Mammographic parenchymal patterns and breast cancer risk. Epidemiol Rev. 1987;9:146-74.
6. **Oza AM, Boyd NF.** Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol Rev. 1993;15:196-208.
7. **Warner E, Lockwood G, Tritchler D, Boyd NF.** The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev. 1992;16:67-72.
8. **Brisson J, Morrison AS, Khalid N.** Mammographic parenchymal features and breast cancer in the breast cancer detection demonstration project. J Natl Cancer Inst. 1988;80:1534-40.
9. **Egan RL, Mosteller RC.** Breast cancer mammography patterns. Cancer. 1977;40:2087-90.
10. **Bergkvist L, Tabar L, Adami HO, Persson I, Bergstrom R.** Mammographic parenchymal patterns in women receiving noncontraceptive estrogen treatment. Am J Epidemiol. 1989;130:503-10.
11. **Bland KI, Buchanan JB, Weisberg BF, Hagan TA, Gray LA Sr.** The effects of exogenous estrogen replacement therapy of the breast: breast cancer risk and mammographic parenchymal pattern. Cancer. 1980;45:3027-33.
12. **Berkowitz JE, Gatewood OM, Goldblum LE, Gayler BW.** Hormonal replacement therapy: mammographic manifestations. Radiology. 1990;174: 199-201.
13. **McNicholas MM, Heneghan JP, Milner MH, Tunney T, Hourihane JB, MacErlaine DP.** Pain and increased mammographic density in women receiving hormone replacement therapy: a prospective study. AJR Am J Roentgenol. 1994;163:311-5.
14. **Kaufman Z, Garstin WI, Hayes R, Michell MJ, Baum M.** The mammographic parenchymal patterns of women on hormonal replacement therapy. Clin Radiol. 1991;43:389-92.
15. **Laya MB, Gallagher JC, Schreiman JS, Larson EB, Watson P, Weinstein L.** Effect of postmenopausal hormonal replacement therapy on mammographic density and parenchymal pattern. Radiology. 1995;196:433-7.
16. **Stomper PC, Van Voorhis BJ, Ravnikar VA, Meyer JE.** Mammographic changes associated with postmenopausal hormone replacement therapy: a longitudinal study. Radiology. 1990;174:487-90.
17. **Espeland MA, Bush TL, Mebane-Sims I, Stefanick ML, Johnson S, Sherwin R, et al.** Rationale, design, and conduct of the PEPI Trial. Postmenopausal Estrogen/Progestin Interventions. Control Clin Trials. 1995;16(Suppl 4): 3S-19S.
18. **American College of Radiology.** Breast imaging reporting and data system (BI-RADS). 2d ed. Reston, VA: American Coll Radiology; 1995.
19. **Spitzer RL, Cohen J, Fleiss JL, Endicott J.** Quantification of agreement in psychiatric diagnosis. Arch Gen Psychiatry. 1967;17:83-7.
20. **Byng JW, Boyd NF, Little L, Lockwood G, Fishell E, Jong RA, et al.** Symmetry of projection in the quantitative analyses of mammographic images. Eur J Cancer Prev. 1996;5:319-27.
21. **Zelen M.** The analysis of several 2 × 2 contingency tables. Biometrika. 1971; 58:129-37.
22. **Ingleby H, Gershon-Cohen J.** Comparative anatomy, pathology and roentgenology of the breast. Philadelphia: Univ of Pennsylvania Pr; 1960.
23. **Bartow SA, Pathak DR, Mettler FA.** Radiographic microcalcification and parenchymal pattern as indicators of histologic "high-risk" benign breast disease. Cancer. 1990;66:1721-5.
24. **Boyd NF, Jensen HM, Cooke G, Han HL.** Relationship between mammographic and histological risk factors for breast cancer. J Natl Cancer Inst. 1992;84:1170-9.
25. **Urbanski S, Jensen HM, Cooke G, McFarlane D, Shannon P, Kruikov V, et al.** The association of histological and radiological indicators of breast cancer risk. Br J Cancer. 1988;58:474-9.
26. **Bright RA, Morrison AS, Brisson J, Burstein NA, Sadowsky NS, Kopans DB, et al.** Relationship between mammographic and histologic features of breast tissue in women with benign biopsies. Cancer. 1988;61:266-71.
27. **Bergkvist L, Tabar L, Adami HO, Persson I, Bergstrom R.** Mammographic parenchymal patterns in women receiving noncontraceptive estrogen treatment. Am J Epidemiol. 1989;130:503-10.
28. **Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, et al.** Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995;87:670-5.
29. **Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C.** The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med. 1989;321:293-7.
30. **Bergkvist L, Frodis E, Hedborg-Mellander C, Hansen J.** Management of accidentally found pathological lymph nodes on routine screening mammography. Eur J Surg Oncol. 1996;22:250-3.
31. **Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al.** The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 1995;332:1589-93.
32. **Key TJ.** Hormones and cancer in humans. Mutat Res. 1995;333:59-67.
33. **Michnovicz JJ, Bradlow HL.** Dietary and pharmacological control of estradiol metabolism in humans. Ann N Y Acad Sci. 1990;595:291-9.
34. **Ginsburg ES, Mello NK, Mendelson JH, Barbieri RL, Teoh SK, Rothman M, et al.** Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA. 1996;276:1747-51.
35. **Greendale GA, Hogan P, Kritz-Silverstein D, Langer R, Johnson SR, Bush T.** Age at menopause in women participating in the postmenopausal estrogen/progestins interventions (PEPI) trial: an example of bias introduced by selection criteria. Menopause. 1995;2:27-34.
36. **Boyd NF, Wolfson C, Moskowitz M, Carlisle T, Petitderc C, Ferri HA, et al.** Observer variation in the classification of mammographic parenchymal pattern. Journal of Chronic Diseases. 1986;39:465-72.
37. **Elmore JG, Wells CK, Lee CH, Howard DH, Feinstein AR.** Variability in radiologists' interpretations of mammograms. N Engl J Med. 1994;331:1493-9.