Estrogen Plus Progestin and Breast Cancer Detection by Means of Mammography and Breast Biopsy

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Background: The effect of combined hormone therapy on breast cancer detection is not established.

Methods: We examined the effect of combined hormone therapy on breast cancer detection in the Women's Health Initiative trial, which randomized 16 608 postmenopausal women to receive conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo. Mammography and breast examinations were performed at baseline and annually per protocol, with breast biopsies based on clinical findings. The effects of conjugated equine estrogens plus medroxyprogesterone acetate on breast cancer detection was determined throughout 5.6 years of intervention using receiver operating characteristic analyses to evaluate mammography results.

Results: Conjugated equine estrogens plus medroxyprogesterone acetate increased the cumulative frequency of mammograms with abnormalities vs placebo (35.0% vs 23.0%; $P<.001$), which had less sensitivity for cancer detection and increased cumulative breast biopsy frequency (10.0% vs 6.1%; $P<.001$). Although breast cancers were significantly increased and were diagnosed at higher stages in the combined hormone group, biopsies in that group less frequently diagnosed cancer (14.8% vs 19.6%; $P=.006$). After discontinuation of combined hormone therapy, its adverse effect on mammograms modulated but remained significantly different from that of placebo for at least 12 months ($P<.001$).

Conclusions: Use of conjugated equine estrogens plus medroxyprogesterone acetate for approximately 5 years resulted in more than 1 in 10 and 1 in 25 women having otherwise avoidable mammogram abnormalities and breast biopsies, respectively, and compromised the diagnostic performance of both. This adverse effect on breast cancer detection should be incorporated into risk-benefit discussions with women considering even short-term combined hormone therapy.

Trial Registration: clinicaltrials.gov Identifier: NCT00000611

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MENOPAUSAL HORMONE therapy remains in common use by women beginning menopause, with approximately 25 million prescriptions written in a recent year in the United States.[1] For women with a uterus considering combined estrogen plus progestin use, identified breast cancer issues represent a concern. In the Women's Health Initiative (WHI) randomized, placebo-controlled clinical trial, combined conjugated equine estrogen plus medroxyprogesterone acetate use significantly increased the number of mammograms with abnormalities and breast cancers that were larger and diagnosed at more advanced stages.[2] Despite these results, the effect of combined hormone therapy on breast cancer detection has been unsettled. Although an adverse effect of menopausal hormone therapy on breast cancer detection has been proposed based on observational study findings,[3-5] the results have been mixed.[6,7] In addition, the time course of hormone therapy effects on breast cancer detection has not been described. We therefore examined the effect of combined hormone therapy on breast cancer detection using mammography and breast biopsy throughout the WHI randomized clinical trial comparing combined conjugated equine estrogen plus medroxyprogesterone acetate use with placebo use.

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Group Information: A short list of the Women's Health Initiative Investigators appears on page 376. A full list can be found at http://www.whi.org.

METHODS

The WHI trial of conjugated equine estrogens plus medroxyprogesterone acetate enrolled 16 608 postmenopausal women at 40 clinical centers between October 29, 1993, and December 31, 1998, using protocols approved by

the institutional review board at each institution. Detailed eligibility criteria and recruitment procedures have been described elsewhere.[8-10] Eligibility included age 50 to 79 years, postmenopausal status, no previous hysterectomy, and written informed consent. Major exclusions included a personal history of breast cancer, other previous cancer within 10 years except nonmelanoma skin cancer, and medical conditions likely to result in death within 3 years. Women using postmenopausal hormones were eligible after a 3-month washout. A baseline mammogram and a breast clinical examination not suggestive of cancer were eligibility requirements. Women in the hormone trial could also participate in the WHI Dietary Modification trial (28.1% joined) and the WHI trial of calcium and vitamin D (59.7% joined).

The trial involved randomization to receive conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily in a single tablet (Prempro; Wyeth Ayerst, Collegeville, Pennsylvania) or an identical-appearing placebo tablet. Randomization was determined by the WHI Clinical Coordinating Center and was implemented at local clinical centers with dispensation of study medications identified with unique bar codes to allow for blinding of participants and staff.

DATA COLLECTION

Participants provided data on demographics; medical, reproductive, and family histories; and lifestyle factors, such as smoking and alcohol use and physical activity, using standardized self-report instruments. Past use of menopausal hormone therapy was ascertained through an interviewer-administered questionnaire. Mammography was performed at WHI clinical centers and at many community sites.[11] Reports of the screening study mammograms were obtained, reviewed at the local clinical centers, and coded for the radiologist recommendation given after assessment was complete. Mammogram reports requiring a physician-directed intervention (short-interval follow-up suggested, suspicious abnormalities, and those highly suggestive of malignancy) were considered mammograms with abnormalities. Mammograms either suspicious or highly suggestive of malignancy required clearance for eligibility.

FOLLOW-UP PROCEDURES

Participants were contacted 6 weeks after randomization to assess symptoms and adherence; were interviewed at 6-month intervals to assess clinical outcomes, including breast cancer; and had annual clinic visits. Mammograms and breast examinations were required annually, and study medications were withheld until their completion and medical clearance of any findings either suspicious or highly suggestive of breast cancer. Decisions regarding workup of breast findings, including recommendations for further imaging studies or biopsy, were directed primarily by community physicians based on clinical findings.

Self-reported breast cancer cases were verified initially by centrally trained WHI physician adjudicators who reviewed medical records and pathologic reports (available for 98.2% of the participants).[12] Breast cancer cases included invasive breast cancer and ductal carcinoma in situ. Final adjudication and coding of histologic findings and receptor status (positive or negative per pathologic report) were performed at the WHI Clinical Coordinating Center using the Surveillance Epidemiology and End Results coding system.[13]

TERMINATION OF THE STUDY

The intervention was stopped when the WHI Data Safety and Monitoring Board determined that more risks than benefits were associated with the use of conjugated equine estrogens plus medroxyprogesterone acetate.[1] Women who were still adherent were instructed to immediately stop taking all study medications; the study results were mailed to all the participants on the date that the trial results were published. Participants continued to be followed up for clinical outcomes at 6-month intervals and were strongly encouraged to continue their annual mammogram screening. After the intervention phase of the study, mammogram findings continued to be collected and recorded at the clinical centers.

STATISTICAL ANALYSES

Baseline characteristics of the participants in the randomization groups were compared using χ^2 statistics or *t* tests. A mammogram result was considered true positive if invasive breast cancer or ductal carcinoma in situ was diagnosed within 12 months of the mammogram. The diagnostic accuracy of mammograms for detecting breast cancer was determined by comparing estimates of their sensitivity, specificity, and positive and negative predictive values. Specificity was defined as the proportion of mammograms without findings either suspicious or highly suggestive of malignancy in women without breast cancer. Sensitivity was defined as the proportion of mammograms with findings either suspicious or highly suggestive of malignancy in women with breast cancer. An overall estimate of accuracy was defined as the maximum of the true-positive and true-negative estimates.

The discriminatory accuracy of mammography in the 2 randomization groups was compared using receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC).[14] The ROC curves plot the true-positive rate (sensitivity) vs the false-positive rate (1–specificity) at a continuum of thresholds; a participant is predicted to have breast cancer if the estimated probability of breast cancer exceeds a particular threshold. An ROC curve that corresponds to a fair–coin toss classifier (a nonpredictive model) is a straight line connecting the coordinates (0, 0) to (1, 1) and has an AUC of 0.50. An ROC curve that corresponds to a perfect classifier is a pair of vertical and horizontal lines connecting the coordinates (0, 0) to (0, 1) to (1, 1) and has an AUC of 1.00. Confidence intervals (CIs) for the AUC were computed using the bootstrap method.

The ROC curves are presented for 3 distinct periods (years 1-2, 3-4, and 5+ after randomization). A generalized estimating equation was used to take into account the correlation between multiple mammogram results for a participant in each period. Testing was performed within the generalized estimating equation model to assess the interaction between randomization group and the mammography result. Statistical significance was determined for each period after categorizing the mammogram result as abnormal or normal.

Using the semiannual reports of breast biopsies, the time to each woman's first biopsy was determined, and the biopsy frequency was compared between randomization groups using a log-rank statistic. A breast biopsy result was considered to be true positive if invasive breast cancer was diagnosed during the 6-month interval when a biopsy was reported or within 2 months after the interval when the biopsy was reported.

To assess the potential effects of nonadherence, adherence-adjusted analyses comparing ROC curves and concordance statistics were conducted by censoring follow-up for women 6 months after they became nonadherent (defined as consuming <80% of the study pills or starting nonstudy hormone therapy during the most recent study interval).

The persistence of abnormal mammogram findings after hormone therapy discontinuation was evaluated after a median of 2.4 years of follow-up in the group of women still adherent to

Table 1. Demographic Characteristics of 16 608 Postmenopausal Women by Randomization Group

Characteristic	Participants, No. (%)[a] CEE + MPA Group (n = 8506)	Placebo Group (n = 8102)
Age group at screening, y		
50-59	2839 (33.4)	2683 (33.1)
60-69	3853 (45.3)	3657 (45.1)
70-79	1814 (21.3)	1762 (21.7)
Ethnicity		
White	7140 (83.9)	6805 (84.0)
Black	549 (6.5)	575 (7.1)
Hispanic	472 (5.6)	416 (5.1)
American Indian	26 (0.3)	30 (0.4)
Asian/Pacific Islander	194 (2.3)	169 (2.1)
Unknown	125 (1.5)	107 (1.3)
Educational level		
0-8 y	202 (2.4)	177 (2.2)
Some high school	373 (4.4)	362 (4.5)
High school/GED diploma	1614 (19.1)	1608 (20.0)
School after high school	3356 (39.7)	3059 (38.0)
College degree or higher	2915 (34.5)	2838 (35.3)
Age at menarche, y		
≤11	1725 (20.3)	1670 (20.7)
12-13	4578 (54.0)	4334 (53.7)
≥14	2182 (25.7)	2061 (25.6)
Body mass index[b]		
Underweight or normal weight (<25)	2579 (30.4)	2479 (30.8)
Overweight (25-29.9)	2992 (35.3)	2834 (35.2)
Obese (≥30)	2899 (34.2)	2737 (34.0)
Physical activity, kcal/wk per kg		
0	1427 (18.6)	1356 (17.9)
0.1-3.5	1501 (19.6)	1519 (20.0)
3.6-8.0	1355 (17.7)	1352 (17.8)
8.1-16.5	1648 (21.5)	1634 (21.5)
>16.5	1739 (22.7)	1735 (22.8)
Alcohol intake		
Nondrinker	972 (11.5)	938 (11.7)
Past drinker	1427 (16.9)	1380 (17.2)
<1 drink/mo	1174 (13.9)	1117 (13.9)
<1 drink/wk	1710 (20.3)	1513 (18.8)
1 to <7 drinks/wk	2113 (25.0)	2038 (25.4)
≥7 drinks/wk	1047 (12.4)	1049 (13.1)
Smoking		
Never smoked	4178 (49.6)	3999 (50.0)
Past smoker	3362 (39.9)	3157 (39.5)
Current smoker	880 (10.5)	838 (10.5)
Gail risk score,[c] 5 y		
<1.25	2806 (33.0)	2717 (33.5)
1.25-1.74	2859 (33.6)	2703 (33.4)
≥1.75	2841 (33.4)	2682 (33.1)
No. of term pregnancies		
Never pregnant	655 (7.7)	633 (7.9)
Never had term pregnancy	201 (2.4)	199 (2.5)
1	690 (8.2)	661 (8.2)
2	1908 (22.5)	1708 (21.2)
3	2020 (23.9)	1952 (24.2)
4	1416 (16.7)	1412 (17.5)
≥5	1575 (18.6)	1500 (18.6)
Age at first birth, y		
Never pregnant/no term pregnancy	860 (11.2)	833 (11.5)
<20	1124 (14.6)	1117 (15.4)
20-29	4996 (64.8)	4698 (64.6)
≥30	727 (9.4)	624 (8.6)
No. of children breastfed		
0	3813 (45.3)	3669 (45.7)
1-2	2606 (31.0)	2485 (31.0)
≥3	2001 (23.8)	1867 (23.3)
No. of first-degree relatives with breast cancer		
0	6954 (87.3)	6676 (88.2)
1	927 (11.6)	816 (10.8)
≥2	82 (1.0)	79 (1.0)
Benign breast disease		
No	6340 (83.5)	6278 (83.2)
Yes, 1 biopsy	967 (12.7)	981 (13.0)
Yes, ≥2 biopsies	290 (3.8)	288 (3.8)
Menopausal hormone therapy status		
Never used	6277 (73.8)	6020 (74.3)
Past user	1671 (19.7)	1588 (19.6)
Current user	554 (6.5)	491 (6.1)

Abbreviations: CEE + MPA, conjugated equine estrogens plus medroxyprogesterone acetate; GED, general educational development.
[a] Numbers may not sum to column totals because of missing data. Percentages may not sum to 100 because of rounding.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] See the National Cancer Institute Web site (http://www.cancer.gov/bcrisktool).

their assigned study medications (combined hormones or placebo) when the intervention was stopped. Women who had stopped study medication use but then restarted before the trial stop date were included in the analysis. The percentage of women with mammograms with abnormalities was serially estimated in intervals after study medication discontinuation, and the frequency of mammograms with abnormalities was compared between randomization groups.

RESULTS

Women participating in this randomized clinical trial were postmenopausal and had a median age of 63 years, with 33.2% of women entering between 50 and 59 years of age. Breast cancer risk factors and factors associated with abnormal mammogram findings were balanced between the hormone and placebo groups (**Table 1**).

As previously reported,[2] 199 invasive breast cancers were diagnosed in the conjugated equine estrogens plus medroxyprogesterone acetate group compared with 150 in the placebo group (hazard ratio, 1.24; 95% CI, 1.01-1.54; $P = .003$). In addition, there was a substantial effect of combined hormone therapy on the incidence of cancers diagnosed at stage IIB or greater, which includes tumors greater than 5 cm or 2 to 5 cm with metastases to auxiliary lymph nodes (hazard ratio, 3.30; 95% CI, 1.43-7.65; $P = .003$).

There were significantly more mammograms with abnormalities in the conjugated equine estrogens plus medroxyprogesterone acetate group vs the placebo group (35.0% vs 23.0%; $P < .001$). Women in the combined hor-

mone group had an approximately 4% greater risk of having a mammogram with abnormalities after 1 year and an approximately 11% greater risk after 5 years ($P<.001$) (**Figure 1**A). The year-by-year performance characteristics of mammograms by randomization group are outlined in **Table 2**. The specificity and the negative predictive value of mammograms were only slightly lower in the conjugated equine estrogens plus medroxyprogesterone acetate group than in the placebo group. However, the sensitivity and the positive predictive value of mammograms were compromised by combined hormone therapy.

The ROC curves and AUC statistics were used to compare mammogram diagnostic performance by study period and randomization group (**Figure 2**). After 1 year, mammograms were significantly poorer in distinguishing cancer in women in the hormone group vs the placebo group (ROC AUC of 0.88 vs 0.80; $P=.02$). For women in the placebo group, the ROC AUCs were 0.90, 0.94, and 0.94 for mammograms performed in years 1 and 2, 3 and 4, and 5+, respectively. For women in the hormone group, the ROC AUCs were 0.85 ($P=.02$), 0.84 ($P=.001$), and 0.92 ($P=.15$) for mammograms performed in years 1 and 2, 3 and 4, and 5+, respectively, with *P* values comparing abnormal vs normal mammogram findings in the estrogen plus progestin group vs the placebo group (Figure 2). In adherence-adjusted analyses that censored follow-up 6 months after women became nonadherent, mammogram diagnostic performance continued to be significantly worse in the hormone group throughout the study ($P=.01$, $P=.001$, and $P=.002$ in years 1-2, 3-4, and 5+, respectively).

The cumulative frequency of participants with clinically indicated breast biopsies by study period and randomization group is outlined in Figure 1B. The mean (SD) time to first biopsy was significantly shorter (3.4 [1.89] years vs 3.6 [1.8] years; $P<.001$) and the cumulative percentage of women with a biopsy was significantly greater for women in the conjugated equine estrogens plus medroxyprogesterone acetate group compared with the placebo group (10.0% vs 6.1%; $P<.001$). Although the number of breast cancers was increased with conjugated equine estrogen plus medroxyprogesterone acetate use and the cancers were found at higher stages, biopsies performed in the hormone group less frequently diagnosed breast cancer. Of 1220 biopsies in the combined hormone group, breast cancer was diagnosed by 180 (14.8%), whereas, of 672 biopsies in the placebo group, breast cancer was diagnosed by 132 (19.6%) ($P=.006$).

In younger postmenopausal women (age 50-59 years), findings were similar to those of the overall group. The time to first biopsy was significantly shorter and the percentage with biopsy after 5 years was significantly greater for younger women in the hormone group vs the placebo group ($P<.001$ for both). For mammograms with abnormalities, there was a 3% higher risk after 1 year and a 9% greater risk after 5 years ($P<.001$) for women in the hormone group.

When the trial intervention ended, 10 130 women were still adherent to the study medication regimen. After the discontinuation of study medication, there continued to

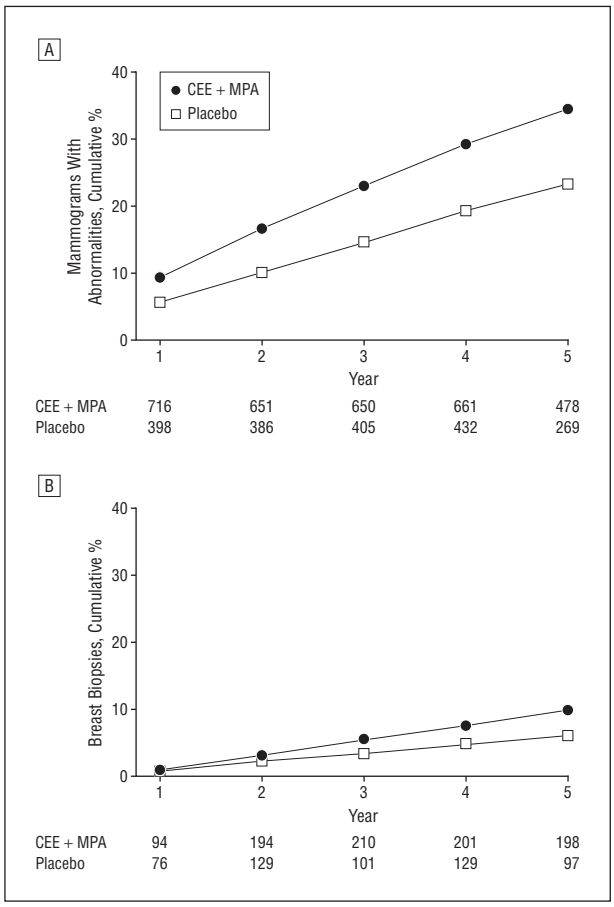

Figure 1. Initial reports of mammograms with abnormalities (A) and breast biopsies (B) by study year and randomization group. Women in the conjugated equine estrogens plus medroxyprogesterone acetate (CEE + MPA) group had an approximately 4% greater risk of mammogram abnormalities after 1 year and a 12% greater risk after 5 years ($P<.001$). Women in the CEE + MPA group had an approximately 4% greater risk of having a biopsy after 5 years ($P<.001$). The number of participants with abnormal mammogram findings (A) or a breast biopsy (B) at each year is given at the bottom of each graph. Error bars represent SE and are plotted at each data point but may not be visible because of their small size relative to the data point.

be more mammograms with abnormalities in women who had been taking combined hormone therapy. Although the effect lessened across time, significantly more mammograms with abnormalities continued to be seen in the combined hormone therapy group 1 year after therapy ended (**Figure 3**).

COMMENT

In the WHI randomized clinical trial, the combined use of conjugated equine estrogens plus medroxyprogesterone acetate increased the number of invasive breast cancers, and they were diagnosed at more advanced stages.[2,15] Combined hormone therapy also increased the frequency of mammograms with abnormalities, increased the frequency of clinically indicated breast biopsies, and compromised the diagnostic performance of both. The adverse effect of combined hormone therapy on the frequency of mammograms with abnormalities modulated but remained significant for at least 12 months after hormone therapy discontinuation.

Table 2. Performance Characteristics of Mammography[a] by Study Year and Randomization Group[b]

Characteristic	Year 1		Year 2		Year 3		Year 4		Year 5		Total	
	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo
Mammograms, No.[c]	7644	7304	7470	7060	7282	6902	6898	6548	4918	4588	38 221	35 699
Sensitivity, %	52.2	56.8	58.6	64.3	37.5	60.0	63.5	70.4	54.1	76.9	56.7	65.0
Specificity, %	99.0	99.4	99.1	99.5	99.0	99.5	98.9	99.3	98.8	99.7	99.0	99.4
Positive predictive value, %	13.6	31.8	19.5	32.1	16.5	36.2	31.4	28.8	25.6	40.0	23.2	33.2
Negative predictive value, %	99.9	99.8	99.8	99.9	99.7	99.8	99.7	99.9	99.6	99.9	99.8	99.8
Accuracy, %	98.9	99.2	98.9	99.3	98.6	99.3	98.7	99.2	98.5	99.6	98.7	99.3

Abbreviation: CEE + MPA, conjugated equine estrogens plus medroxyprogesterone acetate.
[a] Evaluating the performance of mammograms interpreted as either suspicious or highly suggestive of malignancy.
[b] Percentages are relative to predicting any invasive breast cancer or ductal carcinoma in situ within 1 year.
[c] The sum of the row numbers is less than that of the totals because some participants had mammograms beyond year 5 that are not included in the table.

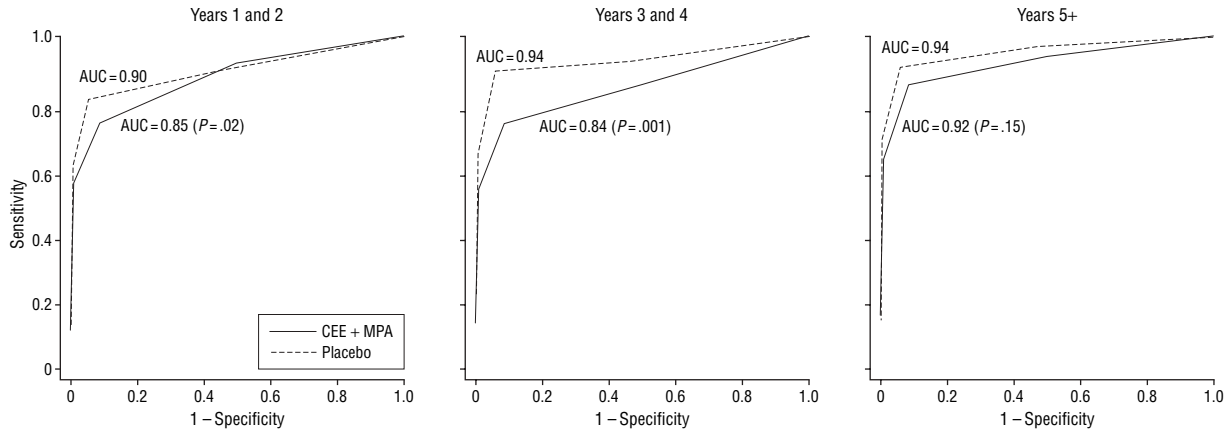

Figure 2. Diagnostic performance for mammograms by study period and randomization group was assessed using receiver operating characteristic (ROC) curves and nested area under the curve (AUC) statistics. The *P* values compare abnormal vs normal mammogram findings in the conjugated equine estrogens plus medroxyprogesterone acetate (CEE + MPA) group vs the placebo group.

Previous observational studies on the effect of menopausal hormone therapy on mammogram diagnostic performance have produced mixed results, with older studies being potentially compromised by lack of adjustment for major confounding factors.[5] A recent cohort study[16] of 113 310 women reported that the sensitivity of mammographic screening was reduced in menopausal hormone therapy users. In another cohort of 87 967 postmenopausal women, current users of combined estrogen plus progestin had more false-positive results than never users (hazard ratio, 1.80; 95% CI, 1.62-2.01).[17] Conversely, Vernet et al[7] described only a "clinically irrelevant" effect of hormone therapy on the accuracy of screening mammography, and hormone therapy was not found to be an independent predictor of accuracy in a cohort of 329 495 women.[6] The present findings from a randomized clinical trial, by controlling for user selection bias and also reporting on the time course of exposure, may provide a more quantitative assessment of this issue. In this trial, mammogram specificity was only slightly lower in the 2 randomization groups, but the sensitivity of mammograms for breast cancer detection was substantially lower in the hormone therapy group. To our knowledge, this is the first comprehensive description of the time course of the effect of conjugated equine estrogens plus medroxyprogesterone acetate on the diagnostic performance of mammography and breast biopsy in a randomized clinical trial setting.

Largely anecdotal experiences[18,19] have suggested that any adverse effect of hormone therapy on mammogram findings can be abrogated by discontinuing hormones a few weeks before imaging. Findings from the Million Women's Study observational cohort challenged that suggestion.[17] The present findings, based on 10 130 women instructed to stop study medication use at one time, indicate that significantly more mammograms with abnormalities continued to be seen for at least a year after the discontinuation of hormone therapy. Given these findings, the practice of discontinuing hormone therapy for a short interval before mammography is unlikely to have an effect on either mammogram findings or breast cancer diagnoses.

Differential hormone therapy use after termination of the intervention could potentially have affected these findings if more women in the hormone group continued or restarted nonprotocol hormones. However, in a formal study,[20] when participants in this trial were contacted 8

to 12 months after the intervention ended, nonprotocol prescription hormone use was reported by only 4.3% in the former hormone therapy group and 1.2% in the placebo group.

Estrogen plus progestin use significantly increases breast density,[21,22] a recognized breast cancer risk factor,[23,24] and several observational studies[6,19,25] have suggested that higher breast density is associated with diagnostic delay. Breast density determination was not a component of the present study. However, in an ancillary study involving a subset of participants, McTiernan et al[22] reported that, although use of conjugated equine estrogens plus medroxyprogesterone acetate significantly increased mammograms with abnormalities and breast density, these 2 variables were not significantly associated. The precise role of breast density change in mediating hormone therapy effects on mammographic diagnostic performance remains to be determined.

Previous observational studies of the effects of hormone therapy on mammography findings have not commonly differentiated the effects of estrogen plus progestin from those of estrogen alone. Although we evaluated only 1 dose and schedule of hormone therapy, the present findings likely apply to only combined hormone therapy. In the WHI randomized trial evaluating conjugated equine estrogen therapy in women who had undergone a hysterectomy, there were more mammograms with abnormalities in the group that received conjugated equine estrogens alone but no increase in mammograms with abnormalities either suspicious or highly suggestive of malignancy.[26]

The increase in breast cancer risk, mammograms with abnormalities, and breast biopsies with conjugated equine estrogen plus medroxyprogesterone acetate use has implications for women taking, or considering taking, such therapy. Although a trend toward perhaps lower coronary heart disease risk has been described in women who initiated hormone therapy closer to menopause,[27] the adverse effect of conjugated equine estrogens plus medroxyprogesterone acetate on breast cancer detection and risk was seen even in younger women. In addition, there may be emotional and economic costs associated with abnormal mammogram[28,29] and breast biopsy[30,31] findings regardless of the ultimate clinical outcome. Currently, there is no established approach to mitigate the diagnostic problems presented by combined hormone therapy. Whether digital mammography (more accurate than mammography in women with dense breasts),[32] magnetic resonance imaging (more accurate than mammography in high-risk women),[33] computer-assisted diagnosis,[34] or ultrasound[35] can improve the breast cancer diagnostic performance of mammograms in women using estrogen plus progestin remains to be determined.

In summary, women using combined hormone therapy experience more mammograms with abnormalities, more breast biopsies, and more breast cancers diagnosed at a higher stage than women not using hormone therapy. Combined hormone therapy also compromises the diagnostic performance of mammograms and breast biopsies. The higher frequency of mammograms with abnormalities continued even after the discontinuation of hormone therapy. The usable, quantitative estimates of the adverse effect of conjugated equine estrogens plus medroxyprogesterone acetate on breast cancer detection provided in this article should be incorporated into risk-benefit discussions with women considering even short-term use. Clinical strategies to abrogate these problems have not been established but represent a research priority.

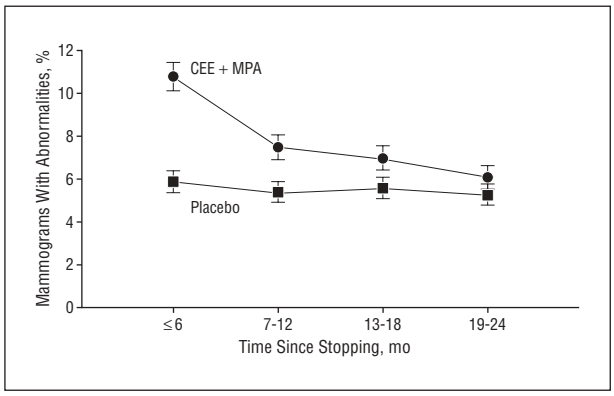

Figure 3. Mammographic findings after the trial intervention ended by interval and randomization group. Women in the conjugated equine estrogens plus medroxyprogesterone acetate (CEE + MPA) group compared with the placebo group had significantly more mammograms with abnormalities through year 1 but not thereafter ($P<.001$, $P=.005$, $P=.07$, and $P=.29$ at 6, 12, 18, and 24 months, respectively). Error bars represent SE.

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Additional Information: Consult the WHI Website (http://www.whiscience.org) for the exact wording of the WHI trials.

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Correction

Misspelled Author Surname. In the article titled "Estrogen Plus Progestin and Breast Cancer Detection by Means of Mammography and Breast Biopsy," published in the February 25th issue of the *Archives* (2008;168[4]: 370-377) the sixth author's surname was misspelled. It should have read: Mary Ann Gilligan, MD, MPH, in the byline on page 370, the "Author Affiliations" section on page 375, right-hand column, and the "Analysis and interpretation of data" and "Critical revision of the manuscript for important intellectual content" subsections of the "Authors Contributions" section on page 375, right-hand column.