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Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials

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IMPORTANCE The influence of menopausal hormone therapy on breast cancer remains unsettled with discordant findings from observational studies and randomized clinical trials.

OBJECTIVE To assess the association of prior randomized use of estrogen plus progestin or prior randomized use of estrogen alone with breast cancer incidence and mortality in the Women's Health Initiative clinical trials.

DESIGN, SETTING, AND PARTICIPANTS Long-term follow-up of 2 placebo-controlled randomized clinical trials that involved 27 347 postmenopausal women aged 50 through 79 years with no prior breast cancer and negative baseline screening mammogram. Women were enrolled at 40 US centers from 1993 to 1998 with follow-up through December 31, 2017.

INTERVENTIONS In the trial involving 16 608 women with a uterus, 8506 were randomized to receive 0.625 mg/d of conjugated equine estrogen (CEE) plus 2.5 mg/d of medroxyprogesterone acetate (MPA) and 8102, placebo. In the trial involving 10 739 women with prior hysterectomy, 5310 were randomized to receive 0.625 mg/d of CEE alone and 5429, placebo. The CEE-plus-MPA trial was stopped in 2002 after 5.6 years' median intervention duration, and the CEE-only trial was stopped in 2004 after 7.2 years' median intervention duration.

MAIN OUTCOMES AND MEASURES The primary outcome was breast cancer incidence (protocol prespecified primary monitoring outcome for harm) and secondary outcomes were deaths from breast cancer and deaths after breast cancer.

RESULTS Among 27 347 postmenopausal women who were randomized in both trials (baseline mean [SD] age, 63.4 years [7.2 years]), after more than 20 years of median cumulative follow-up, mortality information was available for more than 98%. CEE alone compared with placebo among 10 739 women with a prior hysterectomy was associated with statistically significantly lower breast cancer incidence with 238 cases (annualized rate, 0.30%) vs 296 cases (annualized rate, 0.37%; hazard ratio [HR], 0.78; 95% CI, 0.65-0.93; $P = .005$) and was associated with statistically significantly lower breast cancer mortality with 30 deaths (annualized mortality rate, 0.031%) vs 46 deaths (annualized mortality rate, 0.046%; HR, 0.60; 95% CI, 0.37-0.97; $P = .04$). In contrast, CEE plus MPA compared with placebo among 16 608 women with a uterus was associated with statistically significantly higher breast cancer incidence with 584 cases (annualized rate, 0.45%) vs 447 cases (annualized rate, 0.36%; HR, 1.28; 95% CI, 1.13-1.45; $P < .001$) and no significant difference in breast cancer mortality with 71 deaths (annualized mortality rate, 0.045%) vs 53 deaths (annualized mortality rate, 0.035%; HR, 1.35; 95% CI, 0.94-1.95; $P = .11$).

CONCLUSIONS AND RELEVANCE In this long-term follow-up study of 2 randomized trials, prior randomized use of CEE alone, compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality, whereas prior randomized use of CEE plus MPA, compared with placebo, among women who had an intact uterus, was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality.

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Supplemental content

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Conjugated equine estrogen was introduced in US clinical practice in 1942,[1] but the influence of menopausal hormone therapy on breast cancer incidence and breast cancer mortality remains controversial, with discordant findings reported from prospective observational studies[2-4] compared with randomized clinical trials.[5-8]

In a series of reports from the Women's Health Initiative (WHI) randomized hormone therapy trials,[5,7,9,10] complex patterns of the effect of hormone therapy on breast cancer risk and outcome have emerged. In the trial that evaluated conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA), the increased breast cancer risk observed during a median of 5.6 years of the intervention was followed by a modest attenuation of this elevated risk,[8,9] but a sustained adverse effect on breast cancer risk was observed through 13 years of cumulative follow-up.[8,11] In the CEE-alone trial, breast cancer risk reduction seen with a median of 7.2 years of the intervention was sustained through 13 years of cumulative follow-up.[11]

Findings regarding hormone therapy and breast cancer from recently reported observational studies stand in contrast to the findings from these randomized clinical trials, especially with respect to use of estrogen alone. In a meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer, both estrogen plus progestin and estrogen alone were associated with statistically significantly higher breast cancer risk.[2] In the Million Women Study, both estrogen plus progestin and estrogen alone were associated with statistically significantly higher risk of breast cancer mortality.[4]

The objective of this study was to report updated findings regarding breast cancer incidence and breast cancer mortality over 20 years of follow-up of the randomized trials that evaluated CEE plus MPA in postmenopausal women with an intact uterus and CEE-alone in postmenopausal women with prior hysterectomy.

Key Points

Question What is the association of estrogen plus progestin or estrogen alone with breast cancer incidence and breast cancer mortality?

Findings In long-term follow up of 2 placebo-controlled randomized clinical trials involving 27 347 postmenopausal women, prior randomized use of conjugated equine estrogen (CEE), compared with placebo, among women with prior hysterectomy was significantly associated with lower risk of breast cancer (annualized incidence, 0.30% vs 0.37%; hazard ratio [HR], 0.78); and breast cancer mortality (annualized mortality, 0.031% vs 0.046%; HR, 0.60), whereas prior randomized use of CEE plus medroxyprogesterone acetate (MPA), compared with placebo, among women with an intact uterus, was significantly associated with higher risk of breast cancer (annualized incidence, 0.45% vs 0.36%; HR, 1.28) and no significant difference in breast cancer mortality (annualized mortality, 0.045% vs 0.035%; HR, 1.35).

Meaning Among postmenopausal women, prior randomized use of CEE in women with prior hysterectomy was significantly associated with a lower risk of breast cancer incidence and mortality, whereas prior randomized use of CEE plus MPA in women with an intact uterus was significantly associated with a higher risk of breast cancer incidence and no significant difference in breast cancer mortality.

Methods

Study Design

The design and implementation of the 2 hormone therapy trials have been described.[12,13] Postmenopausal women were enrolled from 1993 to 1998 at 40 US centers. All participants gave written informed consent. The study design was approved by the institutional review boards at participating centers. All participants provided consent for survival linkage at baseline and these linkage studies have been approved by institutional review boards. Consent withdrawals refer to women who declined further active follow-up for clinical outcomes (mail and phone contact) by the WHI, but these did not restrict mortality follow-up. The full study protocol is available in Supplement 1.

Briefly, eligible women were postmenopausal, were aged 50 through 79 years, had provided written informed consent, and had baseline mammogram not suggestive of cancer. Women with prior breast cancer or anticipated survival of less than 3 years were excluded. Information on demographics, medical history, breast cancer risk factors, and lifestyle were collected with self-report questionnaires. Information on past hormone therapy use was obtained by trained interviewers using structured questionnaires. Given the limited information regarding hormone therapy influence on chronic disease among women of ethnic minorities,[13,14] race/ethnicity data were collected with race/ethnicity determined by participant self-report against fixed categories.

Yearly mammograms and clinical breast examinations were required annually during the intervention period and study drugs were held until evidence of screening completion. Annual mammography was encouraged after the intervention, and information on frequency was collected.

Participants were contacted at 6-month intervals regarding clinical outcomes through 2005, and then annually. Breast cancers were verified by centrally trained physician adjudicators at local clinical centers after medical record review. Final adjudication and coding was performed at the Clinical Coordinating Center. Deaths were documented with death certificates and medical record review with cause of death determined centrally by physician adjudicators. Information on deaths from breast cancer and after breast cancer, were enhanced by National Death Index (NDI) queries that were conducted at 10 time points through December 31, 2017. The NDI capture 98% of US deaths and provides breast cancer mortality information regardless of reconsent status.[15]

Both trials were stopped early after median intervention periods of 5.6 years in the CEE-plus-MPA trial and 7.2 years in the CEE- alone trial. Participants were informed by mail to immediately stop study pills coincident with publication of study findings (February 29, 2004, for CEE alone and July 7, 2002, for CEE plus MPA). Surveys conducted 8 to 12 months after the intervention found limited nonprotocol

hormone therapy use: 4.3% in the CEE-plus-MPA group[16] and 4.5% in the CEE-alone group.[17] Subsequent assessments, collected annually between 2005 and 2010, found less than 4% of women reported personal use of hormone therapy during the first extension phase, and personal use of hormone therapy, collected once (2011-2012) during the second extension, remained low (<4%).

Current analyses report on cumulative follow-up through December 31, 2017. For breast cancer incidence, follow-up after March 31, 2005, was based on surviving participants who provided additional written informed consent for postintervention follow-up through September 30, 2010, and over an open-ended subsequent period. More than 80% of surviving participants provided written consent on each occasion (eFigure 1 in Supplement 2). Characteristics of participants consenting for ongoing follow-up by randomization group are outlined in the eTables 1 to 4 in Supplement 2.

Outcomes

For both trials, the primary protocol-defined monitoring outcome for benefit was coronary heart disease and the primary monitoring outcome for harm was invasive breast cancer; thus, breast cancer incidence was a primary study outcome. Secondary outcomes for the current analyses include deaths from breast cancer (breast cancer followed by death attributed to the breast cancer) and death after breast cancer (breast cancer followed by death from any cause) ascertained for all participants measured from randomization.

Statistical Methods

Randomization was conducted at the Clinical Coordinating Center by permuted-block algorithm, with random block sizes of 5, 10, or 15, stratified by clinical center and age group[18] and implemented at local clinical centers using a barcode dispensing procedure for staff and participant blinding. For each trial, analyses included all participants according to their randomization assignment, using time-to-event methods. Participants contributed follow-up time until the end of the intervention period (or December 31, 2017, for cumulative follow-up), date of their first invasive breast cancer, death, or loss to follow-up whichever came first. Hazard ratios (HRs) were estimated using Cox regression models with baseline hazard functions stratified by age group, randomization status in the WHI dietary modification trial, prior hormone therapy use, race/ethnicity, randomization year, and study period (time-dependent).

Statistical tests were based on a 2-sided stratified score (log-rank) test, with nominal (unadjusted) *P* values ≤.05 considered statistically significant. Inferences on subgroup analyses and tumor characteristics rely on tests for interaction. Participants with missing values were omitted from corresponding analysis (the number missing is noted in the Figure legends). Because of the potential for type I error due to multiple comparisons, findings from sequential analyses, subgroup analyses, and sensitivity analyses should be interpreted as exploratory.

The proportionality assumption for mortality outcomes was tested in each trial. Previous analyses detected significant temporal incidence variation in the CEE-plus-MPA trial[8,9] and nonsignificant variation for the CEE-alone trial.[7,8] Therefore, temporal associations between hormone therapy and incidence were estimated by cumulative HR plots. Specifically, cumulative HRs (95% CIs) were calculated under proportional hazards assumptions and plotted as a function of increasing cumulative follow-up time from randomization.[19,20] In addition, period specific HRs (95% CIs) were overlaid for the intervention period, postintervention period (through planned closeout; extension I) and late postintervention period (extension II). The potential for type I error due to sequential analyses is partially offset by plotting annually computed stratified score (log-rank) statistics to illustrate that cumulative findings are not a statistical aberration related to the specific length of follow-up used in these analyses.[21] Analyses based on breast cancer subgroups were not prespecified and are exploratory in nature.

Sensitivity analyses were conducted to examine potential sources of bias. To address the potential effect of censoring those not consenting for extended follow-up, consent rates by randomization assignment were compared (eTables 1 to 4) and adjusted HR analysis using inverse-probability weighting were conducted using pertinent methods.[6] Screening behavior during extension II was examined by comparison of mammography utilization rates and adjusted HR analysis that included mammogram use as a time-dependent variable.

Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc) and R software version 3.4 (R Foundation for Statistical Computing, http://www.r-project.org/; R-packages survival and rmeta).

Results

A total of 27 347 postmenopausal women enrolled in the 2 hormone therapy trials. Women with a uterus were randomized to receive 0.625 mg/d of CEE and 2.5 mg/d of MPA (n = 8506) or placebo (n = 8102). Women with prior hysterectomy were randomized to receive 0.625 mg/d of CEE alone (n = 5310) or placebo (n = 5429). Baseline characteristics were balanced between randomization groups in both hormone therapy trials (**Table**). Although participants were similar in age, CEE-alone trial participants were more likely to be Black, obese, report prior hormone therapy use, and have had bilateral oophorectomy than women in the CEE-plus-MPA trial. Participant flow in both trials is outlined in eFigure 1 in Supplement 2 after a median of 20.3 years (interquartile range [IQR], 17.1-21.4 years) of cumulative median follow-up through December 31, 2017, when mortality was more than 98% complete, based on NDI evaluation.[15] Follow-up for breast cancer incidence depended on participant consent and therefore had shorter cumulative median follow-up of 16.2 years (IQR, 9.1-20.8 years) for the CEE-alone trial and 18.9 years (IQR, 10.5-21.0 years) for the CEE-plus-MPA trial. Participants who provided consent to extended follow-up beyond September 30, 2010, had cumulative median follow-up of 20.7 years (IQR, 19.7-21.7); comparison of consent rates by randomization group and

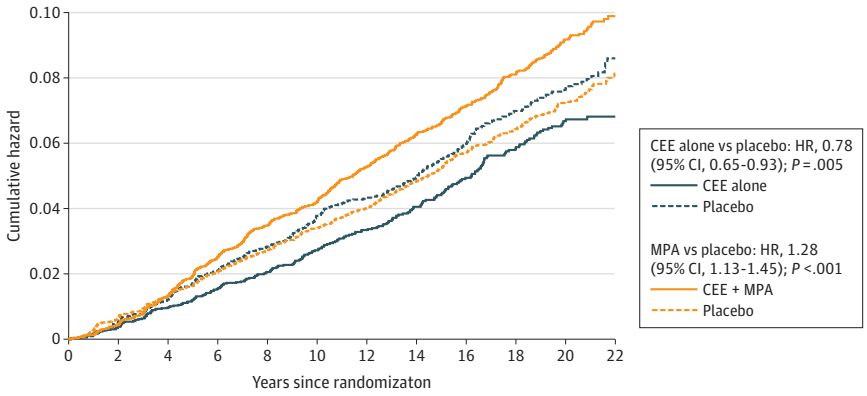
Table. Baseline Characteristics of Participants in the Women's Health Initiative Trials of Menopausal Hormone Therapy

Characteristic	No. (%) of women			
	CEE-alone trial		CEE + MPA trial	
	CEE alone (n = 5310)	Placebo (n = 5429)	CEE+MPA (n = 8506)	Placebo (n = 8102)
Age at screening, mean (SD), y	63.6 (7.3)	63.6 (7.3)	63.2 (7.1)	63.3 (7.1)
Age group at screening, y				
50-59	1639 (30.9)	1674 (30.8)	2837 (33.4)	2683 (33.1)
60-69	2386 (44.9)	2465 (45.4)	3854 (45.3)	3655 (45.1)
70-79	1285 (24.2)	1290 (23.8)	1815 (21.3)	1764 (21.8)
Race/ethnicity				
White	4009 (75.5)	4075 (75.1)	7141 (84.0)	6805 (84.0)
Black	781 (14.7)	835 (15.4)	548 (6.4)	574 (7.1)
Hispanic	319 (6.0)	332 (6.1)	471 (5.5)	415 (5.1)
American Indian	41 (0.8)	34 (0.6)	25 (0.3)	30 (0.4)
Asian/Pacific Islander	86 (1.6)	78 (1.4)	194 (2.3)	169 (2.1)
Unknown	74 (1.4)	75 (1.4)	127 (1.5)	109 (1.3)
College degree or higher	1217 (23.2)	1327 (24.6)	2915 (34.4)	2839 (35.3)
Body mass index[a]				
<25	1110 (21.0)	1096 (20.3)	2579 (30.4)	2479 (30.8)
25-29	1798 (34.0)	1915 (35.5)	2992 (35.3)	2835 (35.2)
≥30	2375 (45.0)	2385 (44.2)	2899 (34.2)	2737 (34.0)
Smoking				
Never	2723 (51.9)	2705 (50.4)	4178 (49.6)	3999 (50.0)
Past	1986 (37.8)	2090 (38.9)	3362 (39.9)	3157 (39.5)
Current	542 (10.3)	571 (10.6)	880 (10.5)	838 (10.5)
Age at menarche, y				
≤11	1215 (23.0)	1280 (23.7)	1725 (20.3)	1670 (20.7)
12-13	2805 (53.1)	2853 (52.8)	4578 (54.0)	4334 (53.7)
≥14	1259 (23.8)	1274 (23.6)	2182 (25.7)	2061 (25.6)
Age at first birth, y				
Never pregnant or no term pregnancies	491 (10.4)	463 (9.5)	860 (11.2)	833 (11.5)
<20	1193 (25.2)	1234 (25.3)	1124 (14.6)	1117 (15.4)
20-29	2846 (60.0)	2914 (59.8)	4996 (64.8)	4698 (64.6)
≥30	210 (4.4)	260 (5.3)	727 (9.4)	624 (8.6)
Benign breast disease				
No	3894 (80.8)	3787 (78.4)	6340 (83.6)	6278 (83.3)
Yes, 1 biopsy	678 (14.1)	748 (15.5)	956 (12.6)	972 (12.9)
Yes, ≥2 biopsies	250 (5.2)	295 (6.1)	290 (3.8)	288 (3.8)
First-degree female relatives with breast cancer	696 (14.2)	685 (13.6)	1009 (12.7)	895 (11.8)
Gail 5-y risk score				
<1.25	2129 (40.1)	2149 (39.6)	2806 (33.0)	2717 (33.5)
1.25-<1.75	1620 (30.5)	1688 (31.1)	2859 (33.6)	2703 (33.4)
≥1.75	1561 (29.4)	1592 (29.3)	2841 (33.4)	2682 (33.1)
Bilateral oophorectomy	1938 (39.5)	2111 (42.0)	29 (0.3)	24 (0.3)
Years since menopause				
<10	827 (18.4)	817 (17.6)	2780 (36.2)	2711 (36.1)
10-<20	1438 (32.0)	1500 (32.4)	3049 (39.7)	2992 (39.9)
≥20	2230 (49.6)	2319 (50.0)	1850 (24.1)	1805 (24.0)
Hormone therapy use status				
Never	2769 (52.2)	2769 (51.0)	6277 (73.8)	6022 (74.4)
Past	1871 (35.2)	1947 (35.9)	1671 (19.7)	1587 (19.6)
Current[b]	669 (12.6)	709 (13.1)	554 (6.5)	490 (6.1)

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Required a 3-month washout period prior to randomization.

Figure 1. Kaplan-Meier Estimates for the Association of Menopausal Hormone Therapy With Invasive Breast Cancer During Cumulative Follow-up



No. at risk

CEE + MPA												
CEE + MPA	8506	8329	8114	7802	7016	6248	5743	5006	4517	4143	3239	881
Placebo	8102	7916	7726	7472	6700	5944	5515	4808	4360	3991	3159	769
CEE alone												
CEE alone	5310	5167	5010	4845	4271	3673	3378	2873	2565	2307	1811	496
Placebo	5429	5280	5105	4915	4307	3717	3387	2892	2567	2307	1807	498

The overall median length of follow-up for participants receiving conjugated equine estrogen (CEE) alone was 16.2 years (interquartile range [IQR], 9.1-20.8 years) and 20.7 years (IQR, 19.7-21.7 years) for those participating in extension II; for participants receiving CEE plus medroxyprogesterone acetate (MPA), the overall median length of follow-up was 18.9 years (IQR, 10.5-21.0 years) and was 20.7 years (IQR, 19.8 – 21.7) for those participating in extension II. Summary statistics are from a Cox proportional hazards regression model stratified by 5-year age group, randomization status in the dietary trial, prior hormone therapy use, race/ethnicity, randomization year, and study phase (time-dependent). The *P* value corresponds to a 2-sided stratified score (log-rank) test. HR indicates hazard ratio.

baseline characteristics are shown in eTables 1 through 4 in Supplement 2.

Use of CEE alone, compared with placebo, was associated with statistically significantly lower breast cancer incidence through cumulative follow-up (238 cases [annualized incidence 0.30%] vs 296 [annualized incidence, 0.37]; HR, 0.78; 95% CI, 0.65-0.93; *P* = .005) (**Figure 1**). Information on temporal associations of use of CEE alone on breast cancer incidence is provided in **Figure 2**A, in which the dots represent cumulative hazard ratios in 3-month increments from randomization; the vertical "whiskers" represent 95% CIs. The horizontal bars in the 3 colored panels represent the period-specific hazard ratios (HRs): intervention (HR, 0.76; 95% CI, 0.58-0.98), early postintervention (HR, 0.76; 95% CI, 0.55-1.05), and late postintervention periods (HR, 0.84; 95% CI, 0.59-1.20).

The association of CEE-alone therapy with breast cancer incidence was examined in 11 subgroup analyses defined by participant characteristics and hormone therapy history, and 2 were significant at the .05 level for interaction. The association with lower breast cancer incidence was greater among woman with no first-degree relative with breast cancer (*P* = .04) and among women with no previous breast biopsy (*P* = .05). No statistically significant interaction (*P* = .30) was seen in women by gap time (time from menopause to earlier of first hormone therapy use or randomization) or any other subgroup (**Figure 3**) based on tests for interaction.

In terms of CEE alone and breast cancer characteristics, a statistically significant interaction was seen considering combined estrogen and progesterone receptor status (*P* = .03), and the association with lower risk was strongest for estrogen receptor (ER)-positive and progesterone receptor (PR)-negative cancers (HR, 0.44; 0.27-0.74). Stronger associations with CEE-alone and breast cancer incidence were seen for *ERBB2* (formerly *HER2*)-negative cancers (*P* = .05) and the breast cancers were more commonly diagnosed with negative lymph nodes (*P* = .05) (**Figure 4**).

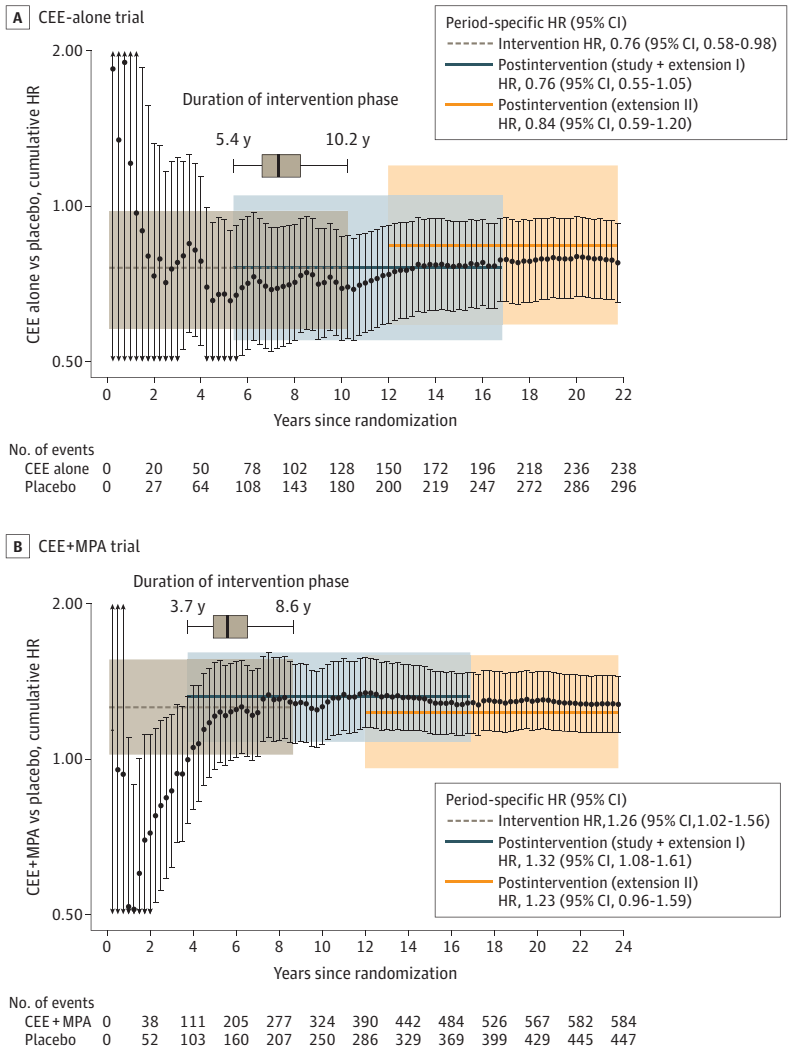
CEE-alone use was associated with statistically significantly fewer deaths from breast cancer. Of those receiving the treatment, 30 women's deaths (annualized mortality, 0.031% compared with 46 (annualized mortality, 0.046%) receiving placebo were directly attributed to breast cancer (HR, 0.60; 95% CI, 0.37-0.97; *P* = .04) (Figure 4). Deaths after breast cancer was not significantly associated with use of CEE alone: 100 women (annualized mortality, 0.12%) in the treatment group vs 121 women (annualized mortality, 0.15%; HR, 0.80; 95% CI, 0.60-1.05; *P* = .11).

Figure 5 depicts nominal stratified score (log-rank) statistics updated annually on data accumulated from randomization for breast cancer events. The association between CEE alone and lower breast cancer incidence became statistically significant in year 5 and remained so subsequently.

Use of CEE plus MPA was associated with statistically significantly higher breast cancer incidence through cumulative follow-up: 584 women (annualized incidence, 0.45%) in the treatment group vs 447 women (annualized incidence, 0.36%) in the placebo group being diagnosed with breast cancer (cumulative HR, 1.28; 95% CI, 1.13-1.45; *P* < .001) (Figure 1). The cumulative HRs summarize the temporal influence for increasingly longer periods of cumulative follow-up (dots and whiskers; Figure 2). The period-specific HRs, represented by horizontal bars, for the intervention group was 1.26 (95% CI; 1.02-1.56); for the early postintervention, 1.32 (95% CI, 1.08-1.61); and for the late postintervention period 1.23 (95% CI, 0.96-1.59) (Figure 2). The association of CEE plus MPA with higher breast cancer incidence became statistically significant in year 6 and remained significant subsequently (Figure 5).

Eleven subgroup analyses, defined by participant characteristics and hormone therapy history, examined the

Figure 2. Plot of Cumulative Hazard Ratios From Randomization Through Increasingly Longer Periods of Cumulative Follow-up



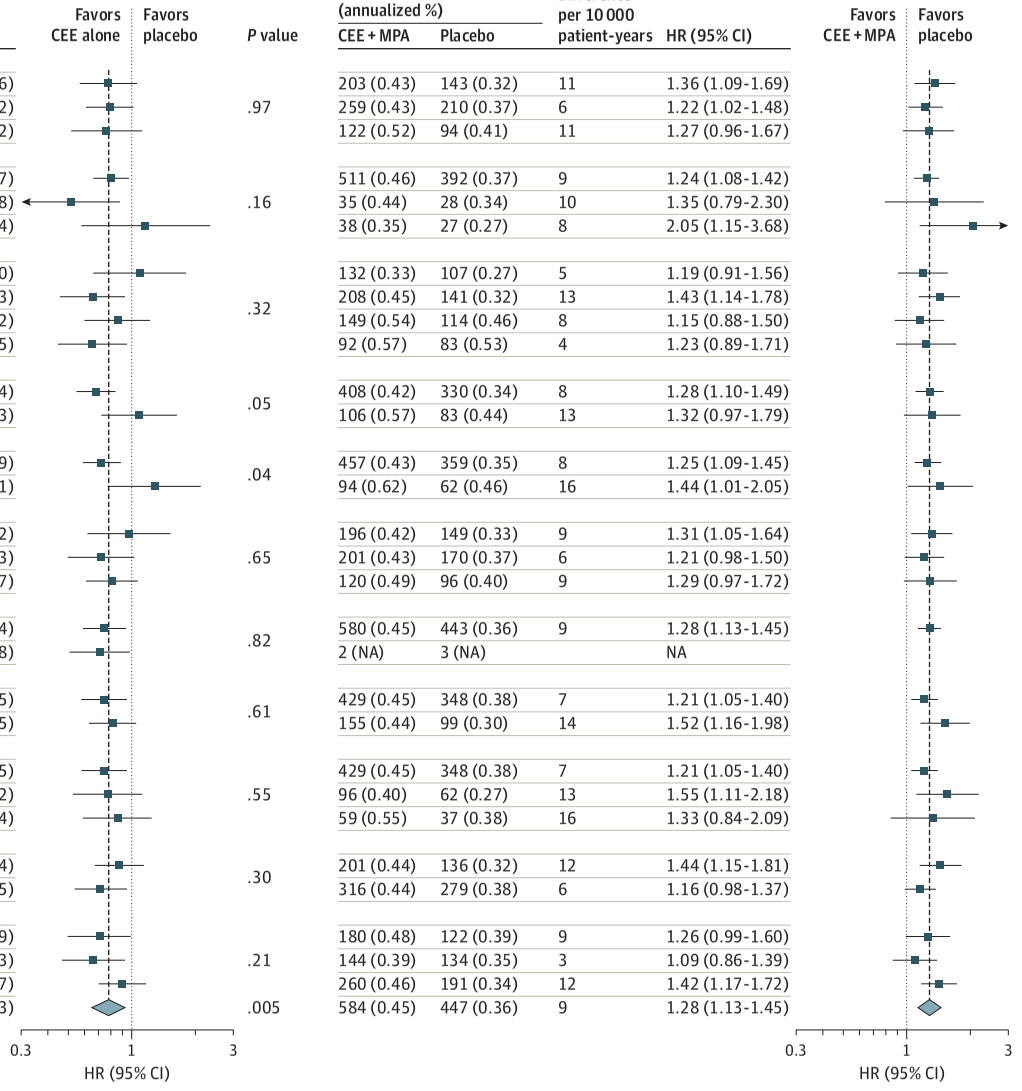
There were 10 739 women in the trial evaluating conjugated equine estrogen (CEE) alone and 16 608 in the trial evaluating CEE plus medroxyprogesterone acetate (MPA). Follow-up data were updated until all cases in both trials were included. Treatment durations varied due to the trial designs because randomization occurred from 1993 to 1998; box plots (for the CEE-alone trial on February 29, 2004, [minimum, 5.4 years; quartile 1, 6.6 years; median, 7.3 years; quartile 3, 8.2 years; and maximum, 10.2 years] and for the CEE-plus-MPA trial on July 7, 2002 [minimum, 3.7 years; quartile 1, 4.9 years; median, 5.6 years; quartile 3, 6.5 years; and maximum, 8.6 years]). Consequently, the intervention period and postintervention periods partially overlap. Summary statistics are derived from Cox regression models described in Figure 1. Dots represent cumulative hazard ratios (HRs), illustrating the temporal trend for each 3-month cumulative follow-up; whiskers, 95% CIs; horizontal bars in the colored boxes, period-specific HRs.

association of use of CEE plus MPA with breast cancer incidence; none were statistically significant, and HRs were above 1 in all categories (Figure 3). With respect to breast cancer characteristics, use of CEE plus MPA was associated with breast cancers that were more commonly diagnosed at higher stage (P = .04) and with lymph node involvement (P = .02) (Figure 4). No other statistically significant interactions were observed. However, use of CEE plus MPA was not statistically significantly associated with death from breast cancer. Seventy-one deaths from breast cancer occurred in the group using CEE plus MPA (annualized mortality, 0.045%) vs 53 in the placebo group (annualized mortality, 0.035%; HR, 1.35; 0.94 to 1.95, P = .11). A total of 213 women (annualized mortality, 0.16%) who used CEE plus MPA died after breast cancer diagnosis vs 172 women (annualized mortality, 0.13%) in the placebo group (HR, 1.19; 0.97-1.47; P = .10; Figure 4).

Mammography utilization rates were balanced between randomization groups during the intervention and extension I.[8] During extension II, self-reported annual mammography rates were not statistically different between randomization groups with median annualized rates of 0.41 (IQR, 0.14 - 0.72) for the CEE-alone group vs 0.41 (IQR, 0.14-0.69) for the placebo group (P = .96) and were 0.41 (IQR, 0.14-0.69) for the CEE-plus-MPA group vs 0.41 (IQR, 0.14-0.69) for the placebo group (P = .52), derived from a Wilcoxon 2-sample test. Adjustment for mammogram use as a time-dependent variable did not influence results. For each trial, consent rates for extended follow-up were comparable between randomization groups, even when stratified by participant characteristics (eTables 1 to 4 in Supplement 2), but nominally significant differences ($P \le .05$) were detected for Gail 5-year risk of breast cancer, family history of breast cancer, and body mass index. Consent rates were higher among participants who were younger and more likely to be non-Hispanic white. However, incidence HRs were similar when using inverse probability weighting to account for censoring due to those not providing consent for postintervention follow-up.

Figure 3. Association of Hormone Therapy With Breast Cancer Incidence by Baseline Subgroups During Cumulative Follow-up

Subgroups	CEE-alone trial (N = 10 739) No. of events (annualized %) CEE alone	Placebo	Difference per 10 000 patient-years	HR (95% CI)	P value	CEE + MPA trial (N = 16 608) No. of events (annualized %) CEE + MPA	Placebo	Difference per 10 000 patient-years	HR (95% CI)	P value
Age, y										
50-59	77 (0.29)	95 (0.36)	-7	0.77 (0.57-1.06)	.97	203 (0.43)	143 (0.32)	11	1.36 (1.09-1.69)	.62
60-69	108 (0.31)	139 (0.38)	-7	0.79 (0.61-1.02)		259 (0.43)	210 (0.37)	6	1.22 (1.02-1.48)	
70-79	53 (0.33)	62 (0.38)	-5	0.76 (0.52-1.12)		122 (0.52)	94 (0.41)	11	1.27 (0.96-1.67)	
Race/ethnicity										
Non-Hispanic White	189 (0.31)	232 (0.38)	-7	0.80 (0.66-0.97)	.16	511 (0.46)	392 (0.37)	9	1.24 (1.08-1.42)	.24
Non-Hispanic Black	24 (0.22)	49 (0.42)	-20	0.52 (0.31-0.88)		35 (0.44)	28 (0.34)	10	1.35 (0.79-2.30)	
Other	25 (0.36)	15 (0.23)	13	1.16 (0.58-2.34)		38 (0.35)	27 (0.27)	8	2.05 (1.15-3.68)	
Body mass index										
<25	36 (0.22)	36 (0.23)	-1	1.09 (0.66-1.80)	.32	132 (0.33)	107 (0.27)	5	1.19 (0.91-1.56)	.79
25-<30	63 (0.23)	99 (0.35)	-11	0.66 (0.46-0.93)		208 (0.45)	141 (0.32)	13	1.43 (1.14-1.78)	
30-<35	70 (0.35)	80 (0.40)	-5	0.86 (0.60-1.22)		149 (0.54)	114 (0.46)	8	1.15 (0.88-1.50)	
≥35	67 (0.46)	78 (0.54)	-9	0.65 (0.45-0.95)		92 (0.57)	83 (0.53)	4	1.23 (0.89-1.71)	
History of benign breast disease										
No previous biopsy	156 (0.28)	209 (0.38)	-11	0.68 (0.55-0.84)	.05	408 (0.42)	330 (0.34)	8	1.28 (1.10-1.49)	.87
Previous biopsies ≥1	55 (0.40)	61 (0.40)	0	1.08 (0.72-1.63)		106 (0.57)	83 (0.44)	13	1.32 (0.97-1.79)	
First-degree relative with breast cancer										
No	168 (0.27)	228 (0.36)	-9	0.72 (0.59-0.89)	.04	457 (0.43)	359 (0.35)	8	1.25 (1.09-1.45)	.47
Yes	54 (0.53)	45 (0.44)	9	1.28 (0.77-2.11)		94 (0.62)	62 (0.46)	16	1.44 (1.01-2.05)	
Years since menopause										
<10	42 (0.31)	45 (0.34)	-3	0.97 (0.62-1.52)	.65	196 (0.42)	149 (0.33)	9	1.31 (1.05-1.64)	.86
10-<20	60 (0.28)	83 (0.37)	-9	0.72 (0.50-1.03)		201 (0.43)	170 (0.37)	6	1.21 (0.98-1.50)	
≥20	102 (0.33)	124 (0.39)	-6	0.81 (0.61-1.07)		120 (0.49)	96 (0.40)	9	1.29 (0.97-1.72)	
Bilateral oophorectomy										
No	150 (0.34)	174 (0.41)	-7	0.74 (0.59-0.94)	.82	580 (0.45)	443 (0.36)	9	1.28 (1.13-1.45)	
Yes	69 (0.24)	106 (0.34)	-10	0.71 (0.51-0.98)		2 (NA)	3 (NA)		NA	
Prior use of HT										
No	125 (0.31)	157 (0.40)	-9	0.74 (0.58-0.95)	.61	429 (0.45)	348 (0.38)	7	1.21 (1.05-1.40)	.14
Yes	113 (0.30)	139 (0.35)	-5	0.82 (0.63-1.05)		155 (0.44)	99 (0.30)	14	1.52 (1.16-1.98)	
Duration of prior HT, y										
Never	125 (0.31)	157 (0.40)	-9	0.74 (0.58-0.95)	.55	429 (0.45)	348 (0.38)	7	1.21 (1.05-1.40)	.35
<5	54 (0.27)	70 (0.34)	-6	0.77 (0.53-1.12)		96 (0.40)	62 (0.27)	13	1.55 (1.11-2.18)	
≥5	59 (0.33)	69 (0.37)	-4	0.86 (0.59-1.24)		59 (0.55)	37 (0.38)	16	1.33 (0.84-2.09)	
Gap time, y										
<5	110 (0.31)	127 (0.36)	-4	0.87 (0.67-1.14)	.30	201 (0.44)	136 (0.32)	12	1.44 (1.15-1.81)	.13
≥5	94 (0.31)	125 (0.39)	-9	0.71 (0.54-0.95)		316 (0.44)	279 (0.38)	6	1.16 (0.98-1.37)	
Randomization year										
1993-1995	62 (0.29)	89 (0.39)	-10	0.71 (0.50-0.99)	.21	180 (0.48)	122 (0.39)	9	1.26 (0.99-1.60)	.36
1996	58 (0.26)	81 (0.36)	-10	0.66 (0.47-0.93)		144 (0.39)	134 (0.35)	3	1.09 (0.86-1.39)	
1997-1998	118 (0.35)	126 (0.38)	-3	0.90 (0.70-1.17)		260 (0.46)	191 (0.34)	12	1.42 (1.17-1.72)	
Overall effect	238 (0.30)	296 (0.37)	-7	0.78 (0.65-0.93)	.005	584 (0.45)	447 (0.36)	9	1.28 (1.13-1.45)	<.001



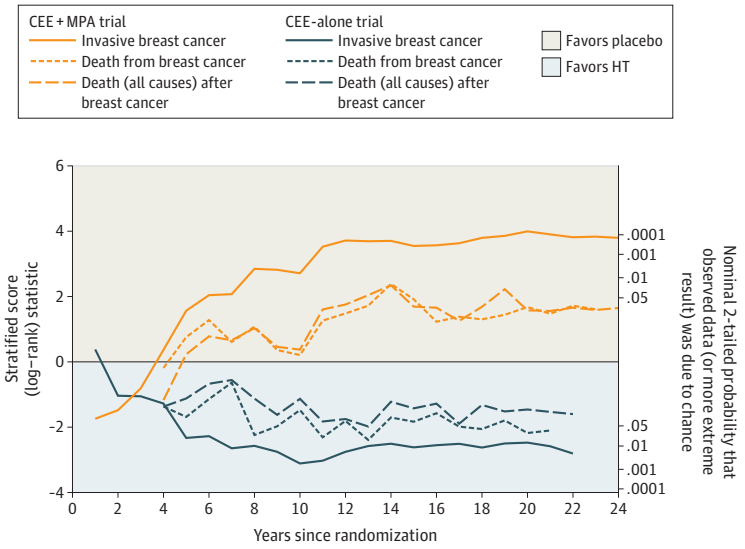
Data were missing. See Figure 1 for statistical details. Not applicable (NA), indicates too few participants.

Figure 4. Association of Hormone Therapy With Tumor Characteristics and Breast Cancer Mortality During Cumulative Follow-up

Breast cancer events	CEE-alone trial (N = 10 739)				CEE + MPA trial (N = 16 608)				P value
	No. of events (annualized %)		Difference per 10 000 patient-years	HR (95% CI)	No. of events (annualized %)		Difference per 10 000 patient-years	HR (95% CI)	
	CEE alone	Placebo			CEE + MPA	Placebo			
Invasive breast cancer	238 (0.30)	296 (0.37)	-7	0.78 (0.65-0.93)	584 (0.45)	447 (0.36)	9	1.28 (1.13-1.45)	<.001
Breast cancer characteristics									
Histology									
Ductal	140 (0.18)	197 (0.25)	-7	0.69 (0.55-0.86)	374 (0.29)	298 (0.24)	5	1.23 (1.05-1.44)	
Lobular	29 (0.037)	27 (0.034)	0	1.05 (0.61-1.81)	57 (0.044)	33 (0.026)	2	1.80 (1.14-2.83)	.29
Ductal and lobular	28 (0.036)	32 (0.040)	0	0.76 (0.45-1.27)	85 (0.065)	57 (0.046)	2	1.45 (1.03-2.04)	
Other	38 (0.049)	37 (0.047)	0	1.07 (0.66-1.71)	66 (0.051)	57 (0.046)	0	1.08 (0.75-1.56)	
Estrogen receptor status									
Positive	175 (0.22)	235 (0.30)	-7	0.73 (0.60-0.89)	484 (0.37)	360 (0.29)	8	1.30 (1.13-1.50)	.57
Negative	43 (0.055)	41 (0.052)	0	0.98 (0.63-1.53)	74 (0.057)	53 (0.042)	1	1.46 (1.01-2.09)	
Progesterone receptor status									
Positive	152 (0.19)	185 (0.23)	-4	0.81 (0.65-1.01)	413 (0.32)	308 (0.25)	7	1.30 (1.12-1.52)	.79
Negative	64 (0.082)	86 (0.11)	-3	0.70 (0.50-0.98)	137 (0.10)	99 (0.079)	3	1.36 (1.04-1.77)	
Estrogen progesterone status									
ER+PR+	150 (0.19)	181 (0.23)	-4	0.82 (0.66-1.03)	404 (0.31)	303 (0.24)	7	1.29 (1.11-1.50)	.94
ER+PR−	23 (0.029)	49 (0.062)	-3	0.44 (0.27-0.74)	72 (0.055)	52 (0.042)	1	1.34 (0.93-1.93)	
ER−PR−	41 (0.053)	37 (0.047)	1	1.05 (0.66-1.66)	65 (0.050)	47 (0.038)	1	1.38 (0.94-2.02)	
ERBB2 overexpression									
Yes	32 (0.041)	25 (0.032)	1	1.35 (0.78-2.34)	74 (0.057)	45 (0.036)	2	1.62 (1.11-2.36)	.40
No	165 (0.21)	212 (0.27)	-6	0.74 (0.60-0.92)	407 (0.31)	294 (0.24)	8	1.36 (1.16-1.58)	
Triple-negative tumor									
Yes	29 (0.037)	21 (0.027)	1	1.34 (0.75-2.38)	43 (0.033)	28 (0.022)	1	1.52 (0.93-2.48)	.68
No	166 (0.21)	213 (0.27)	-6	0.75 (0.61-0.93)	430 (0.33)	307 (0.25)	8	1.37 (1.18-1.59)	
Stage									
Local	160 (0.20)	220 (0.28)	-7	0.70 (0.57-0.87)	430 (0.33)	351 (0.28)	5	1.19 (1.03-1.37)	.04
Regional or distant	72 (0.092)	69 (0.087)	0	1.02 (0.73-1.43)	146 (0.11)	90 (0.072)	4	1.62 (1.24-2.12)	
Grading									
Well differentiated	52 (0.067)	72 (0.091)	-2	0.71 (0.49-1.03)	160 (0.12)	105 (0.084)	4	1.55 (1.20-1.99)	.22
Moderately differentiated	92 (0.12)	125 (0.16)	-4	0.71 (0.53-0.93)	228 (0.17)	189 (0.15)	2	1.14 (0.94-1.39)	
Poorly differentiated	63 (0.081)	72 (0.091)	-1	0.87 (0.61-1.23)	139 (0.11)	112 (0.090)	2	1.24 (0.96-1.60)	
Tumor size, cm									
<1	59 (0.076)	87 (0.11)	-3	0.66 (0.47-0.93)	158 (0.12)	137 (0.11)	1	1.14 (0.90-1.44)	.08
1-<2	84 (0.11)	110 (0.14)	-3	0.74 (0.55-1.00)	218 (0.17)	150 (0.12)	5	1.36 (1.10-1.69)	
≥2	72 (0.092)	77 (0.097)	-1	0.88 (0.63-1.22)	171 (0.13)	115 (0.092)	4	1.53 (1.20-1.95)	
Positive lymph nodes									
Yes	63 (0.081)	61 (0.077)	0	1.03 (0.71-1.47)	126 (0.096)	75 (0.060)	4	1.69 (1.26-2.27)	.02
No	136 (0.17)	195 (0.25)	-7	0.67 (0.53-0.84)	370 (0.28)	313 (0.25)	3	1.15 (0.98-1.34)	
Death from breast cancer	30 (0.031)	46 (0.046)	-2	0.60 (0.37- 0.97)	71 (0.045)	53 (0.035)	1	1.35 (0.94-1.95)	.11
Death (all-causes) after breast cancer	100 (0.12)	121 (0.15)	-2	0.80 (0.60-1.05)	213 (0.16)	172 (0.13)	2	1.19 (0.97-1.47)	.10

Data were missing from all categories for both trials. Definitions of summary statistics and *P* values are described in the Figure 1 legend.

Figure 5. Plot of Stratified Score (Log-Rank) Statistics Updated Annually Based on Cumulative Data



Data accumulated from randomization for breast cancer–related events in the trials evaluating conjugated equine estrogen (CEE) alone (n = 10 739) and evaluating CEE plus medroxyprogesterone acetate (MPA) (n = 16 608) during cumulative follow-up. Test statistics are 2 sided, correspond to the stratified score (log-rank) test obtained from the Cox regression model described in Figure 1, and were updated until all observed cases were included.

Specifically, the HR in the CEE-alone trial changed from 0.78 (95% CI, 0.65-0.93) to 0.78 (95% CI, 0.66-0.93), and for the CEE-plus-MPA trial, estimates did not change. Mortality results were based on NDI data so are essentially complete and do not rely on consent.

Discussion

In this study based on long-term follow-up of 2 parallel randomized, placebo-controlled clinical trials, prior randomized use of CEE alone, compared with placebo, among women with prior hysterectomy was associated with a statistically significantly lower breast cancer incidence that persisted for more than a decade after discontinuing use and was associated with statistically significantly lower breast cancer mortality. In contrast, prior randomized use of CEE plus MPA, compared with placebo, among women with an intact uterus, was associated with a statistically significantly higher breast cancer incidence that persisted for more than a decade after discontinuing use, but there was not a significant difference in breast cancer mortality. While the CEE plus MPA findings are generally consistent with observational studies, the findings for CEE-alone on breast cancer incidence and breast cancer mortality contrast most prospective observational studies.

Compared with previous reports from these 2 clinical trials, the updated data in this study include 424 more breast cancer cases (1565 in this report vs 1141 in previous reports[8,11]) and 36 more deaths from breast cancer (200 in this report vs 164 in a previous report[10]).

Prior use of CEE alone is, to our knowledge, the first pharmacologic intervention demonstrated to be associated with a statistically significantly reduction in deaths from breast cancer. Despite the statistically significant reduction in breast cancer incidence previously reported with CEE alone,[7] use for breast cancer prevention has not been endorsed based on stroke risk and hormone-targeted drugs with greater influence on breast cancer incidence.[21,22] However, emerging information suggests the issue is becoming more complex. Of interventions proven to reduce breast cancer incidence (tamoxifen, raloxifene, aromatase inhibitors), only 2 tamoxifen trials with relatively long-term follow-up have reported on breast cancer mortality. Across the 2 trials, despite 201 fewer breast cancers, there were 6 more deaths from breast cancer in the tamoxifen groups.[22-24] Thus, while reducing breast cancer incidence has clinical benefit, there is no evidence that these pharmacologic interventions reduce breast cancer mortality.[25] Taken together, these findings suggest that reexamination of current breast cancer risk reduction strategies is needed.

Findings from a meta-analysis of international observational studies[2] that examined the association of estrogen plus progestin or estrogen alone with breast cancer incidence and findings from the Million Women Study[4] that examined breast cancer mortality suggested only quantitative differences in the relationship between these 2 hormone therapy regimens and breast cancer risk with adverse effects seen with both regimens. In contrast, the differences between the associations of prior use of CEE plus MPA or prior use of CEE alone with breast cancer incidence and breast cancer mortality in the WHI randomized trials suggest qualitative differences of the 2 regimens on breast cancer.

The discordance between the findings from randomized clinical trials and observational studies are perhaps possible to reconcile. First, participants in the randomized trials in this study were, on average, older with longer time from menopause to first hormone use (gap time) than hormone therapy users in observational studies. Second, mammography use is a potential confounder of observational studies, especially in studies conducted before implementation of wide-scale screening programs because women using

hormone therapy undergo mammography more than those who do not [26] and mammography leads to greater breast cancer detection.[27] Third, there is biological plausibility for estrogen alone and estrogen plus progestin having differential influence on breast cancer.[28]

Preclinical[28] and clinical[29] findings indicate that, after a period of estrogen deprivation, adaptive changes result in tumor sensitivity to estrogen-induced apoptosis.[28,29] During the intervention period of the CEE-alone trial, reduction in breast cancer incidence was initially greater in women with a gap time of 5 or more years.[7] In the observational Million Women study, estrogen-only use was associated with little or no increase in breast cancer risk if use began 5 or more years after menopause (risk ratio [RR], 1.05; 95% CI, 0.89-1.24), particularly after obesity was considered in the analysis (RR, 0.91; 95% CI, 0.73-1.14).[30] In addition, in the current update of the CEE-alone trial, with longer cumulative follow-up, gap time interactions were attenuated. Thus, additional mechanisms,[31,32] unrelated to gap time, also may mediate the lower breast cancer incidence and deaths from breast cancer associated with use of CEE alone.

To address the differential results in observational studies compared with the randomized trials, the authors of Collaborative Group meta-analysis of observational studies[2] suggested the decrease in breast cancer with use of estrogen alone in randomized trials arose "mainly by the play of chance" augmented by increased breast density with "reduction in mammographic sensitivity."[2] However, although CEE alone increases breast density to a degree[33] when mammography performance was formally evaluated, CEE alone had no adverse influence on breast cancer detection.[34] In addition, the reduction in deaths from breast cancer associated with randomized use of prior CEE alone in this study is evidence against a screening artifact; detection delay would likely increase, rather than decrease, breast cancer mortality.

The play of chance to explain the influence of CEE alone on reducing breast cancer incidence, first proposed 16 years ago,[35] is challenged by the current long-term study results and the development of plausible biological hypotheses regarding estrogen alone and mammary tumor growth, including estrogen influence on estrogen-dependent apoptosis, antiproliferative effects of CEE,[31] and effects of coordinated estrogen withdrawal[32] on tumor growth (eFigure 2 in Supplement 2).

Despite the association of prior use of CEE alone with lower risk of death from breast cancer, in absolute terms the reduction is modest; for every 10 000 person-years of women following prior use of CEE alone, there would be 2 fewer deaths as a result of breast cancer and 2 fewer deaths after breast cancer. However, with 56 million postmenopausal women in the United States[36] as a potential target, the possible influence at the population level could be considerable.

A biological rationale for the maintained increase in breast cancer risk associated with use of CEE plus MPA after the intervention and drug exposure ended is that a progestin-induced increase in the breast epithelium stem cell pool leaves former estrogen plus progestin users with a persistent and long-term increase in breast cancer risk.[37] In addition, anti-inflammatory effects of MPA may have neutralized estrogen-induced apoptosis.[38] The increased breast cancer risk, which appears to continue for more than a decade after discontinuation of CEE plus MPA, changes the risk-benefit calculation for this regimen.

Decisions regarding use of any hormone therapy regimen should consider the full range of risk and benefits, as outlined in detail elsewhere,[10,11,39] involve shared decision-making with the patient, and recognize that risk-benefit balance is altered by additional factors such as age, time from menopause, oophorectomy status, and prior hysterectomy, with some outcomes persisting and some attenuating after stopping use.

Strengths of the current follow-up study include the use of data from randomized, double-blind clinical trials, a large and diverse study population, mammogram clearance before entry and subsequent annual protocol-mandated mammography, central adjudication of breast cancers, and long follow-up. Information on breast cancer mortality, enhanced by serial NDI queries, was essentially complete regardless of reconsent status.

Limitations

This study has several limitations. First, because the breast cancer mortality analyses were not protocol specified, study limitations include those associated with secondary analyses. However, death from breast cancer is the most clinically relevant breast cancer outcome. Second, these clinical trials evaluated only 1 dose, route of administration, and formulation for each trial, and findings are not necessarily generalizable to other preparations. Third, results reflected study drug adherence; during intervention, 54% of study participants discontinued using CEE alone[12] and 42% discontinued using CEE plus MPA.[13] Fourth, information about breast cancer recurrence was not available. Fifth, although gap-time analyses were conducted, numbers were insufficient to rigorously examine the association of initiating CEE alone shortly after oophorectomy, onset of menopause, or both with the risk of breast cancer incidence and mortality. Although preclinical studies have suggested differential effects of estradiol and CEE on mammary tumors,[31] no differences in breast cancer findings have been reported in observational studies for estrogen-alone preparations (CEE vs estradiol) or for estrogen plus progestin by progestin constituents.[2]

Conclusions

In this long-term follow-up study of 2 randomized trials, prior randomized use of CEE alone, compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality, whereas prior randomized use of CEE plus MPA, compared with placebo, among women who had an intact uterus, was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality.

ARTICLE INFORMATION

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Drafting of the manuscript: Chlebowski, Aragaki, Manson, Stefanick.
Critical revision of the manuscript for important intellectual content: Chlebowski, Anderson, Manson, Pan, Barrington, Kuller, Simon, Lane, Johnson, Rohan, Gass, Cauley, Paskett, Sattari, Prentice.
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Supervision: Chlebowski, Anderson, Stefanick, Johnson, Cauley, Paskett, Prentice.

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Additional information: A full list of all the investigators who have contributed to Women's Health Initiative science appears at http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf.

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