Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy

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Context The Women's Health Initiative Estrogen-Aone trial comparing conjugated equine estrogens (CEE) with placebo was stopped early because of an increased stroke incidence and no reduction in risk of coronary heart disease. Preliminary results suggesting possible reduction in breast cancers warranted more detailed analysis.

Objective To determine the effects of CEE on breast cancers and mammographic findings.

Design, Setting, and Participants Following breast cancer risk assessment, 10 739 postmenopausal women aged 50 to 79 years with prior hysterectomy were randomized to CEE or placebo at 40 US clinical centers from 1993 through 1998. Mammography screenings and clinical breast examinations were performed at baseline and annually. All breast cancers diagnosed through February 29, 2004, are included.

Intervention A dose of 0.625 mg/d of CEE or an identical-appearing placebo.

Main Outcome Measures Breast cancer incidence, tumor characteristics, and mammogram findings.

Results After a mean (SD) follow-up of 7.1 (1.6) years, the invasive breast cancer hazard ratio (HR) for women assigned to CEE vs placebo was 0.80 (95% confidence interval [CI], 0.62-1.04; $P=.09$) with annualized rates of 0.28% (104 cases in the CEE group) and 0.34% (133 cases in the placebo group). In exploratory analyses, ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99) were reduced in the CEE group vs placebo group; however, the test for interaction by tumor type was not significant ($P=.054$). At 1 year, 9.2% of women in the CEE group had mammograms with abnormalities requiring follow-up vs 5.5% in the placebo group ($P<.001$), a pattern that continued through the trial to reach a cumulative percentage of 36.2% vs 28.1%, respectively ($P<.001$); however, this difference was primarily in assessments requiring short interval follow-up.

Conclusions Treatment with CEE alone for 7.1 years does not increase breast cancer incidence in postmenopausal women with prior hysterectomy. However, treatment with CEE increases the frequency of mammography screening requiring short interval follow-up. Initiation of CEE should be based on consideration of the individual woman's potential risks and benefits.

Trial Registration clinicaltrials.gov Identifier: NCT00000611

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In the Women's Health Initiative (WHI) randomized Estrogen plus Progestin (E + P) trial in postmenopausal women, oral conjugated equine estrogens (CEE) combined with medroxyprogesterone acetate produced more health risks than benefits,[1] including a higher incidence of invasive breast cancers, which were diagnosed at a more advanced stage, and a substantially greater proportion of abnormal mammograms compared with placebo.[2] The parallel WHI Estrogen-Alone trial, which randomized women with prior hysterectomy to CEE only or placebo, was stopped early based on available data representing an average of 6.8 years of follow-up because of increased stroke incidence and no reduction in risk of coronary heart disease.[3] In contrast to substantial epidemiological evidence associating exogenous estrogens with in-

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creased breast cancer incidence,[4-9] preliminary analyses found fewer breast cancers in women in the CEE group, prompting a detailed updated analysis of breast cancer incidence and mammographic reports. The completed trial results reported herein include all events occurring prior to the stopping of the intervention and unblinding. Biologically plausible explanations for the possibility of decreased incidence of breast cancer with CEE are considered and examined in exploratory analyses, including interactions of treatment assignment with baseline risk factors.

METHODS

The WHI Estrogen-Alone trial enrolled 10 739 postmenopausal women with prior hysterectomy from 1993 through 1998 at 40 US clinical centers.[10] Women were recruited primarily by mass mailings and were eligible if they were aged 50 to 79 years at study entry, postmenopausal, and likely to reside in the same area for 3 years. Special attempts were made to recruit minority women in an effort to study the effects of hormone therapy in a cohort that reflected the ethnicity/racial diversity of postmenopausal women aged 50 to 79 years in the US population.

Individual women classified themselves regarding their race/ethnicity. The protocol and consent forms were reviewed and approved by the institutional review boards at each participating clinical center. Each woman provided written informed consent. The study exclusions included prior incidence of breast cancer and medical conditions likely to result in death within 3 years. Menopausal hormone use at screening required a 3-month washout before enrollment. All women had a baseline mammography screening and a clinical breast examination; suspicious findings required clearance before study entry. Breast cancer risk was assessed by interview and standardized questionnaires. Definitions of demographic and general health characteristics, and reproductive, medical, and family history, including hormone use, have been published.[10] Ovarian preservation was defined as no self-report of bilateral oophorectomy.

Women were randomly assigned to 0.625 mg of CEE (Premarin, Wyeth, Collegeville, Pa) or an identical-appearing placebo. Randomization was carried out using a database distributed by the WHI clinical coordinating center; study pill bottles had unique bar codes and computer-based selection to ensure double-blinded dispensing. Study medication was discontinued for development of breast cancer, deep vein thrombosis or pulmonary emboli, malignant melanoma, level of triglycerides higher than 1000 mg/dL (>11.3 mmol/L), or use of tamoxifen, raloxifene, or any nonstudy estrogen, progestin, or androgen.

Follow-up Procedures

Participants were contacted 6 weeks after study entry to assess symptoms and promote adherence, at 6-month intervals to assess clinical outcomes, and annually for clinic visits. Study medications were withheld until completion of required annual mammography screenings and breast examinations. Initial outcomes were ascertained by self-administered questionnaires. Breast cancer outcomes were confirmed by local clinic physician adjudicator review of medical records and pathology reports. Cases were then adjudicated at the clinical coordinating center using the Surveillance, Epidemiology, and End Results coding system.[11] Total breast cancers included the first of either invasive or in situ breast cancer.

Mammographic reports were obtained and reviewed locally at the clinical centers and coded for radiologist recommendation (negative, benign finding/negative, short interval follow-up suggested, suspicious abnormality, and highly suggestive of malignancy). Mammograms with suggested short interval follow-up and those with suspicious or highly suggestive findings were considered abnormal, with the latter 2 categories requiring clearance before dispensing ongoing study medication. Medical decisions regarding workup of breast findings were directed primarily by community physicians.

Study Termination

The sample size was based on hypothesized effects of estrogen on coronary heart disease after a proposed 9 years of follow-up. For monitoring purposes, a global index of benefit and risk was defined as time to the first event among coronary heart disease, invasive breast cancer, stroke, colorectal cancer, pulmonary embolus, hip fracture, and death from other causes. The National Institutes of Health stopped the trial earlier than planned because an increased risk of stroke in healthy women was considered unacceptable in the absence of a reduction in risk of coronary heart disease. At that time, 218 adjudicated invasive breast cancers were described and the in situ breast cancers had not been quantified.[3] The current study provides analyses of 237 invasive and 55 in situ centrally adjudicated breast cancers diagnosed by February 29, 2004, the date participants were instructed to stop taking their study pills, resulting in a mean (SD) follow-up of 7.1 (1.6) years.

Statistical Analysis

Primary results were assessed with time-to-event methods and were based on the intention-to-treat principle. Hazard ratios (HRs) are based on Cox proportional hazards analyses stratified by age and randomization status in the WHI Dietary Modification trial. Nominal 95% confidence intervals (CIs) were used for inferences regarding invasive breast cancer because these were similar to CIs that acknowledge the sequential monitoring due to proximity of the stopping date to the planned study termination. In exploratory analyses, subgroup effects were tested as interactions between randomization assignment and selected baseline characteristics in Cox proportional hazards models that included both factors as main effects. *P* values for interaction were computed from likelihood ratio tests using a continuous variable for the baseline characteristic, wherever pos-

sible. Nominal *P* values are presented, reflecting statistical significance without adjustment for multiple comparisons. Because 20 interactions with baseline characteristics were tested, chance alone would be expected to produce 1 significant interaction test at the .05 level of significance and 2 at the .10 level. Women with missing values for a given risk factor were omitted only from analyses requiring that variable.

The HRs by time since randomization were calculated from Cox proportional hazards models and tests for trends with time were obtained by incorporating a linear time interaction term. Kaplan-Meier plots describe breast cancer event rates over time. To assess the potential effect of nonadherence, adherence-adjusted analyses were conducted by censoring follow-up for a woman 6 months after she became nonadherent (defined as consuming <80% of study pills or starting nonstudy hormone therapy during the most recent study interval). Comparisons of selected breast cancer tumor characteristics were based on χ^2, Fisher exact, or *t* tests. Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of Study Population

All women had prior hysterectomy and 41% had prior bilateral oophorectomy. Prior oophorectomy was somewhat less common in the CEE group. Women with bilateral oophorectomy differed from those with ovarian preservation but there were no substantial differences by treatment assignment.

Baseline breast cancer risk was comparable in the 2 study groups. Participants were at a moderate risk for their age,[12] with a mean (SD) 5-year Gail risk estimate[13] of 1.6% (1.0%) (median, 1.4% [interquartile range, 1.03%-1.88%]) (TABLE 1 and TABLE 2). A slightly lower proportion of women in the CEE group reported prior benign breast biopsies (19.3% vs 21.7%; *P*=.004).

Fifty-two percent of all participants had never taken hormone therapy before study entry, less than 5% had ever taken estrogen combined with a progestin, and the remainder had taken estrogen only. Women with no prior hormone use differed from those with prior use in most variables shown in Table 2,

Table 1. Demographics of Participants at Baseline by Treatment Group

	No. (%) of Participants*		
	CEE Alone (n = 5310)	Placebo (n = 5429)	*P* Value†
Age at screening, y			
50-59	1637 (30.8)	1673 (30.8)	.85
60-69	2387 (45.0)	2465 (45.4)	
70-79	1286 (24.2)	1291 (23.8)	
Race/ethnicity			
White	4007 (75.5)	4075 (75.1)	.81
Black	782 (14.7)	835 (15.4)	
Hispanic	322 (6.1)	333 (6.1)	
American Indian	41 (0.8)	34 (0.6)	
Asian/Pacific Islander	86 (1.6)	78 (1.4)	
Unknown	72 (1.4)	74 (1.4)	
Education			
None or some high school	535 (10.2)	518 (9.6)	.12
High school diploma/GED	1233 (23.5)	1188 (22.1)	
Post–high school study	2271 (43.2)	2350 (43.7)	
College degree or higher	1216 (23.1)	1327 (24.7)	
Age at menarche, y			
≤11	1215 (23.0)	1280 (23.7)	.72
12-13	2805 (53.1)	2853 (52.8)	
≥14	1259 (23.8)	1274 (23.6)	
Oral contraceptive use ever			
No	3257 (61.4)	3377 (62.2)	.38
Yes	2048 (38.6)	2050 (37.8)	
Body mass index‡			
<25	1110 (21.0)	1096 (20.3)	.26
25-29.9	1795 (34.0)	1912 (35.5)	
≥30	2376 (45.0)	2383 (44.2)	
Physical activity, metabolic equivalents/wk			
None	1081 (22.2)	1043 (21.3)	.43
>0-3.5	887 (18.2)	930 (19.0)	
>3.5-8.0	983 (20.1)	983 (20.0)	
>8.0-16.5	981 (20.1)	945 (19.3)	
>16.5	948 (19.4)	1003 (20.5)	
Alcohol use			
None	718 (13.7)	737 (13.7)	.88
Past drinker	1277 (24.3)	1270 (23.6)	
<1 drink/mo	767 (14.6)	766 (14.2)	
<1 drink/wk	1001 (19.1)	1049 (19.5)	
1-<7 drinks/wk	1027 (19.6)	1091 (20.2)	
≥7 drinks/wk	457 (8.7)	475 (8.8)	
Smoking			
Never	2723 (51.9)	2705 (50.4)	.33
Past	1986 (37.8)	2089 (38.9)	
Current	542 (10.3)	571 (10.6)	
NSAID use			
No	4987 (93.9)	5100 (93.9)	.96
Yes	323 (6.1)	329 (6.1)	

Abbreviations: CEE, conjugated equine estrogens; GED, general equivalency diploma; NSAID, nonsteroidal anti-inflammatory drug.
*Due to information missing for some variables, category denominators do not always equal group total shown in column heading.
†*P* values are from χ^2 tests.
‡Calculated as weight in kilograms divided by height in meters squared.

Table 2. Medical History of Participants at Baseline by Treatment Group

	No. (%) of Participants*		
	CEE Alone (n = 5310)	Placebo (n = 5429)	*P* Value†
5-y Gail risk score, %‡			
<1.25	2129 (40.1)	2149 (39.6)	
1.25-1.74	1620 (30.5)	1688 (31.1)	.79
≥1.75	1561 (29.4)	1592 (29.3)	
No. of term pregnancies			
Never pregnant	365 (6.9)	348 (6.5)	
Never had term pregnancy	126 (2.4)	115 (2.1)	
1	381 (7.2)	445 (8.2)	.18
2-4	3201 (60.7)	3308 (61.3)	
≥5	1197 (22.7)	1179 (21.9)	
Age at first birth, y			
Never pregnant/no term pregnancy	491 (10.4)	463 (9.5)	
<20	1193 (25.2)	1234 (25.3)	.12
20-29	2846 (60.0)	2914 (59.8)	
≥30	210 (4.4)	260 (5.3)	
No. of children breastfed			
None	2468 (47.2)	2491 (46.7)	
1-2	1621 (31.0)	1732 (32.4)	.25
≥3	1138 (21.8)	1116 (20.9)	
Age at hysterectomy, y			
<40	2100 (39.8)	2149 (39.8)	
40-49	2281 (43.2)	2275 (42.2)	.39
≥50	902 (17.1)	970 (18.0)	
Oophorectomy			
No	2171 (44.2)	2090 (41.6)	
Yes			
Partial	802 (16.3)	827 (16.4)	.02
Bilateral	1938 (39.5)	2111 (42.0)	
Age at oophorectomy, y			
<40	946 (34.9)	1021 (35.2)	
40-49	1230 (45.4)	1304 (44.9)	.93
≥60	533 (19.7)	579 (19.9)	
Prior estrogen only use, y			
No	2872 (54.1)	2891 (53.3)	
Yes			
<2	738 (13.9)	792 (14.6)	.64
2-5	579 (10.9)	576 (10.6)	
>5	1121 (21.1)	1170 (21.6)	
Prior estrogen plus progestin use, y			
No	5093 (95.9)	5178 (95.4)	
Yes			
<2	88 (1.7)	95 (1.8)	.48
2-5	56 (1.1)	63 (1.2)	
>5	73 (1.4)	93 (1.7)	
Recency of hormone use, y			
Current	669 (26.3)	708 (26.7)	
<2	248 (9.8)	272 (10.2)	.83
2-5	318 (12.5)	314 (11.8)	
>5	1305 (51.4)	1362 (51.3)	
Relatives with breast cancer			
First-degree			
None	4202 (85.8)	4352 (86.4)	
1	634 (12.9)	597 (11.9)	.05
≥2	63 (1.3)	88 (1.7)	
Second-degree			
None	4347 (95.3)	4485 (95.4)	
1	209 (4.6)	204 (4.3)	.69
≥2	7 (0.2)	10 (0.2)	
Benign breast disease			
No	3894 (80.7)	3787 (78.3)	
Yes			
1 Biopsy	683 (14.1)	756 (15.6)	.01
≥2 Biopsies	250 (5.2)	295 (6.1)	

Abbreviation: CEE, conjugated equine estrogens.
*Due to information missing for some variables, category denominators do not always equal group total shown in column heading.
†*P* values are from χ^2 tests.
‡Gail risk score incorporates age, history of benign breast disease (atypia status unknown in the Women's Health Initiative), age at menarche, age at first live birth, race/ethnicity, and numbers of mothers and sisters with breast cancer.[13]

but there were no substantial differences by treatment assignment.

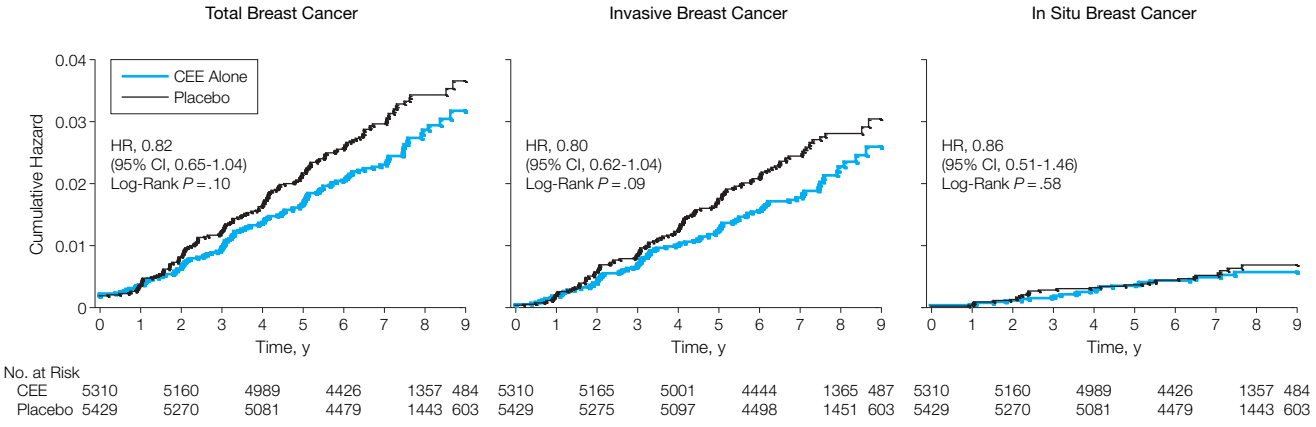
Only 5.2% of participants withdrew or were lost to follow-up and these losses were similar between the CEE group and the placebo group.[3] At study termination, 54% of participants were no longer adherent to study medication. Study pill discontinuation rates did not differ significantly by randomization assignment. Although women offered many reasons for discontinuation of study medication, the distribution of reasons was similar across both groups. The largest difference in reasons for stopping was in reported symptoms that are commonly associated with menopause or initiating menopausal hormones (24.5% for CEE vs 19.8% for placebo) with most of this difference attributed to breast symptoms (5.8% vs 1.6%). Use of nonstudy medications was reported by 8.4% of participants assigned to placebo and 5.3% of participants assigned to CEE.

Clinical Outcomes

In intention-to-treat analyses of all events (n=237 cases) occurring prior to intervention termination, nonsignificant reductions were observed for invasive breast cancer (HR, 0.80; 95% CI, 0.62-1.04; *P*=.09) and for total breast cancer (HR, 0.82; 95% CI, 0.65-1.04; *P*=.10) in women randomized to CEE only, while no effect on in situ disease was found (FIGURE 1). These results were not altered by adjusting for the small differences in the number of first-degree relatives with breast cancer or history of benign breast disease. There was no evidence of a trend with time in the invasive breast cancer HR (*P*=.29).

In further analyses, fewer breast cancers with localized disease were diagnosed in the CEE group than in the placebo group (HR, 0.69; 95% CI, 0.51-0.95), while the incidence of cancers of more advanced stage was comparable in the 2 groups (TABLE 3). A similar reduction was found for ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99) but not for lobular disease. The interac-

Figure 1. Cumulative Hazard for Total, Invasive, and In Situ Breast Cancer



CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

tion between treatment assignment and histology (ductal vs lobular) approached significance ($P=.054$), whereas there was no significant interaction between treatment assignment and stage (localized vs regional, $P=.09$) or tumor grade (well- vs moderately vs poorly differentiated/anaplastic, $P=.74$).

In adherence-adjusted analyses that censored follow-up 6 months after a woman became nonadherent (FIGURE 2), a larger and significant reduction in the incidence of invasive breast cancer was observed in the CEE group compared with the placebo group (HR, 0.67; 95% CI, 0.47-0.97; $P=.03$).

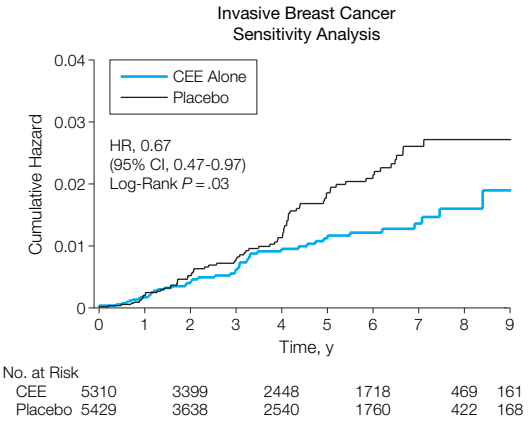
Significant interactions were seen between treatment assignment (FIGURE 3) and estimated 5-year breast cancer risk ($P=.01$), history of benign breast disease ($P=.005$), and number of first-degree relatives with breast cancer ($P=.01$). There was an apparent protective effect of CEE on breast cancer incidence observed in categories associated with lower risk in all 3 of these circumstances. No interaction was seen with oophorectomy status, body mass index (calculated as weight in kilograms divided by the height in meters squared), age at screening, menarche, first birth or menopause, prior oral contraceptive use, or nonsteroid anti-inflammatory drug use. No significant interaction of CEE with prior estrogen-only use was observed; however, although the data were sparse, the in-

Table 3. Clinical Outcomes by Treatment Group

	Incidence (Annualized %)		
	CEE Alone (n = 5310)	Placebo (n = 5429)	HR (95% CI)*
Follow-up, mean (SD), mo	85.0 (19.6)	85.4 (19.8)	
Total breast cancer†	129 (0.34)	161 (0.42)	0.82 (0.65-1.04)
Invasive	104 (0.28)	133 (0.34)	0.80 (0.62-1.04)
In situ	25 (0.07)	30 (0.08)	0.86 (0.51-1.46)
SEER stage‡			
Localized	66 (0.18)	98 (0.25)	0.69 (0.51-0.95)
Regional	35 (0.09)	31 (0.08)	1.15 (0.71-1.86)
Missing	3 (0.01)	4 (0.01)	0.78 (0.17-3.50)
Histology‡			
Ductal	61 (0.16)	88 (0.23)	0.71 (0.52-0.99)
Lobular	18 (0.05)	12 (0.03)	1.56 (0.75-3.24)
Ductal and lobular	12 (0.03)	12 (0.03)	1.00 (0.45-2.23)
Tubular	1 (<0.01)	4 (0.01)	NA
Other	12 (0.03)	16 (0.04)	0.76 (0.36-1.61)
Missing	0	1 (<0.01)	NA
Morphology, grade‡			
Well differentiated	19 (0.05)	26 (0.07)	0.74 (0.41-1.33)
Moderately differentiated	31 (0.08)	52 (0.13)	0.61 (0.39-0.96)
Poorly differentiated	26 (0.07)	35 (0.09)	0.77 (0.46-1.28)
Anaplastic	3 (0.01)	3 (0.01)	NA
Missing	25 (0.07)	17 (0.04)	1.52 (0.82-2.81)
Receptor status‡			
Estrogen-receptor assay			
Positive	72 (0.19)	95 (0.25)	0.78 (0.57-1.06)
Negative	19 (0.05)	21 (0.05)	0.92 (0.49-1.72)
Borderline	1 (<0.01)	0	NA
Missing	12 (0.03)	17 (0.04)	0.73 (0.35-1.53)
Progesterone-receptor assay			
Positive	56 (0.15)	70 (0.18)	0.82 (0.58-1.17)
Negative	33 (0.09)	42 (0.11)	0.80 (0.51-1.27)
Borderline	2 (0.01)	2 (0.01)	NA
Missing	13 (0.03)	19 (0.05)	0.71 (0.35-1.43)

Abbreviations: CEE, conjugated equine estrogens; CI, confidence interval; HR, hazard ratio; NA, data not calculable; SEER, Surveillance, Epidemiology, and End Results.
*From unweighted Cox proportional hazards models, stratified by age and Dietary Modification trial randomization assignment.
†Total breast cancer is the first of either invasive or in situ breast cancer.
‡Invasive subtypes of breast cancer.

Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis



Participants with less than 80% adherence to study medications were censored 6 months after their first episode of nonadherence. CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

teraction of CEE with prior use of combined E + P was nominally significant (P=.03). The stratum-specific results suggested the possibility that an effect of CEE was concentrated in women without prior hormone exposure of any type (FIGURE 4). No interactions were seen with duration or recency of prior hormone therapy use of any type. An analysis examining HRs by time since randomization revealed no significant trends overall or by prior hormone use.

Tumor Characteristics

Invasive breast cancers among women assigned to CEE were larger compared with those in women assigned to placebo (mean [SD], 1.8 cm [1.2] vs 1.5 cm [0.9]; P=.03) and a higher proportion tended to be node positive (35.5% vs 23.3%, respectively; P=.07) (TABLE 4).

Mammograms and Breast Biopsies

At baseline, detailed readings (other than cancer/no cancer) were available for 9844 mammograms and the frequency of mammograms with abnormalities was closely comparable in the 2 study groups (TABLE 5). After the first year, the percentage of mammograms with abnormalities requiring follow-up was substantially higher in the CEE group compared with the placebo group (436 [9.2%] of 4718 vs 260 [5.5%] of 4763, respectively; P<.001). Each year thereafter, the percentage of mammograms requiring follow-up was significantly higher in the CEE group resulting in a cumulative percentage of 36.2% in the CEE group and 28.1% in the placebo group (P<.001) over the course of the trial. This difference was concentrated in the category of recommended short interval follow-up. The number of reports of breast biopsy or aspiration was similar between the 2 groups at year 1 but from year 2 onward the number of such reports was higher in the CEE group each year (range of difference, 27-43) to total 198 more biopsies or aspirations over the study duration (Table 5).

COMMENT

In the WHI Estrogen-Alone trial, invasive breast cancer incidence did not differ significantly between women randomized to 0.625 mg/d of CEE compared with placebo over an average 7.1 years of follow-up. Preliminary results suggesting a lower breast cancer incidence in women in the CEE group were regarded as surprising in relation to prior evidence[14] and warranted a more detailed analysis. In the completed trial database, the invasive breast cancer incidence did not differ significantly between the CEE group and the placebo group (HR, 0.80; 95% CI, 0.62-1.04). However, exploratory analyses suggested that CEE might decrease breast cancer incidence in certain subgroups. In contrast, the proportion of mammograms with abnormalities requiring follow-up was significantly increased in the CEE group in the first year and in each year thereafter.

Although substantial evidence indicates that breast cancer risk is increased by both reproductive factors—which influence endogenous estrogen levels[15]—and exogenous estrogen combined with progestin therapy, the evidence regarding an effect of exogenous estrogen only on breast cancer risk has been mixed.[6-9,16-19] The preponderance of older observational studies that reported a modest increase in breast cancer diagnoses with use of unopposed estrogen were largely uncontrolled for mammography screening[4,6] and detection bias may have confounded results. However, even recent reports differ. In the Million Women Study[9] (a combined cross-sectional and cohort analysis), there was an increase in breast cancers with short-term estrogen alone use whereas another similarly sized observational study reported no increase in breast cancer with estrogen only[16] and neither did 2 other studies reported during this period.[17,18] In fact, Kerlikowske et al[19] reported an 8% decrease (95% CI, –16% to 0%) in breast cancer incidence among women taking estrogen alone for more than 5 years compared with those not taking hormones in a large cohort of women seen in community-based mammography practices.

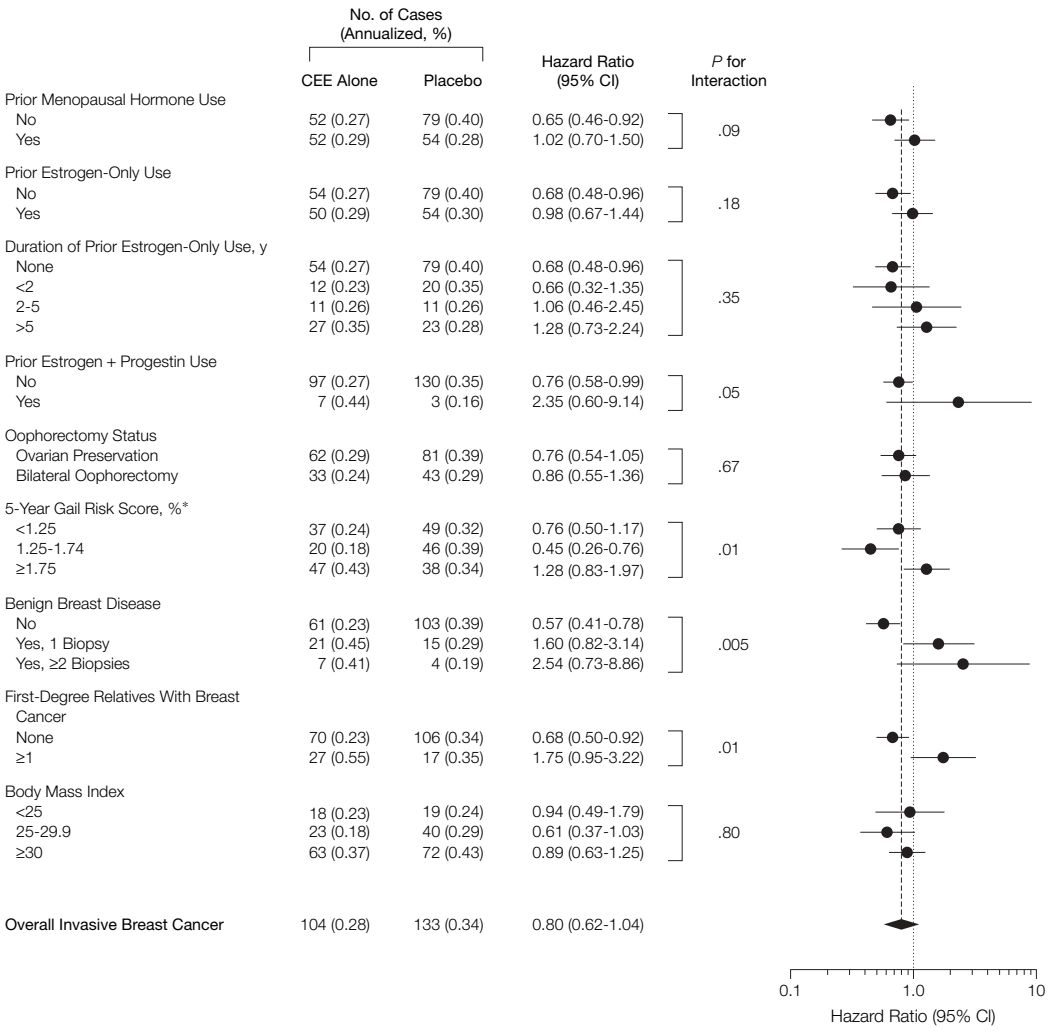
A conceptual model based solely on stimulation of breast cancer growth by estrogen addition and inhibition by estrogen reduction cannot explain available clinical and preclinical findings.[20] In preclinical models, breast cancer cells[21,22] and breast cancer xenographs[23,24] demonstrate apoptosis or tumor regression in response to low-dose estradiol after prior estrogen deprivation. In postmenopausal breast cancer patients, estrogen reduction with aromatase inhibitors[25] and estrogen

blockade with selective estrogen-receptor modulators like tamoxifen,[25] and exogenous estrogen[24-28] have anticancer effects. In addition, withdrawal of hormone therapy[29] (tamoxifen),[30] selective estrogen-receptor modulators, or the aromatase inhibitor exemestane[31] can result in breast cancer regression. These data are consistent with breast cancer cells being susceptible to estrogen fluctuations either above or below that tolerated by normal breast glandular tissues.

In subgroup analyses, which require cautious interpretation, significant reductions were observed in ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99) but not lobular tumors, and in invasive breast cancers in women who were adherent to study medications (HR, 0.67; 95% CI, 0.47-0.97; $P=.03$). An effect of CEE on breast cancer was seen in some subgroups at lower risk (lower Gail risk estimate, no first-degree relative with breast cancer, or absence of benign breast disease). Such findings suggest a stronger influence of CEE on breast cancer not linked to family history and/or those less likely to be associated with microcalcification, a mammography finding that often leads to recommendation for breast biopsy.

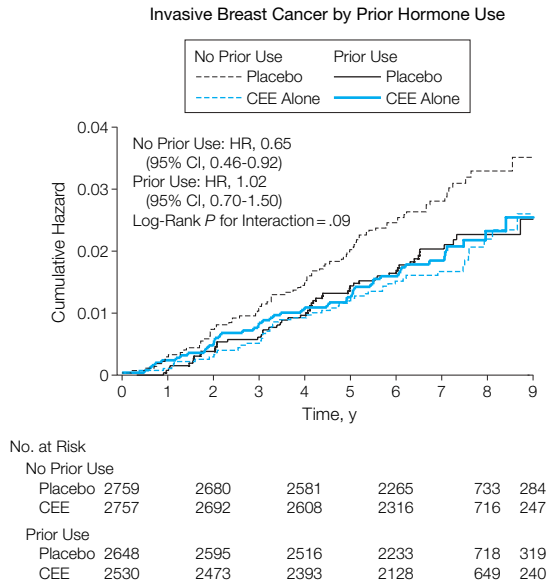
The observation of a lower breast cancer incidence with CEE relative to placebo in women with no prior hormone use but not in women with prior hormone use generates a hypothesis that subsequent or continued estrogen use would not reduce risk further because sensitive breast cancer cells already had exogenous estrogen exposure. In this regard, similar annual breast cancer incidence rates (between 0.26% and 0.29%) were seen in

Figure 3. Invasive Breast Cancers (Annualized %) by Baseline Characteristics and Randomization Assignment



CEE indicates conjugated equine estrogens; CI, confidence interval.
*Gail risk score incorporates age, history of benign breast disease (atypia status unknown in the Women's Health Initiative), age at menarche, age at first birth, race/ethnicity, and numbers of mothers and sisters with breast cancer.[13]

Figure 4. Cumulative Hazard for Invasive Breast Cancer by Prior Hormone Use and Randomization Assignment



CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

Table 4. Characteristics of Invasive Breast Cancers by Treatment Group

	No. (%) of Participants*		
	CEE Alone (n = 104)	Placebo (n = 133)	*P* Value†
Tumor size, mean (SD), cm‡	1.80 (1.18)	1.45 (0.88)	.03§
No tumor found/no primary mass	2 (2.4)	1 (0.9)	.32§
Microscopic focus or foci	2 (2.4)	2 (1.8)	
Tumor not clinically palpable	0	1 (0.9)	
≤0.5	7 (8.4)	16 (14.5)	
>0.5-1	23 (27.7)	28 (25.5)	
>1-2	26 (31.3)	44 (40.0)	
>2-5	22 (26.5)	16 (14.5)	
>5	1 (1.2)	2 (1.8)	
Missing	21 (20.2)	23 (17.3)	.57‖
Lymph nodes examined			
No	11 (10.7)	11 (8.5)	.58§
Yes	92 (89.3)	118 (91.5)	
Missing	1 (1.0)	4 (3.0)	.39‖
No. of lymph nodes examined, mean (SD)¶	10.6 (9.7)	10.1 (7.4)	.66§
No. of positive lymph nodes, mean (SD)#	1.4 (3.6)	1.0 (3.2)	.34§
No. of positive lymph nodes			
None	60 (64.5)	92 (76.7)	.14§
1-3	22 (23.7)	20 (16.7)	
≥4	11 (11.8)	8 (6.7)	
Missing	11 (10.6)	13 (9.8)	.84‖
Lymph nodes positive (yes)	33 (35.5)	28 (23.3)	.07§

Abbreviation: CEE, conjugated equine estrogens.
*Unless otherwise indicated.
†From a 2-sample *t* test for continuous variables or from a χ^2 or Fisher exact test for categorical variables.
‡Applies to those with a known tumor size (n = 76 for CEE and n = 102 for placebo).
§Test of association by using only known values of the characteristic.
‖Test of association by using the percentage missing for the characteristic.
¶Applies to those with a known number of lymph nodes examined, including those with zero nodes examined (n = 103 for CEE and n = 130 for placebo).
#Applies to those with a known number of positive lymph nodes examined (n = 93 for CEE and n = 120 for placebo).

the 3 groups with prior or current estrogen use while a higher annual incidence rate (0.40%) was seen only in the women with no prior estrogen exposure who were randomized to placebo (Figure 4). Alternatively, the subgroup with the higher incidence may have simply occurred by chance.

In the WHI E + P trial, CEE combined with medroxyprogesterone acetate significantly increased mammograms with recommended short interval follow-up as well as those suspicious or highly suggestive of malignancy.[2] In the current trial, CEE alone increased mammograms with recommended short interval follow-up but not those with more suspicious findings. Variability in radiologist use of a recommendation for short interval follow-up as well as the relation of such findings to breast cancer risk is recognized.[32-34] Nonetheless, a mammogram with this recommendation in clinical practice requires a repeat mammography screening after 6 months[32-34] with associated emotional and economic costs.[35-38] This finding should be included in discussions of risk and benefit of CEE use.

A total of 198 more biopsies without a cancer diagnosis were reported by women in the CEE group over the course of the trial. Only about 20% of biopsies in such a screened population would have proliferative breast disease,[39] a finding that is associated with a modest 2% or 3% risk of breast cancer in the next decade,[40] thus differential removal of precancerous lesions in the CEE group by biopsies cannot explain the study findings.

Combined hormone use increases mammogram breast density compared with placebo or estrogen alone.[41-43] Further studies are needed to define any mediating role for breast density change on the differences in mammogram findings seen in the 2 WHI hormone trials.

Observational studies regarding characteristics of breast cancers diagnosed while taking estrogen alone also have been mixed.[19,44] In the current randomized trial, the finding of a reduced incidence of localized tumors with no in-

crease in higher-stage disease rates is consistent with the modest increase in average tumor size seen in women assigned to CEE. A relative reduction in invasive ductal compared with lobular carcinomas also could contribute because the latter demonstrates lower sensitivity to mammography detection.[45,46] Analyses indirectly exploring diagnostic delay by considering prior hormone use were not definitive and hence this also remains a potential contributor. However, the relatively short breast cancer doubling time of about 150 days[47-49] and the continued divergence of the incidence curves through more than 6 years of follow-up argues against a masking hypothesis as a major influence. Further follow-up to provide additional data regarding long-term consequences of CEE exposure is ongoing.

A relatively consistent interaction of body mass index with menopausal hormones on breast cancer has been reported in observational studies with greater hormone effects in women with lower body mass index.[7,8,43,50] Nonetheless, no significant interaction of CEE and body mass index on breast cancer risk was seen in either the current Estrogen-Alone trial or in the WHI combined E + P trial.[2]

Regarding differences in findings between the E + P and Estrogen-Alone trials, the study cohorts differed by uterine status (ie, all estrogen-alone par-

Table 5. Mammographic Findings and Reports of Breast Biopsy or Aspiration by Treatment Group and Time From Study Entry*

	Baseline		Year 1		Year 2	
	CEE Alone	Placebo	CEE Alone	Placebo	CEE Alone	Placebo
Mammography performance of women due for visit with mammography in study period, %	100	100	89.3	88.0	85.8	85.8
Mammography recommendation						
Negative	2521 (54.0)	2507 (54.0)	2335 (49.5)	2540 (53.3)	2249 (50.0)	2423 (52.4)
Benign finding (negative)	1866 (40.0)	1880 (40.5)	1947 (41.3)	1963 (41.2)	1832 (40.7)	1888 (40.9)
Abnormal (total)	279 (6.0)	256 (5.5)	436 (9.2)†	260 (5.5)	421 (9.4)†	310 (6.7)
Short interval follow-up suggested	247 (5.3)	226 (4.9)	384 (8.1)	205 (4.3)	363 (8.1)	251 (5.4)
Suspicious abnormality	31 (0.7)	30 (0.6)	49 (1.0)	54 (1.1)	54 (1.2)	55 (1.2)
Highly suggestive of malignancy	1 (<0.1)	0 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)	4 (0.1)
Breast biopsy or aspiration	NA	NA	41 (0.8)	46 (0.9)	112 (2.3)	85 (1.7)
	Year 3		Year 4		Year 5	
	CEE Alone	Placebo	CEE Alone	Placebo	CEE Alone	Placebo
Mammography performance of women due for visit with mammography in study period, %	85.2	84.4	83.7	82.9	81.6	80.5
Mammography recommendation						
Negative	2115 (47.7)	2352 (52.2)	2024 (46.8)	2219 (50.5)	1912 (45.6)	2072 (49.0)
Benign finding (negative)	1909 (43.0)	1836 (40.7)	1890 (43.7)	1871 (42.5)	1921 (45.8)	1877 (44.3)
Abnormal (total)	414 (9.3)‡	318 (7.1)	413 (9.5)†	308 (7.0)	357 (8.5)‡	287 (6.8)
Short interval follow-up suggested	355 (8.0)	270 (6.0)	364 (8.4)	258 (5.9)	313 (7.5)	244 (5.8)
Suspicious abnormality	52 (1.2)	44 (1.0)	44 (1.0)	45 (1.0)	38 (0.9)	40 (0.9)
Highly suggestive of malignancy	7 (0.2)	4 (0.1)	5 (0.1)	5 (0.1)	6 (0.1)	3 (0.1)
Breast biopsy or aspiration	112 (2.3)	80 (1.6)	127 (2.6)	93 (1.9)	115 (2.4)	78 (1.6)
	Year 6		Year 7 and Later		Cumulative	
	CEE Alone	Placebo	CEE Alone	Placebo	CEE Alone	Placebo
Mammography performance of women due for visit with mammography in study period, %	83.2	82.1	84.2	81.9	97.4	97.1
Mammography recommendation						
Negative	1657 (43.6)	1821 (47.4)	1872 (46.1)	2062 (49.6)	646 (12.6)	793 (15.1)
Benign finding (negative)	1799 (47.3)	1739 (45.3)	1843 (45.4)	1817 (43.7)	2635 (51.2)	2983 (56.8)
Abnormal (total)	344 (9.1)‡	279 (7.3)	348 (8.6)§	277 (6.7)	1865 (36.2)†	1475 (28.1)
Short interval follow-up suggested	295 (7.8)	237 (6.2)	299 (7.4)	225 (5.4)	1542 (30.0)	1170 (22.3)
Suspicious abnormality	43 (1.1)	38 (1.0)	47 (1.2)	43 (1.0)	291 (5.7)	277 (5.3)
Highly suggestive of malignancy	6 (0.2)	4 (0.1)	2 (0.1)	9 (0.2)	32 (0.6)	28 (0.5)
Breast biopsy or aspiration	89 (1.9)	59 (1.2)	151 (2.0)	108 (1.4)	747 (2.0)	549 (1.5)

Abbreviations: CEE, conjugated equine estrogens; NA, not applicable.
*Data are presented as number (percentage) unless otherwise indicated.
†$P<.001$ for comparison of frequency of abnormal mammogram (short interval follow-up suggested, suspicious abnormality, highly suggestive of malignancy) in the CEE group compared with the placebo group.
‡$P<.01$ for comparison of frequency of abnormal mammogram (short interval follow-up suggested, suspicious abnormality, highly suggestive of malignancy) in the CEE group compared with the placebo group.
§$P = .02$ for comparison of frequency of abnormal mammogram (short interval follow-up suggested, suspicious abnormality, highly suggestive of malignancy) in the CEE group compared with the placebo group.

ticipants had a prior hysterectomy) and by a large number of other baseline characteristics.[51] Nonetheless, the mean 5-year Gail breast cancer risk estimates were similar (1.6% in the Estrogen-Alone trial and 1.5% in the E + P trial) and annualized rates of invasive breast cancer were similar for the placebo groups in the 2 trials (0.34% in Estrogen-Alone trial and 0.33% in E + P trial). Thus, cross-study differences in the study cohorts do not explain the differences in breast cancer effects seen and the results strongly suggest a role for progestin in relation to increasing breast cancer risk.

In conclusion, CEE alone for 7.1 years does not increase breast cancer incidence in postmenopausal women with hysterectomy and may decrease the risk of early stage disease and ductal carcinomas. This result is in clear contrast to the WHI trial of CEE combined with medroxyprogesterone acetate in women with a uterus, which showed a significant increase in breast cancer incidence over a mean of 5.6 years of follow-up.[2] Both trials showed a substantial increase in the frequency of mammograms requiring follow-up from the first year onward. However, this increase was seen only for recommended short-interval follow-up mammograms in the Estrogen-Alone trial, whereas it applied also to those with suspicious abnormality or highly suggestive of malignancy in the E + P trial.[2] Initiation of CEE alone in women after hysterectomy should continue to be based on careful consideration of potential risks and benefits for a given individual.

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