Health Outcomes After Stopping Conjugated Equine Estrogens Among Postmenopausal Women With Prior Hysterectomy

A Randomized Controlled Trial

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Context The Women's Health Initiative Estrogen-Alone Trial was stopped early after a mean of 7.1 years of follow-up because of an increased risk of stroke and little likelihood of altering the balance of risk to benefit by the planned trial termination date. Postintervention health outcomes have not been reported.

Objective To examine health outcomes associated with randomization to treatment with conjugated equine estrogens (CEE) among women with prior hysterectomy after a mean of 10.7 years of follow-up through August 2009.

Design, Setting, and Participants The intervention phase was a double-blind, placebo-controlled, randomized clinical trial of 0.625 mg/d of CEE compared with placebo in 10 739 US postmenopausal women aged 50 to 79 years with prior hysterectomy. Follow-up continued after the planned trial completion date among 7645 surviving participants (78%) who provided written consent.

Main Outcome Measures The primary outcomes were coronary heart disease (CHD) and invasive breast cancer. A global index of risks and benefits included these primary outcomes plus stroke, pulmonary embolism, colorectal cancer, hip fracture, and death.

Results The postintervention risk (annualized rate) for CHD among women assigned to CEE was 0.64% compared with 0.67% in the placebo group (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.75-1.25), 0.26% vs 0.34%, respectively, for breast cancer (HR, 0.75; 95% CI, 0.51-1.09), and 1.47% vs 1.48%, respectively, for total mortality (HR, 1.00; 95% CI, 0.84-1.18). The risk of stroke was no longer elevated during the postintervention follow-up period and was 0.36% among women receiving CEE compared with 0.41% in the placebo group (HR, 0.89; 95% CI, 0.64-1.24), the risk of deep vein thrombosis was lower at 0.17% vs 0.27%, respectively (HR, 0.63; 95% CI, 0.41-0.98), and the risk of hip fracture did not differ significantly and was 0.36% vs 0.28%, respectively (HR, 1.27; 95% CI, 0.88-1.82). Over the entire follow-up, lower breast cancer incidence in the CEE group persisted and was 0.27% compared with 0.35% in the placebo group (HR, 0.77; 95% CI, 0.62-0.95). Health outcomes were more favorable for younger compared with older women for CHD ($P = .05$ for interaction), total myocardial infarction ($P = .007$ for interaction), colorectal cancer ($P = .04$ for interaction), total mortality ($P = .04$ for interaction), and global index of chronic diseases ($P = .009$ for interaction).

Conclusions Among postmenopausal women with prior hysterectomy followed up for 10.7 years, CEE use for a median of 5.9 years was not associated with an increased or decreased risk of CHD, deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality. A decreased risk of breast cancer persisted.

Trial Registration clinicaltrials.gov Identifier: NCT00000611

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The Women's Health Initiative (WHI) Estrogen-Alone Trial was a double-blind, placebo-controlled, randomized clinical trial evaluating the effects of conjugated equine estrogens (CEE) on chronic disease incidence among postmenopausal women with prior hysterectomy. The trial intervention was stopped 1 year early after a mean of 7.1 years of follow-up because of an increased risk of stroke and little likelihood of altering the balance of risk to benefit by the planned termination date. Analyses of outcomes during the intervention period suggested that treatment effects differed by age; compared with older women, younger women receiving CEE had a lower risk of coronary heart disease (CHD), colorectal cancer, total death, and the global index of chronic diseases.[1] However, the tests for interaction of age with

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treatment were only statistically significant for colorectal cancer.[1]

All previous reports of this trial were limited to outcomes occurring during the intervention phase. Herein, we report data on postintervention outcomes through a mean of 10.7 years of follow-up. This preplanned analysis had 3 objectives: (1) to assess the long-term effects of the CEE intervention on health outcomes; (2) to determine whether effects of CEE on health outcomes differed between the intervention and postintervention periods; and (3) to determine if previously identified suggestions of age-specific differences in effects of CEE on health outcomes persisted after stopping the intervention.

METHODS

Intervention Phase

Details of the WHI Estrogen-Alone Trial have been published.[1,2] Briefly, postmenopausal women aged 50 to 79 years were recruited at 40 US clinical centers between 1993 and 1998. Women were eligible if they had a prior hysterectomy, were not taking hormone therapy, and had an anticipated 3-year survival. Women were excluded if they had prior breast cancer or other cancer within 10 years (except non–melanoma skin cancer), or prior venous thromboembolism (if screened after 1997). The study protocol was approved by institutional review boards at the participating institutions and all participants provided written informed consent.

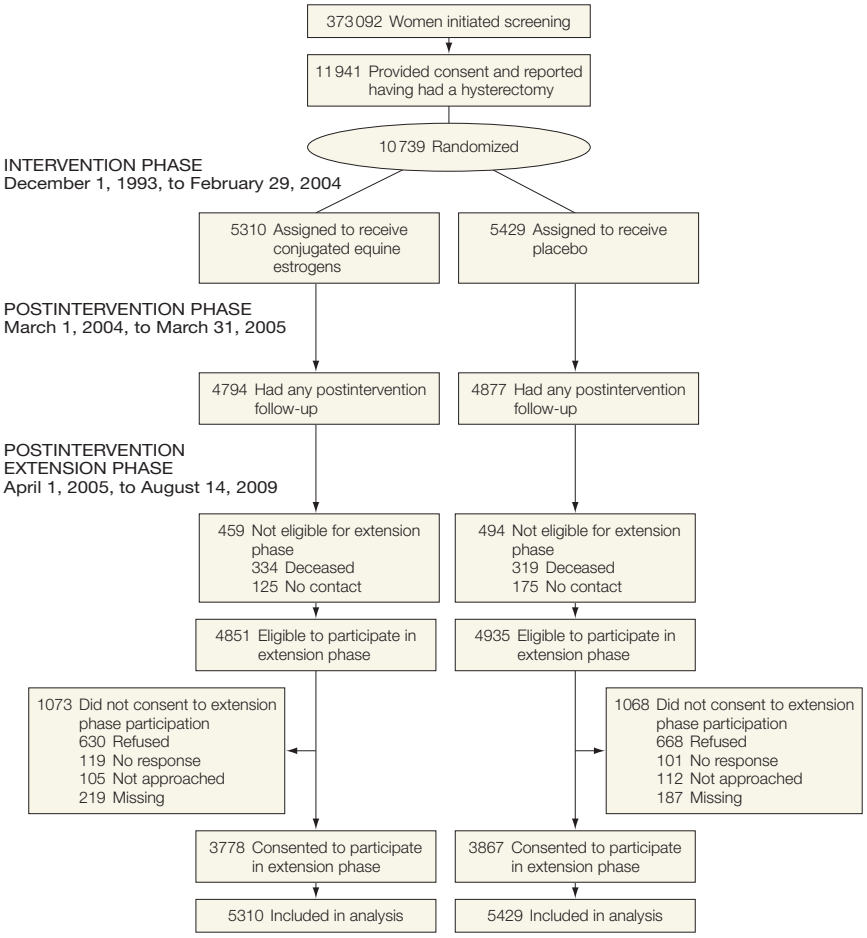
A total of 10 739 women were randomly assigned to receive orally either 0.625 mg/d of CEE (Premarin, Wyeth Ayerst, Philadelphia, Pennsylvania) or matching placebo. Randomization was implemented at the WHI Clinical Coordinating Center using a permuted block algorithm, stratified by clinical center and age group.[1] The clinical trial target size of 12 375 was calculated to provide 81% power to detect a 21% reduction in CHD at 9 years of follow-up. With the actual randomized sample size, the power estimate was 72% for a 21% reduction in CHD.

When the intervention phase ended after a mean of 7.1 years on February 29, 2004, vital status was known for 95% of participants, of whom 5.4% were deceased. By this time, 54% of participants had stopped taking their study medication. Median time receiving treatment was 5.9 years in the CEE group vs 5.8 years in the placebo group (interquartile range, 2.5-7.3 years). The median adherent time receiving treatment (ingestion of >80% of study pills) was 3.5 years in both groups (interquartile range, 1.5-6.5 years).

Clinical outcomes were collected through semiannual mailed questionnaires and annual clinic visits. Outcomes were verified[3] initially by trained physician adjudicators at the local clinical centers by medical record review, followed by final adjudication at the WHI Clinical Coordinating Center. All adjudicators were blinded to treatment assignment.

Demographic characteristics and medical history were collected by self-report using standardized questionnaires. Race/ethnicity was reported by participants within predefined categories matching the US Census. This in-

Figure 1. Women's Health Initiative Hormone Therapy Estrogen-Alone Trial Through Extended Follow-up



The intervention phase ran from December 1, 1993, to February 29, 2004. The postintervention phase began on March 1, 2004, the day participants were instructed to stop study medication use (conjugated equine estrogens or placebo) and continued through the original trial completion date (March 31, 2005). The postintervention extension phase began on April 1, 2005, and includes follow-up for participants who provided additional consent (78% of those eligible) through August 14, 2009.

formation was required by the funding agency to monitor nonwhite representation in the trial.

Postintervention Period and Extension

The postintervention period began on March 1, 2004, when participants were instructed to discontinue taking the study pills. The current report reflects a mean (SD) postintervention follow-up duration of 47.2 (20.7) months through August 14, 2009. After the protocol-specified termination date of March 31, 2005, subsequent participant follow-up required additional written consent, which was obtained from 77.9% of surviving participants in the CEE group (n=3778) and 78.4% of surviving participants in the placebo group (n=3867). The outcomes identified from the annual mailed questionnaires were verified by medical record review as described.[3] Annual mammograms were encouraged and tracked by annual mammography report review. During the postintervention period, 3.6% to 4.7% of women from the CEE group and 2.7% to 3.0% of women from the placebo group reported estrogen-alone use (any route of administration) on annual questionnaires.

Statistical Analyses

The primary analyses included all randomized participants using time-to-event methods and were based on the intention-to-treat principle as described previously.[4] Thus, all participants were included in the analyses according to their randomized group assignment until they provided their last follow-up information (FIGURE 1). Baseline characteristics for women who provided additional consent were compared by randomization group using χ^2 and *t* test statistics.

Annualized rates of clinical events were estimated for the intervention period, the postintervention period, and the entire follow-up period by dividing the number of events by the corresponding person-time in each phase. Cumulative incidence curves were drawn for each trial phase with quintiles of intended duration of intervention (ie, elapsed time from randomization until the intervention ended on February 29, 2004). The hazard ratios (HRs) were estimated using Cox proportional hazards models[5] stratified by age, prior disease (if appropriate), and randomization status in the WHI Dietary Modification Trial.[6] Models were constructed for each clinical end point in which women contributed follow-up time until the end of the interval, the date of their first relevant clinical event, or the date of death or withdrawal from the study (whichever came first). Formal tests of the differences between the HRs in the intervention compared with the postintervention phase were calculated by inclusion of a binary term for trial phase as a time-dependent variable as described.[4] Absolute rates and attributable risks (rate differences between CEE and placebo groups) also were calculated. All statistical tests were 2-sided.

Table. Baseline Characteristics[a]

	No. (%) of Participants		
	CEE (n = 3778)	Placebo (n = 3867)	*P* Value[b]
Age group at screening, y			
50-59	1223 (32.4)	1232 (31.9)	.88
60-69	1740 (46.1)	1799 (46.5)	
70-79	815 (21.6)	836 (21.6)	
Race/ethnicity			
White	2945 (78.0)	3001 (77.6)	.27
Black	514 (13.6)	565 (14.6)	
Hispanic	189 (5.0)	181 (4.7)	
American Indian	31 (0.8)	18 (0.5)	
Asian/Pacific Islander	54 (1.4)	49 (1.3)	
Unknown	45 (1.2)	53 (1.4)	
Hormone therapy use			
Never	1929 (51.1)	1916 (49.6)	.43
Past	1304 (34.5)	1373 (35.5)	
Current	544 (14.4)	575 (14.9)	
Duration of hormone therapy use, y			
<5	960 (51.9)	1036 (53.1)	.52
5-10	348 (18.8)	377 (19.3)	
>10	541 (29.3)	538 (27.6)	
BMI[c]			
<25	785 (20.9)	771 (20.1)	.21
25-<30	1289 (34.3)	1391 (36.2)	
≥30	1687 (44.9)	1683 (43.8)	
Smoking status			
Never	1988 (53.1)	1972 (51.5)	.30
Past	1417 (37.9)	1489 (38.9)	
Current	336 (9.0)	370 (9.7)	
Parity			
Never pregnant (no term pregnancy)	350 (9.3)	307 (8.0)	.04
≥1 term pregnancy	3400 (90.7)	3539 (92.0)	
Age at first birth, y			
<20	822 (27.0)	872 (27.3)	.53
20-29	2060 (67.7)	2128 (66.7)	
≥30	163 (5.4)	190 (6.0)	
Hysterectomy age group, y			
<40	1495 (39.8)	1501 (39.0)	.17
40-49	1643 (43.7)	1662 (43.2)	
50-54	345 (9.2)	412 (10.7)	
≥55	275 (7.3)	271 (7.0)	

(continued)

Table. Baseline Characteristics[a] (continued)

	No. (%) of Participants		
	CEE (n = 3778)	Placebo (n = 3867)	*P* Value[b]
Medical history			
Bilateral oophorectomy	1370 (39.0)	1507 (41.8)	.01
Treated diabetes (pills or injections)	243 (6.4)	250 (6.5)	.95
Hypertensive (self-report or high blood pressure)	1806 (51.1)	1844 (51.2)	.92
High cholesterol (requiring pills)	490 (14.3)	536 (15.5)	.16
Statin use	288 (7.6)	302 (7.8)	.76
Aspirin use ≥80 mg for ≥30 d	712 (18.8)	784 (20.3)	.12
Angina	243 (6.5)	253 (6.6)	.82
CABG or PTCA	69 (1.9)	70 (1.8)	.96
Stroke	51 (1.3)	47 (1.2)	.60
DVT or PE	65 (1.7)	60 (1.6)	.56
Fracture and age ≥55 y	455 (16.5)	447 (15.8)	.51
No. of times fell in last 12 mo			
0	2368 (67.5)	2331 (65.2)	.16
1	680 (19.4)	722 (20.2)	
2	296 (8.4)	346 (9.7)	
≥3	164 (4.7)	174 (4.9)	

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CEE, conjugated equine estrogens; DVT, deep vein thrombosis; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty.
[a] This table contains data from Women's Health Initiative participants who consented to extended follow-up after enrollment in the Estrogen-Alone Trial (April 2005).
[b] Test of association.
[c] Calculated as weight in kilograms divided by height in meters squared.

Nominal *P* values are reported without adjustment for multiple outcomes or sequential looks during the clinical trial follow-up period. Age-stratified subgroup analyses are reported for 10 outcomes. At the .05 level of significance, 0 to 1 interaction *P* values could be statistically significant based on chance alone.

To determine whether not providing consent to postintervention follow-up influenced risk estimates, inverse-probability weighting analyses were conducted using the methods described.[4] Adherence sensitivity analyses also were conducted by censoring follow-up at 6 months after participants became nonadherent (ingestion of <80% of study pills or starting nonprotocol hormone therapy). For these analyses, participants who provided additional consent or were adherent were included in analyses that used the inverse of the participant's estimated reconsent or adherence probability as a weighting factor.

All statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina) and R software version 2.11 (R Foundation for Statistical Computing, http://www.r-project.org/).

RESULTS

Baseline Characteristics

Participant movement through the study is outlined in Figure 1. Among the women who provided additional consent, baseline characteristics remained similar to those previously published[1] and were evenly distributed by randomized treatment assignment (TABLE). Small differences were observed for parity and bilateral oophorectomy between randomization groups. A comparison of the percentage of trial participants who consented to additional follow-up by treatment group is provided in eTable 1 at http://www.jama.com.

Comparison of Intervention and Postintervention Findings

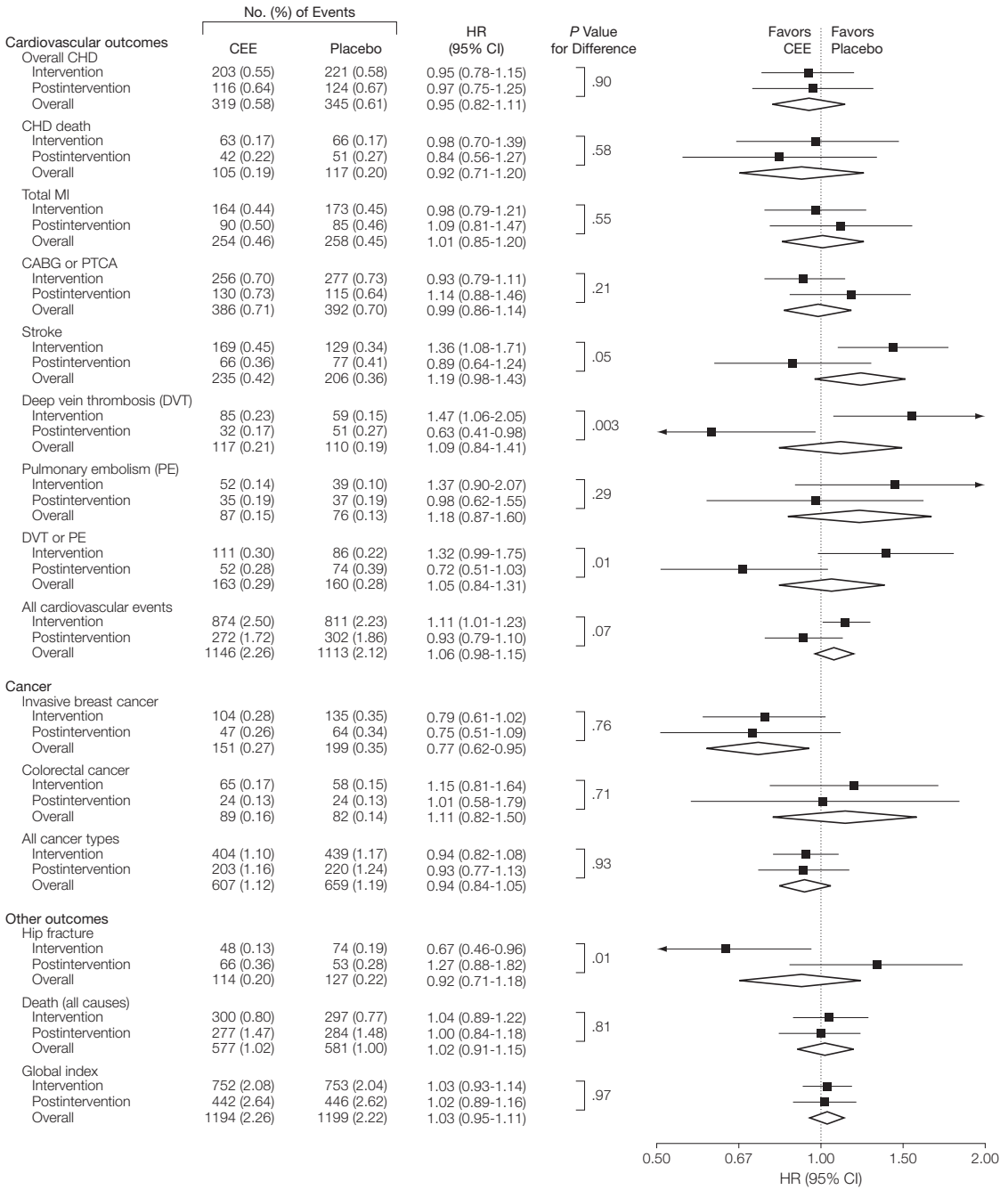
Incident clinical events by randomization assignment and corresponding HRs for the intervention, postintervention, and overall follow-up periods are summarized in FIGURE 2 and eTable 2 at http://www.jama.com. The HRs for CHD during the postintervention follow-up period were close to unity and similar to those observed during the intervention (Figure 2 and FIGURE 3). The increased stroke risk seen during the intervention phase was not present during the postintervention phase (0.36% [n=66] in the CEE group vs 0.41% [n=77] in the placebo group; HR, 0.89 [95% confidence interval {CI}, 0.64-1.24]; *P*=.05 for difference). Similarly, the increase in deep vein thrombosis and pulmonary embolism with CEE use compared with placebo during the intervention phase was not maintained during the postintervention phase (0.28% [n=52] vs 0.39% [n=74], respectively; HR, 0.72 [95% CI, 0.51-1.03]). For all cardiovascular events, the cumulative HR associated with CEE use was 1.06 (95% CI, 0.98-1.15) (2.26% in the CEE group [n=1146] vs 2.12% in the placebo group [n=1113]; Figure 2).

During the postintervention phase, 81.2% of women in the CEE group and 81.3% of women in the placebo group had at least 1 mammogram. The HRs comparing rates of invasive breast cancer in women randomized to CEE vs placebo were similar during the intervention (HR, 0.79; 95% CI, 0.61-1.02) and postintervention phases (HR, 0.75; 95% CI, 0.51-1.09) (Figure 2 and Figure 3). Consequently, a statistically significant lower cumulative breast cancer incidence of 0.27% was seen in the CEE group (n=151) compared with 0.35% in the placebo group (n=199) (HR, 0.77 [95% CI, 0.62-0.95]; *P*=.02). Colorectal cancer incidence did not differ between the women in the CEE group and the placebo group during the intervention or postintervention periods (Figure 2 and FIGURE 4).

The reduced hip fracture risk seen during the intervention phase with CEE was not maintained in the postintervention phase (0.36% in the CEE group [n=66] vs 0.28% in the placebo group [n=53]) (HR, 1.27 [95% CI, 0.88-1.82]; *P*=.01 for difference; Figure 2)

resulting in an overall HR of 0.92 (95% CI, 0.71-1.18]; 0.20% in the CEE group [n=114] vs 0.22% in the placebo group [n=127]). During the postintervention phase, hip fracture incidence was slightly higher in the CEE group compared with the placebo group (Figure 4). Randomization to CEE did not influence total mortality or the

Figure 2. Effects of Conjugated Equine Estrogens (CEE) Compared With Placebo on Clinical Outcomes During the Intervention and Postintervention Phases in the Women's Health Initiative Estrogen-Alone Trial



The hazard ratios (HRs) are derived from proportional hazards models stratified by prior disease (for outcomes in which women were eligible for enrollment with and without the prevalent condition), age, and dietary modification randomization group. The *P* values for differences between the intervention and postintervention phases were calculated from models for the overall mean follow-up period that also included a time-dependent term for trial phase. For the intervention and overall phases, time to event equals 0 on date of randomization. For the postintervention phase, time to event equals 0 on February 29, 2004. CABG indicates coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; and PTCA, percutaneous transluminal coronary angioplasty.

global index of chronic diseases either during the intervention phase or during the postintervention phase (Figure 2 and Figure 4).

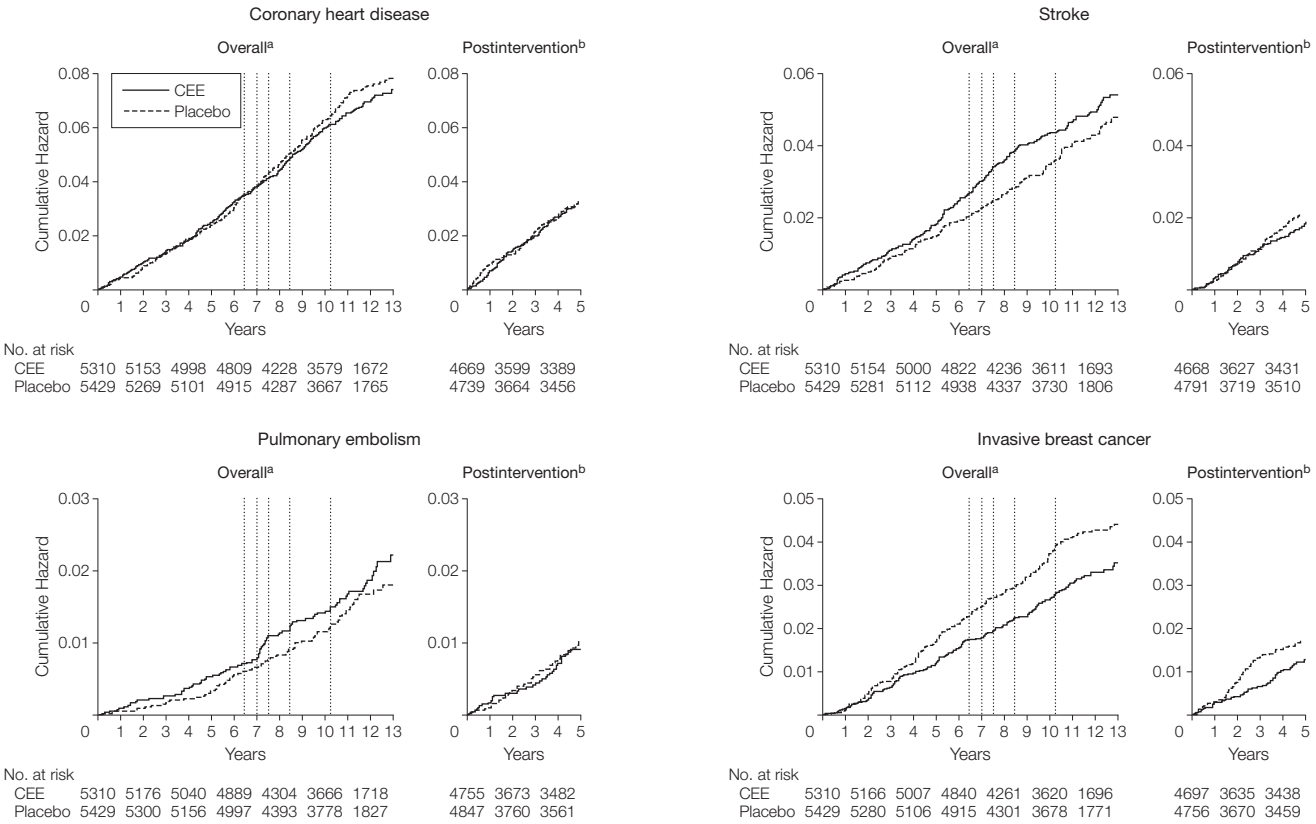
Age-Specific Comparisons

The age-specific intervention results for a mean follow-up of 10.7 years are displayed in FIGURE 5. The overall HRs for CHD differed among women aged 50 to 59 years (HR, 0.59 [95% CI, 0.38-0.90]; 0.18% [n=33] in the CEE group vs 0.31% in the placebo group [n=56]) compared with older women in which the HRs were near unity ($P=.05$ for interaction). For total myocardial infarction (MI), the HR was 0.54 (95% CI, 0.34-0.86; 0.15% in the CEE group [n=27] vs 0.27% in the placebo group [n=50]) for women aged 50 to 59 years; 1.05 (95% CI, 0.82-1.35; 0.51% [n=126] vs 0.48% [n=124], respectively) for women aged 60 to 69 years; and 1.23 (95% CI, 0.92-1.65; 0.82% [n=101] vs 0.66% [n=84], respectively) for women aged 70 to 79 years ($P=.007$ for interaction). A similar pattern was seen when time since menopause (as previously defined[7]) instead of age was examined for both coronary end points (data not shown). Overall, stroke risks were nonsignificantly elevated for all age groups ($P=.91$ for interaction). For deep vein thrombosis and pulmonary embolism, no age-specific differences emerged but the increased risks observed during the intervention phase subsided during the postintervention phase.

There were fewer invasive breast cancers in the CEE group compared with the placebo group in all 3 age groups ($P=.96$ for interaction). The previously observed age interaction for colorectal cancer was significant throughout the entire follow-up period. Women aged 70 to 79 years at entry experienced a nearly 2-fold increased risk of colorectal cancer in the CEE group (0.30% [n=38] vs 0.16% in the placebo group [n=21]) (HR, 1.83 [95% CI, 1.08-3.12]; $P=.04$ for interaction).

The HRs for total mortality and the global index of chronic diseases differed by age as previously suggested.[7] Younger postmenopausal women (aged 50-59 years) who were randomized to CEE vs placebo had a lower risk of death (0.35% [n=65] vs 0.48% [n=89], respectively; HR, 0.73 [95% CI, 0.53-1.00]) compared with no increased risk among women in their 60s (1.00% [n=254] vs 0.96% [n=253], respec-

Figure 3. Cumulative Incidence of Coronary Heart Disease, Stroke, Pulmonary Embolism, and Invasive Breast Cancer



Vertical dotted lines represent quintiles of duration of intended intervention and follow-up in the study population (elapsed time from randomization until the end of the intervention on February 29, 2004). CEE indicates conjugated equine estrogens.
[a] Includes events from randomization to August 14, 2009.
[b] Includes events from March 1, 2004, to August 14, 2009.

tively; HR, 1.04 [95% CI, 0.88-1.24]), and a slight increased risk of death among women in their 70s (2.02% [n=258] vs 1.83% [n=239], respectively; HR, 1.12 [95% CI, 0.94-1.33]; *P*=.04 for interaction). A similar pattern was observed by age for women randomized to CEE vs placebo for the global index of chronic diseases with a possible overall benefit among younger women (aged 50-59 years: 1.04% [n=184] vs 1.22% [n=217], respectively; HR, 0.85 [95% CI, 0.70-1.03]) and possible harm among the oldest women (aged 70-79 years: 4.04% [n=466] vs 3.56% [n=423], respectively; HR, 1.15 [95% CI, 1.01-1.32]; *P*=.009 for interaction).

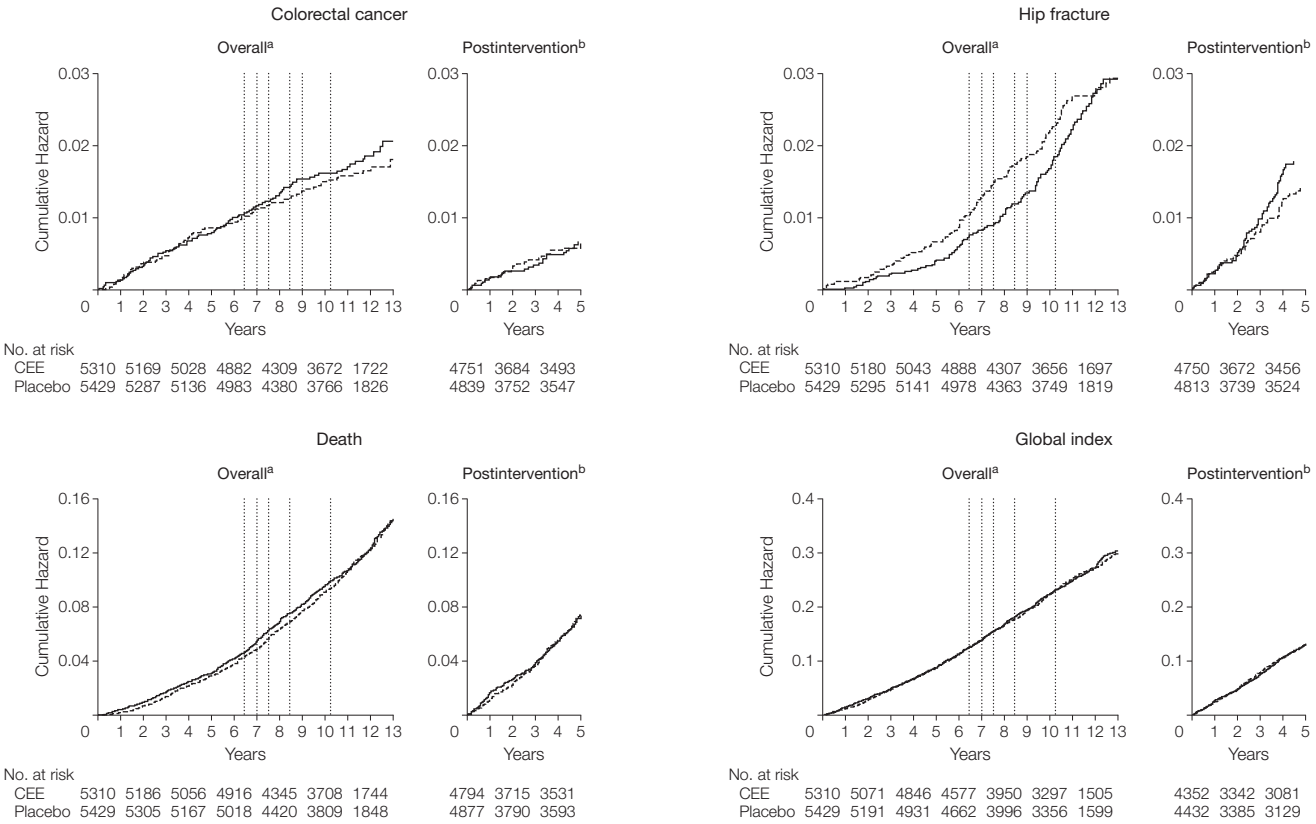
Expressed as absolute rates per 10 000 women annualized over the average follow-up period of 10.7 years, women aged 50 to 59 years who received CEE compared with women who received placebo had 12 fewer acute MIs, 13 fewer deaths, and 18 fewer adverse events in the global index of chronic diseases. In contrast, women aged 70 to 79 years who received CEE compared with women who received placebo had 16 excess MIs, 19 excess deaths, and 48 excess adverse events in the global index of chronic diseases.

Sensitivity Analyses

The results were similar when using inverse-probability weighting to account for censoring due to those not providing consent for postintervention follow-up. The HR for breast cancer for the cumulative follow-up period became 0.81 (95% CI, 0.64-1.01). Age-stratified results were virtually identical to those described herein with *P* values for interaction reflecting some loss of precision with the inverse-probability weights: CHD (*P*=.23); total MI (*P*=.01); colorectal cancer (*P*=.09); death (*P*=.13); and global index of chronic diseases (*P*=.02). In each case, women in their 50s had more favorable HRs than older women (aged 70-79 years).

The results also were similar when women were censored 6 months after becoming nonadherent to study medication during the intervention period. Adherence-adjusted HRs for the overall follow-up period using inverse-probability weighting showed an increased risk of stroke with CEE use (HR, 1.50; 95% CI, 1.11-2.05) and a lower risk of breast cancer (HR, 0.68; 95% CI, 0.49-0.95). No significant age

Figure 4. Cumulative Incidence of Colorectal Cancer, Hip Fracture, Death, and Global Index of Chronic Diseases



Vertical dotted lines represent quintiles of duration of intended intervention and follow-up in the study population (elapsed time from randomization until the end of the intervention on February 29, 2004). CEE indicates conjugated equine estrogens.
[a] Includes events from randomization to August 14, 2009.
[b] Includes events from March 1, 2004, to August 14, 2009.

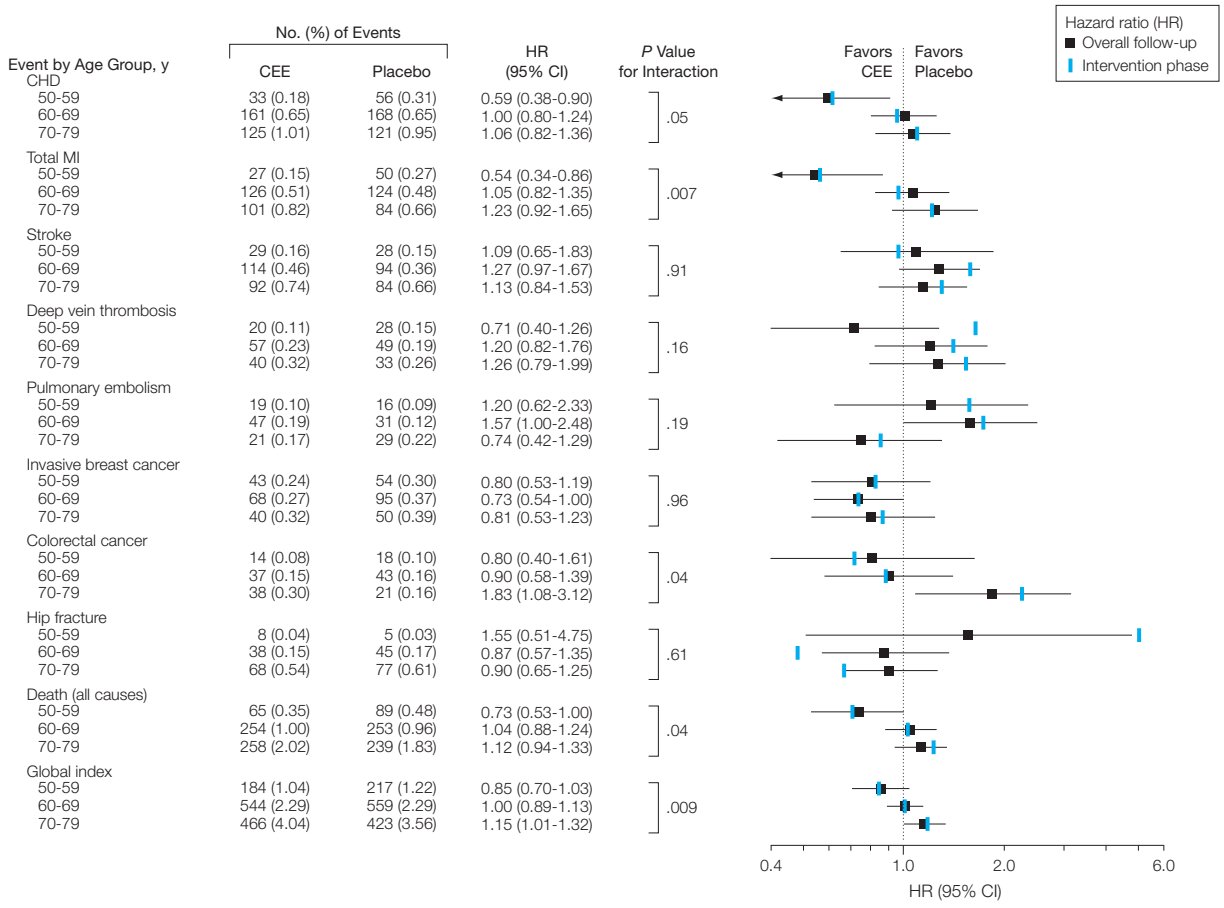
interactions emerged for any outcome in the adherence-adjusted analyses; however, power was limited due to substantial censoring.

COMMENT

Among postmenopausal women with prior hysterectomy who stopped taking CEE after a median of 5.9 years of use, several patterns of health risks and benefits seen during the intervention period were not maintained during the postintervention period, while other trends persisted. For CHD (a primary trial end point), the HRs remained null after stopping the intervention and overall. The increases in risk of stroke and venous thromboembolism seen among women randomized to CEE during the intervention period rapidly dissipated during the postintervention period as did the protective effect on risk of hip fracture. The lower incidence of breast cancer seen among women randomized to CEE during the intervention period became statistically significant with extended follow-up. Considering the entire follow-up period, rates of total mortality and the global index of chronic diseases were essentially the same in the CEE and placebo groups. Statistically significant age interactions for CEE use, suggesting greater safety and possible benefit among women in their 50s and potential harm among older women, were observed for CHD, total MI, colorectal cancer, total mortality, and the global index of chronic diseases.

The statistically significant reduction in breast cancer incidence seen with CEE use continued a trend that emerged during the intervention period.[8,9] This finding differs from the preponderance[10-12] but not all[13,14] observational studies that suggest CEE use, especially in lean women[15,16] and after long duration of exposure,[17] increases breast cancer incidence. We previously reported no significant differences by body mass index for CEE effects on breast cancer incidence among participants in this trial.[8]

Figure 5. Cumulative Annualized Incidence Rates for Clinical Outcomes in the Women's Health Initiative Estrogen-Alone Trial According to 10-Year Age Groups at Enrollment



Event by Age Group, y	No. (%) of Events CEE	No. (%) of Events Placebo	HR (95% CI)	*P* Value for Interaction
CHD				
50-59	33 (0.18)	56 (0.31)	0.59 (0.38-0.90)	
60-69	161 (0.65)	168 (0.65)	1.00 (0.80-1.24)	.05
70-79	125 (1.01)	121 (0.95)	1.06 (0.82-1.36)	
Total MI				
50-59	27 (0.15)	50 (0.27)	0.54 (0.34-0.86)	
60-69	126 (0.51)	124 (0.48)	1.05 (0.82-1.35)	.007
70-79	101 (0.82)	84 (0.66)	1.23 (0.92-1.65)	
Stroke				
50-59	29 (0.16)	28 (0.15)	1.09 (0.65-1.83)	
60-69	114 (0.46)	94 (0.36)	1.27 (0.97-1.67)	.91
70-79	92 (0.74)	84 (0.66)	1.13 (0.84-1.53)	
Deep vein thrombosis				
50-59	20 (0.11)	28 (0.15)	0.71 (0.40-1.26)	
60-69	57 (0.23)	49 (0.19)	1.20 (0.82-1.76)	.16
70-79	40 (0.32)	33 (0.26)	1.26 (0.79-1.99)	
Pulmonary embolism				
50-59	19 (0.10)	16 (0.09)	1.20 (0.62-2.33)	
60-69	47 (0.19)	31 (0.12)	1.57 (1.00-2.48)	.19
70-79	21 (0.17)	29 (0.22)	0.74 (0.42-1.29)	
Invasive breast cancer				
50-59	43 (0.24)	54 (0.30)	0.80 (0.53-1.19)	
60-69	68 (0.27)	95 (0.37)	0.73 (0.54-1.00)	.96
70-79	40 (0.32)	50 (0.39)	0.81 (0.53-1.23)	
Colorectal cancer				
50-59	14 (0.08)	18 (0.10)	0.80 (0.40-1.61)	
60-69	37 (0.15)	43 (0.16)	0.90 (0.58-1.39)	.04
70-79	38 (0.30)	21 (0.16)	1.83 (1.08-3.12)	
Hip fracture				
50-59	8 (0.04)	5 (0.03)	1.55 (0.51-4.75)	
60-69	38 (0.15)	45 (0.17)	0.87 (0.57-1.35)	.61
70-79	68 (0.54)	77 (0.61)	0.90 (0.65-1.25)	
Death (all causes)				
50-59	65 (0.35)	89 (0.48)	0.73 (0.53-1.00)	
60-69	254 (1.00)	253 (0.96)	1.04 (0.88-1.24)	.04
70-79	258 (2.02)	239 (1.83)	1.12 (0.94-1.33)	
Global index				
50-59	184 (1.04)	217 (1.22)	0.85 (0.70-1.03)	
60-69	544 (2.29)	559 (2.29)	1.00 (0.89-1.13)	.009
70-79	466 (4.04)	423 (3.56)	1.15 (1.01-1.32)	

Annualized incidence rates were estimated for the overall follow-up period by dividing the number of events by the corresponding person-time for participants in each age stratum. The black squares indicate the HRs for the overall follow-up period. For comparison, the HRs for the intervention phase are shown as blue bars. CEE indicates conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

Investigators from the Million Women Study have suggested,[18] based on recent findings,[9,19,20] that time from menopause (longer in the WHI vs shorter in usual clinical practice and observational study cohorts) may account for some of the differences in risk estimates from various studies. Alternatively, confounding by differential mammogram use in the observational studies (higher in estrogen users) may explain the finding of higher breast cancer incidence among hormone therapy users.[20] Future subgroup analyses in this trial, which are beyond the scope of the current study, will explore this issue.

It is unlikely that diagnostic delay explains our breast cancer results because CEE only modestly influenced breast density[21] and mammogram diagnostic performance.[22] In terms of biological plausibility, preclinical[23,24] and clinical[25] studies suggest that the adaptive changes to gene expression profiles that occur during estrogen exposure and after estrogen deprivation[26] may render mammary tumors susceptible to inhibition by estrogen. In contrast to these results from the Estrogen-Alone Trial, the WHI combined Estrogen Plus Progestin Trial showed that treatment impeded mammographic accuracy, and was associated with significant increase in rates of both breast cancer incidence and breast cancer mortality.[27-29]

With extended follow-up, hip fracture cumulative incidence was the same in the CEE and placebo groups. Rates of hip fracture were somewhat higher among women in the CEE group compared with those in the placebo group after stopping the intervention. These results are consistent with studies showing accelerated bone loss[30] and a short-term increased risk of hip fracture among women who discontinue hormone therapy,[31] and no fracture risk reduction or elevation in past hormone therapy users.[32,33]

Our results suggest that women randomized to CEE while in their 50s had fewer CHD events than those randomized to placebo, findings that are supported by preclinical[34] and clinical data[35-37] but are not applicable to older women. In a subset of WHI participants aged 50 to 59 years at study entry, coronary artery calcium measurements, which are markers for atherosclerotic plaque burden, were lower following trial completion among women randomized to CEE vs placebo.[35] Other support derives from nonhuman primate models[36] and observational studies.[38-40] An important caveat is that study participants took unopposed estrogen for a median duration of less than 6 years and our results cannot be extrapolated to longer or shorter treatment durations.

Our results emphasize the need to counsel women about hormone therapy differently depending on their age and hysterectomy status. A postmenopausal woman who has had a hysterectomy and is considering initiation of CEE should be counseled about the increased risks of venous thromboembolism and stroke during treatment, which diminish with treatment cessation. Among younger women, no new safety concerns emerged and some risk reductions became apparent during the postintervention period. Among older women, risks of colorectal cancer, death, and the global index of chronic diseases were elevated over the cumulative follow-up period. The risks and benefits of CEE use for periods of longer than 5 to 6 years cannot be inferred from these data for any age group. Mechanisms underlying the reduced risks of breast cancer in all women, and coronary events in younger but not older women, warrant further study.

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