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ORIGINAL CONTRIBUTION

Health Risks and Benefits 3 Years After Stopping Randomized Treatment With Estrogen and Progestin

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Context The Women's Health Initiative (WHI) trial of estrogen plus progestin vs placebo was stopped early, after a mean 5.6 years of follow-up, because the overall health risks of hormone therapy exceeded its benefits.

Objective To report health outcomes at 3 years (mean 2.4 years of follow-up) after the intervention was stopped.

Design, Setting, and Participants The intervention phase was a double-blind, placebo-controlled, randomized trial of conjugated equine estrogens (CEE) 0.625 mg daily plus medroxyprogesterone acetate (MPA) 2.5 mg daily, in 16 608 women aged 50 through 79 years, recruited by 40 centers from 1993 to 1998. The postintervention phase commenced July 8, 2002, and included 15 730 women.

Main Outcome Measures Semi-annual monitoring and outcomes ascertainment continued per trial protocol. The primary end points were coronary heart disease and invasive breast cancer. A global index summarizing the balance of risks and benefits included the 2 primary end points plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results The risk of cardiovascular events after the intervention was comparable by initial randomized assignments, 1.97% (annualized rate) in the CEE plus MPA (343 events) and 1.91% in the placebo group (323 events). A greater risk of malignancies occurred in the CEE plus MPA than in the placebo group (1.56% [n=281] vs 1.26% [n=218]; hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.04-1.48). More breast cancers were diagnosed in women who had been randomly assigned to receive CEE plus MPA vs placebo (0.42% [n=79] vs 0.33% [n=60]; HR, 1.27; 95% CI, 0.91-1.78) with a modest trend toward a lower HR during the follow-up after the intervention. All-cause mortality was somewhat higher in the CEE plus MPA than in the placebo group (1.20% [n=233] vs 1.06% [n=196]; HR, 1.15; 95% CI, 0.95-1.39). The global index of risks and benefits was unchanged from randomization through March 31, 2005 (HR, 1.12; 95% CI, 1.03-1.21), indicating that the risks of CEE plus MPA exceed the benefits for chronic disease prevention.

Conclusions The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal and nonfatal malignancies occurred after the intervention in the CEE plus MPA group and the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo.

Trial Registration clinicaltrials.gov Identifier: NCT00000611

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THE WOMEN'S HEALTH INITIATIVE (WHI) trial of estrogen plus progestin assessed whether conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) prevents heart disease and hip fractures and increases the risk of breast cancer in 16 608 postmenopausal, predominantly healthy women with an intact uterus who were 50 through 79 years old at study entry. Study outcomes also included stroke, deep vein thrombosis, pulmonary embolism, endometrial cancer, colorectal cancer, hip, vertebral and other fractures, death from all causes, and a global index of benefit and harm.

Although designed to yield appropriately powered risk estimates after 8 to 9 years, the trial was stopped at a mean 5.6 years of follow-up because of an increased risk of invasive breast can-

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cer and the failure to demonstrate an overall health benefit.[1] Based on outcomes adjudicated through a mean of 5.2 years of follow-up, women in the CEE plus MPA group had higher risks of cardiovascular disease (CVD), coronary heart disease (CHD), stroke, venous thromboembolism, and breast cancer and had lower risks of fracture and colorectal cancer. Mortality was not affected during the trial. Detailed information has since been provided for the study outcomes ascertained during the trial,[2-11] guidelines for menopausal hormone therapy have changed,[12,13] and prescriptions written have declined.[14]

This analysis, which includes adjudicated outcomes through the planned trial duration of 8.5 years, was a planned point of analysis to better understand the changes in hormone-relevant health conditions when postmenopausal hormone therapy is stopped. We report the health risks and benefits experienced by 15 730 trial participants who had follow-up after the intervention from July 8, 2002, to March 31, 2005.

METHODS

Intervention Phase

Details of the WHI design have been reported.[15] Briefly, postmenopausal women aged 50 through 79 years with an intact uterus who gave written informed consent were enrolled in the WHI at 40 Clinical Centers in the United States. A total of 16 608 eligible women were randomly assigned to receive active treatment (8506) or placebo (8102) and were followed up for an average of 5.6 years. Treatment consisted of 0.625 mg of CEE, and 2.5 mg of MPA (Prempro, Wyeth Ayerst, Philadelphia, Pennsylvania), or matching placebo. At semiannual contacts in the clinic or by telephone and at annual visits to the WHI clinic, standardized information was collected on symptoms, adverse events, adherence to study pills, and potential trial clinical outcomes. Potential outcomes were verified by obtaining medical records and death certificates that were reviewed by physician adjudicators blinded to treatment assignment. Herein, the outcomes designated "clinical trial or intervention phase" include outcomes adjudicated after the analysis performed at 5.2 years and previously reported in the trial primary outcomes article.[1] Details regarding trial exclusions and the protocol for randomization, event ascertainment and adjudication, study discontinuation, and the calculation of the global index have been reported.[15] Race and ethnicity were self-identified according to categories of the 1990 census. The protocol and consent forms were approved by the institutional review boards at all participating institutions.

Postintervention Phase

The period between the early termination of the intervention (July 7, 2002) and the end of the predefined trial period (March 31, 2005) defines the postintervention phase. Follow-up during a mean of 2.4 years accrued under strict observance of the trial protocol for semiannual end point ascertainment and verification, as well as annual mammography surveillance.[1,15]

The postintervention phase includes events accrued through March 31, 2005, and adjudicated by September 30, 2005, at which point adjudication was 98% to 99% complete. From randomization to July 7, 2002, 250 women died in the CEE plus MPA group and 239 women in the placebo group. Of 8506 women originally randomized to CEE plus MPA, postintervention information for the period July 8, 2002, to March 31, 2005, was available for 8052 women (95%). Of 8102 women randomized to placebo, postintervention information through March 31, 2005, was available for 7678 (95%).

Statistical Analyses

Baseline characteristics of the women in the CEE plus MPA and placebo groups with any postintervention information were compared by χ^2 or *t* test. Annualized rates of events in each treatment group were estimated for the intervention phase, postintervention phase, and overall by dividing the number of events by the corresponding survival time in each phase. The estimates for the clinical trial–intervention phase, postintervention phase, and overall (baseline through March 30, 2005) apply the time-to-event and intention-to-treat methods previously used in the analysis of the trial results.[1] Hazard ratios (HRs) were estimated from Cox proportional hazards analyses stratified by age, prior disease if appropriate, and randomization assignment in the dietary modification trial. The beginning point of the survival times ($t=0$) of the intervention phase, postintervention phase, and overall were defined to be the date of randomization, date of trial termination (July 7, 2002), and date of randomization, respectively. *P* values are nominal and not adjusted for sequential looks during the clinical trial follow-up period.

We performed a formal test of whether the HR in the clinical trial phase equals the HR during the postintervention phase by defining a time-dependent binary covariate, $X(t)$, as equal to 1 for participants taking CEE plus MPA during the postintervention period and 0 otherwise. The baseline hazard functions were also allowed to vary between trial phases. The parametric portion of the estimated log hazard function for the participants taking CEE plus MPA is then $\hat{\beta}+\hat{\delta}\times X(t)$ with $\exp(\hat{\beta})$ equal to the estimated HR during the clinical trial phase and $\exp(\hat{\beta}+\hat{\delta})$ equal to the estimated HR during the postintervention phase. We tested whether $\hat{\delta}$ equals 0 and report the corresponding *P* value, *P* difference.

We performed a sensitivity analysis to assess the risks among women who had been adherent to their study medication (defined as ≥80%) during the intervention phase of the trial. For an appropriate comparison between randomization groups, participants adherent at the end of the intervention phase were included in the postintervention HR estimation procedure that used the inverse of the partici-

pant's estimated adherence probability as a weighting factor. This method[16] yields valid HR estimates among participants meeting adherence criteria provided that probabilities can be accurately estimated. These probabilities were estimated by logistic regression including the baseline variables of age, ethnicity, education, body mass index, smoking, self-reported general health, night sweats, hot flashes, breast tenderness, and treatment assignment, and at year 1, breast tenderness, night sweats, and hot flashes. All analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

Table 1. Baseline Characteristics of Women's Health Initiative Participants With Any Postintervention Follow-up (July 7, 2002-March 31, 2005)

	No. (%) Alive in Follow-up		
	CEE + MPA (n = 8052)	Placebo (n = 7678)	*P* Value[a]
Age at baseline, (mean, SD), y	63.1 (7.1)	63.3 (7.1)	.21
Race/ethnicity			
White	6788 (84.3)	6477 (84.4)	.56
Black	517 (6.4)	533 (6.9)	
Hispanic	426 (5.3)	385 (5.0)	
American Indian	24 (0.3)	27 (0.4)	
Asian/Pacific Islander	180 (2.2)	156 (2.0)	
Unknown	117 (1.5)	100 (1.3)	
Education			
>High school	5959 (74.4)	5580 (73.2)	.09
BMI			
<25	2430 (30.3)	2373 (31.1)	.48
25-<30	2826 (35.3)	2689 (35.2)	
≥30	2760 (34.4)	2568 (33.7)	
Hypertension	2851 (38.5)	2772 (38.0)	.51
Treated diabetes, pills or shots	344 (4.3)	321 (4.2)	.78
Smoking status			
Never smoked	4011 (50.3)	3823 (50.4)	.93
Past smoker	3166 (39.7)	2990 (39.5)	
Current smoker	794 (10.0)	765 (10.1)	
Years since menopause			
<5	1268 (17.4)	1167 (16.4)	.30
5-<10	1405 (19.3)	1432 (20.1)	
10-<15	1545 (21.2)	1494 (21.0)	
≥15	3066 (42.1)	3027 (42.5)	
Medical history			
Myocardial infarction	126 (1.6)	136 (1.8)	.31
Angina	290 (3.6)	302 (4.0)	.28
Coronary revascularization[b]	88 (1.1)	105 (1.4)	.11
Stroke	55 (0.7)	64 (0.8)	.28
DVT or PE	74 (0.9)	61 (0.8)	.40
Breast cancer, female	1213 (15.9)	1110 (15.3)	.29
Fracture >55 y	968 (14.1)	968 (14.3)	.32
High cholesterol requiring pills	873 (12.2)	902 (12.7)	.34
Baseline statin use	544 (6.8)	503 (6.6)	.61
Baseline aspirin use, >80 mg/d	1535 (19.1)	1543 (20.1)	.10
HT usage status			
Never used	5929 (73.7)	5710 (74.4)	.46
Past user	1589 (19.7)	1492 (19.4)	
Current user	530 (6.6)	473 (6.2)	
HT duration, y			
<5	1468 (69.1)	1394 (70.9)	.14
5-<10	405 (19.1)	329 (16.7)	
≥10	250 (11.8)	244 (12.4)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CEE, conjugated equine estrogens; DVT, deep vein thrombosis, HT, hormone therapy; MPA, medroxyprogesterone acetate; PE pulmonary embolism.

[a] Test of association between baseline characteristic and "Alive, in follow-up" for CEE plus MPA and placebo based on χ^2 or *t* test.

[b] Includes coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty.

RESULTS

Baseline Characteristics

Baseline demographic and risk factor characteristics of the women with any postintervention follow-up are shown in TABLE 1. There were no statistically significant differences between the CEE plus MPA and placebo groups across any of the 19 variables examined. Follow-up during the postintervention phase was missing for 389 of 15 730 participants (<2.5%). Women without postintervention follow-up did not differ by treatment assignment (*P* = .63).

Clinical outcomes accrued during the intervention phase and during the posttrial follow-up are presented by randomization assignment in TABLE 2. Women with any postintervention follow-up were included in the analyses. Also shown in Table 2 are the events accumulated from randomization to March 31, 2005 (mean 7.9 years of follow-up).

Postintervention Phase

The increased risks of CVD events in women randomly assigned to CEE plus MPA observed during the trial were not observed in the postintervention phase. During a mean 2.4 years of postintervention follow-up, study participants had comparable CVD event risks by initial randomized assignments (HR, 1.04; 95% confidence interval [CI], 0.89-1.21). Among the individual cardiovascular outcomes analyzed, all HRs were near unity and none were statistically significant. The increased risk of deep vein thrombosis and pulmonary embolism among women taking CEE plus MPA vs placebo during the inter-

vention phase (HR, 1.98; 95% CI, 1.52-2.59) disappeared during the postintervention period (HR, 0.95; 95% CI, 0.63-1.44).

In contrast, the annualized event rates for the outcome "all cancer" was higher during the postintervention follow-up for the CEE plus MPA group (1.56% per year) than the placebo group (1.26% per year), with a corresponding HR of 1.24 (95% CI, 1.04-1.48). Although this reflects a greater risk of invasive breast cancer in the CEE plus MPA group (0.42% per year, n=79) than in the group originally assigned to placebo (0.33% year, n=60), the difference in risk was not statistically significant (HR, 1.27; 95% CI, 0.91-1.78). The rates of colorectal cancer did not differ significantly between the CEE plus MPA and placebo group. Rates of endometrial cancer were lower in the CEE plus MPA group than in the group originally assigned to placebo

Table 2. Clinical Outcomes in the Women's Health Initiative Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate Trial and Its 3-Year Postintervention Follow-up

	Events During Clinical Trial Phase (n = 16 608)[a]					Events During Postintervention Phase (n = 15 730)						Overall Combined Phases Data[b]				
	CEE + MPA (n = 8506)		Placebo (n = 8102)			CEE + MPA (n = 8052)		Placebo (n = 7678)				CEE + MPA (n = 8506)		Placebo (n = 8102)		
Outcomes	No. of Events	Annualized Rates, %	No. of Events	Annualized Rates, %	HR Ratio (95% CI)[c]	No. of Events	Annualized Rates, %	No. of Events	Annualized Rates, %	HR (95% CI)[d]	*P* Difference[e]	No. of Events	Annualized Rates, %	No. of Events	Annualized Rates, %	HR (95% CI)[d]
Follow-up time, mean mo	68.3		67.1			28.9		28.9				95.3		94.3		
CVD																
CHD	196	0.41	154	0.34	1.22 (0.99-1.51)	101	0.53	104	0.57	0.95 (0.73-1.26)	.15	297	0.45	258	0.41	1.11 (0.94-1.31)
CHD death	40	0.08	36	0.08	1.04 (0.67-1.64)	32	0.17	33	0.18	0.96 (0.59-1.56)	.72	72	0.11	69	0.11	0.98 (0.71-1.37)
Total MI	168	0.35	127	0.28	1.26 (1.00-1.59)	80	0.42	79	0.43	0.99 (0.72-1.34)	.20	248	0.37	206	0.33	1.15 (0.96-1.39)
CABG/ PTCA	218	0.46	210	0.47	1.00 (0.82-1.21)	121	0.65	114	0.64	1.04 (0.81-1.35)	.80	339	0.51	324	0.52	1.01 (0.86-1.17)
Stroke	159	0.33	110	0.24	1.34 (1.05-1.71)	76	0.40	64	0.35	1.16 (0.83-1.61)	.48	235	0.35	174	0.28	1.28 (1.05-1.56)
DVT	122	0.26	61	0.14	1.88 (1.38-2.55)	34	0.18	31	0.17	1.07 (0.66-1.75)	.07	156	0.23	92	0.15	1.62 (1.25-2.09)
PE	87	0.18	41	0.09	1.98 (1.36-2.87)	27	0.14	24	0.13	1.07 (0.62-1.86)	.06	114	0.17	65	0.10	1.66 (1.22-2.25)
DVT/PE	168	0.35	79	0.18	1.98 (1.52-2.59)	44	0.23	45	0.25	0.95 (0.63-1.44)	.005	212	0.32	124	0.20	1.62 (1.30-2.03)
All CVD events	**785**	**1.70**	**660**	**1.51**	**1.13 (1.02-1.25)**	**343**	**1.97**	**323**	**1.91**	**1.04 (0.89-1.21)**	**.37**	**1128**	**1.77**	**983**	**1.62**	**1.10 (1.01-1.20)**
Cancer																
Invasive breast	206	0.43	153	0.34	1.26 (1.02-1.55)	79	0.42	60	0.33	1.27 (0.91-1.78)	.97	285	0.43	213	0.34	1.27 (1.06-1.51)
Endometrial	27	0.06	31	0.07	0.81 (0.48-1.35)	17	0.09	21	0.11	0.75 (0.40-1.43)	.83	44	0.07	52	0.08	0.78 (0.52-1.16)
Colorectal	50	0.10	75	0.17	0.62 (0.43-0.89)	34	0.18	30	0.16	1.08 (0.66-1.77)	.07	84	0.12	105	0.17	0.75 (0.57-1.00)
All cancer	**606**	**1.29**	**548**	**1.25**	**1.03 (0.92-1.15)**	**281**	**1.56**	**218**	**1.26**	**1.24 (1.04-1.48)**	**.08**	**887**	**1.37**	**766**	**1.25**	**1.09 (0.99-1.20)**
Fractures																
Hip	53	0.11	75	0.17	0.67 (0.47-0.95)	54	0.28	57	0.31	0.92 (0.64-1.34)	.20	107	0.16	132	0.21	0.78 (0.60-1.00)
Vertebral	56	0.12	78	0.17	0.68 (0.48-0.96)	46	0.24	47	0.26	0.96 (0.64-1.44)	.23	102	0.15	125	0.20	0.78 (0.60-1.01)
Other[f]	650	1.41	800	1.87	0.75 (0.68-0.83)	267	1.52	285	1.75	0.87 (0.74-1.03)	.16	917	1.44	1085	1.84	0.78 (0.72-0.85)
All fractures	**741**	**1.61**	**903**	**2.12**	**0.76 (0.69-0.83)**	**337**	**1.95**	**346**	**2.16**	**0.91 (0.78-1.06)**	**.06**	**1078**	**1.70**	**1249**	**2.14**	**0.80 (0.73-0.86)**
All-cause death	250	0.52	239	0.53	0.97 (0.81-1.16)	233	1.20	196	1.06	1.15 (0.95-1.39)	.27	483	0.71	435	0.68	1.04 (0.91-1.18)
Global index	876	1.89	736	1.68	1.12 (1.02-1.24)	468	2.67	415	2.44	1.11 (0.97-1.27)	.82	1344	2.10	1151	1.89	1.12 (1.03-1.21)

Abbreviations: CABG, coronary artery bypass graft; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty.

[a] Includes all outcomes from randomization through July 7, 2002. The primary results for this trial were reported in Rossouw et al,[1] which included outcomes adjudicated through data closure at 5.2 years of follow up.

[b] Data as of September 12, 2005; Events through March 31, 2005.

[c] From a proportional hazards model stratified by prevalent condition (where appropriate), age, and dietary modification randomization group. Time to event equals 0 on date of randomization.

[d] From a proportional hazards model stratified by prevalent condition (where appropriate), age, and dietary modification randomization group. Time to event equals 0 on July 7, 2002.

[e] From a proportional hazards model stratified by prevalent condition (where appropriate), age, dietary modification randomization group, and trial phase (time-dependent). Time to event equals 0 on date of randomization. Tests whether the HR for the trial phase equals the HR for the posttrial phase.

[f] Other osteoporotic fractures.

(HR, 0.75; 95% CI, 0.40-1.43), but the difference was not statistically significant.

Although women in the CEE plus MPA group had a significantly lower risk of fractures during the intervention phase, differences by treatment group were greatly attenuated after the intervention (HR, 0.91; 95% CI, 0.78-1.06). All HRs were near unity and none were nominally statistically significant. Osteoporotic fractures (other than hip or vertebrae) had the smallest HR of 0.87 (95% CI, 0.74-1.03). Postintervention mortality from all causes was somewhat higher in women previously assigned to CEE plus MPA than in those assigned to placebo (HR, 1.15; 95% CI, 0.95-1.39), a difference that does not reach nominal statistical significant.

Comparison of Intervention and Postintervention Findings

The risk of CVD events in women assigned to CEE plus MPA decreased from a HR of 1.13 (95% CI, 1.02-1.25) during the intervention phase of the trial to 1.04 (95% CI, 0.89-1.21) after the intervention. However, a formal test of whether the HRs in the preintervention and postintervention phases differ does not reach nominal significance: *P* difference = .37. Cumulative hazards of CHD are shown in FIGURE 1, which presents Kaplan-Meier cumulative hazards of each outcome from time of randomization as well as from the time of termination of the intervention through the end of follow-up. Figure 1 indicates that no excess risk of CHD is apparent during the postintervention period for the women randomized to CEE plus MPA.

The Kaplan-Meier cumulative hazards for stroke reflects the overall 28% excess risk of stroke through March 31, 2005, for women assigned to CEE plus MPA, and a smaller—not statistically significant—excess risk of stroke (16%) during the postintervention phase. The estimated HRs in the preintervention and postintervention phases are not statistically significantly different (*P* difference = .48). The cumulative hazards indicate that excess risk of pulmonary embolism seen during the intervention phase of the trial disappeared during the postintervention period. Similar results were seen for deep vein thrombosis (not shown). The change in excess risk was significant (*P* difference = .005) for the combined end point of deep vein thrombosis and pulmonary embolism.

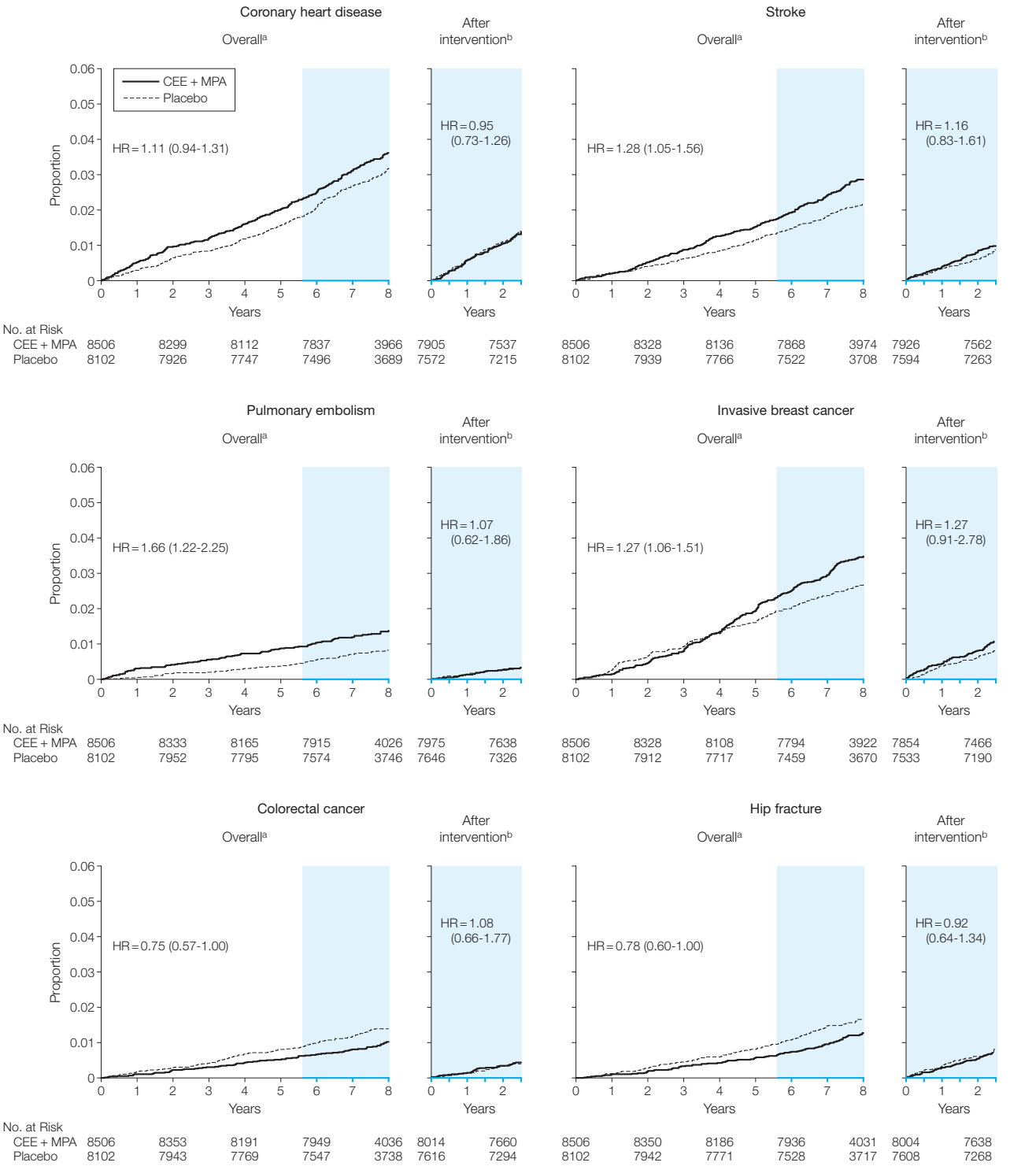
The HR for overall risk of all malignancies increased from 1.03 (95% CI, 0.92-1.15) during the intervention phase to 1.24 (95% CI, 1.04-1.48) in the postintervention period (*P* difference = .08). During the intervention period of the trial an excess risk of invasive breast cancer with CEE plus MPA use emerged with Kaplan-Meier estimates of cumulative hazard compared with placebo crossing in the fourth year (HR, 1.26; 95% CI, 1.02-1.55). Although more breast cancers were diagnosed in the CEE plus MPA group (HR, 1.27; 95% CI, 0.91-1.78) after the intervention, a downward inflection in the temporal trend in cumulative HRs for breast cancer was observed over time (not shown), but the observed change in HR after the intervention is not statistically significant.

The significantly lower colorectal cancer risk observed in the CEE plus MPA group during the intervention phase did not persist after the intervention, and the HR changed from 0.62 (95% CI, 0.43-0.89) to 1.08 (95% CI, 0.66-1.77; *P* difference = .07). In the postintervention period there were 34 and 30 colorectal cancers in the active and placebo groups respectively (Table 2), including 7 colorectal cancer deaths in the active treatment and 6 in the placebo group. The lower HR for endometrial cancer in the active and placebo groups observed during the intervention phase (HR, 0.81; 95% CI, 0.48-1.35) was effectively unchanged during the postintervention follow-up.

The risk of fractures during the postintervention follow-up was comparable among women in the CEE plus MPA and placebo groups for each type of fracture considered: hip, vertebral, and other osteoporotic fractures. This reflects a greater increase in the annualized risk of fractures after the intervention in the women who had been assigned to CEE plus MPA compared with women assigned to placebo, particularly for hip and vertebral fractures. Thus, the protective effects of CEE plus MPA previously evident during the trial were not observed to carry over into the postintervention phase: the HR for all fractures increased from 0.76 (95% CI, 0.69-0.83) during the intervention phase to 0.91 (95% CI, 0.78-1.06) after the intervention. The test of the difference in HRs for all fractures did not reach nominal significance (*P* difference = .06). The Kaplan-Meier curves for hip fracture suggest that the reduced risk observed in the trial was diminished after the intervention, but the difference was not statistically significant (*P* difference = .20).

During the intervention phase all-cause mortality was almost identical in both arms of the trial. During the postintervention phase, mortality from all causes was higher by 15% in the group originally assigned to CEE plus MPA than in those assigned to placebo (FIGURE 2), although this difference was not statistically significant. The plots of cumulative hazards of mortality suggest a change in the temporal trends of mortality prior to and following the termination of the intervention. The number of deaths in each of the prespecified trial outcome categories was small, and they were very similar between the 2 groups. Most deaths were cancer related (101 in the CEE plus MPA group vs 69 in the placebo group), thus accounting for most of the difference in mortality in the postintervention follow-up, but only 27 deaths in the CEE plus MPA group and 16 deaths in the placebo group were associated with breast, colorectal, endometrial, or ovarian cancer (prespecified cancer outcomes). Thus, the other-cancers category accounted for a larger absolute number of deaths, but with a similar pattern of association. Among the other cancers, most were lung cancer events (33 in the CEE plus MPA group vs 15 in the placebo group).

Figure 1. Risks and Benefits by Randomized Assignment to Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate or Placebo Before and After Termination of the Intervention in the Women's Health Initiative Estrogen Plus Progestin Trial



Kaplan-Meier cumulative hazards for clinical outcomes by time in the trial and time after termination of intervention. The unshaded portion of the graphs identifies the intervention period of 5.6 years. The shaded portion of the graphs represents the follow-up time after the intervention.
[a] Overall includes events from randomization to March 31, 2005.
[b] After intervention includes events from July 8, 2002, to March 31, 2005.

The global index of risk vs benefit remained essentially unchanged in the postintervention period, maintaining a nominally significant overall 12% increase from baseline through March 31, 2005, for the women assigned to CEE plus MPA (Figure 2).

At the time the WHI CEE plus MPA trial was stopped, the mean follow-up was 5.6 years (range, 3.5-8.5 years). At that point, 58% of the women assigned to CEE plus MPA and 62% of the women assigned to placebo were taking their study pills.[1] A sensitivity analysis of the postintervention effects reported herein was conducted on the study participants who had never stopped participating, never took nonstudy hormone therapy, and were adherent at 80% or greater of study medications through the trial stopping date of July 7, 2002 (41% of those assigned to active treatment and 47% of those assigned to placebo were available for analysis). Among women adherent to study medication, the HR and 95% CI for the combined end points were as follows: all cardiovascular events, 1.05 (95% CI, 0.81-1.36); all cancers, 1.34 (95% CI, 1.02-1.76); fractures, 0.87 (95% CI, 0.69-1.10); and the global index, 1.19 (95% CI, 0.95-1.49). Thus, although somewhat less precise, these results are quite consistent with the estimated HRs for the entire group, with the notable exception of an increased risk of death from all causes during the postintervention phase for adherers originally assigned to active treatment (HR, 1.53; 95% CI, 1.04-2.24) compared with those assigned to placebo. The corresponding cumulative, annualized mortality among adherers in the active treatment and placebo groups are 0.82% and 0.61%, respectively.

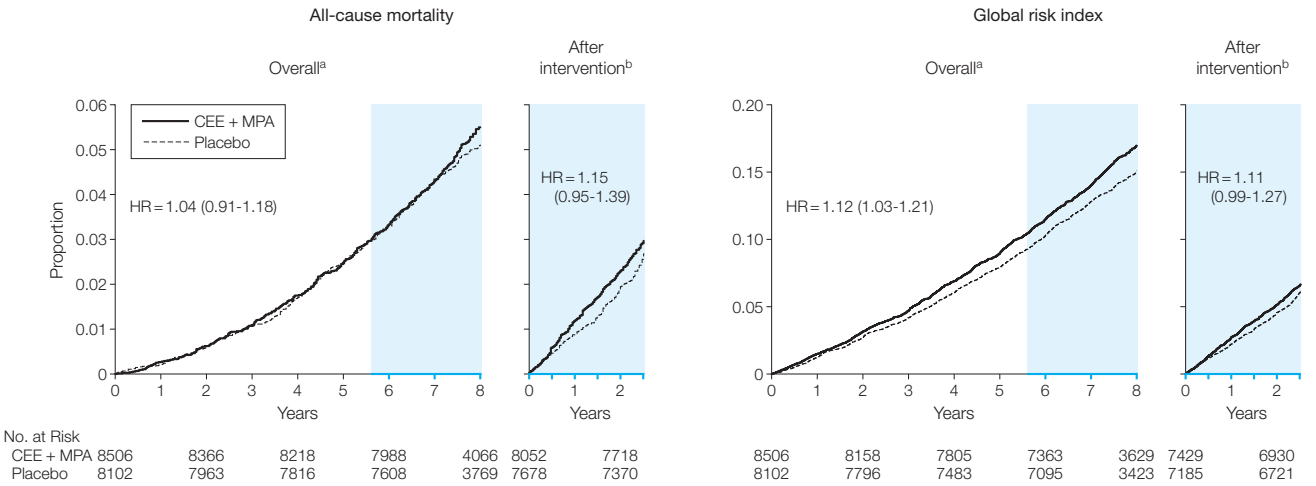
COMMENT

Several patterns of health risks and benefits associated with active treatment vs placebo observed during the WHI CEE plus MPA trial were not maintained during the postintervention phase from July 8, 2002, to March 31, 2005. Within 3 years of cessation of the trial intervention, both CVD risks and total and hip fracture benefits dissipated, and cancer risks increased. As a result, after a mean follow-up of 2.4 years after the intervention, the overall assessment of health risks and benefits associated with CEE plus MPA continued to be weighted toward risk, as suggested by an adverse trend in all-cause mortality and the global index.

The reductions in the risk of CVD reflect short-term temporal trends in the risk of CHD, myocardial infarctions, coronary revascularization procedures, deep vein thrombosis, and pulmonary embolism. Although the increased risk of breast cancer appeared to persist after the intervention, the reduced risk of colon cancer in the CEE plus MPA group during the trial converged toward the null during the postintervention phase. No differences in the risk of fractures by treatment group were apparent during the postintervention phase. Whereas mortality from all causes did not differ by treatment during the trial, a 15% greater mortality in the group assigned to CEE plus MPA was observed after the intervention, although this difference did not reach nominal statistical significance.

In a recent report by Ravdin and colleagues,[17] age-adjusted breast cancer incidence in the United States was reported to have declined 6.7% in 2003, a period in which prescriptions for hor-

Figure 2. Risk of Death From All Causes and Global Risk by Randomized Assignment to Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate or Placebo Before and After Termination of the Intervention in the Women's Health Initiative Estrogen Plus Progestin Trial



Kaplan-Meier cumulative hazards for death and global risk index by time in the trial and time after termination of intervention. The unshaded portion of the graphs identifies the intervention period of 5.6 years. The shaded portion of the graphs represents the follow-up time after the intervention.
[a]Overall includes events from randomization to March 31, 2005.
[b]After intervention includes events from July 8, 2002, to March 31, 2005.

mone therapy were observed to drop rapidly following the release of the WHI CEE plus MPA trial results. Although this finding represents an ecological association, it may reflect the large numbers of women who either discontinued or failed to initiate menopausal hormone therapy use. This decrease in breast cancer incidence from mid-2002 to a lower plateau after 2003 was interpreted by the report's authors as most consistent with a direct effect of hormone-replacement therapy on preclinical disease,[17] without excluding contributions from temporal changes in screening mammography[18] and other factors.

Our results address only women who stopped hormone therapy, with maintenance of annual mammography. The trend of increasing risk of breast cancer during the intervention phase of the trial is seen not to extend beyond the termination of the intervention, but we lacked statistical power to identify a decrease in breast cancer of the order of 9% to 10%, such as that observed in the national data.[17] Further follow-up is needed to characterize the risk of breast cancer in the WHI population. The currently available information after the intervention with CEE plus MPA is insufficient to support or refute any hypothesis regarding the reported temporal decrease in breast cancer incidence.

The juxtaposition of a randomized controlled trial with an observational postintervention phase warrants caution in the interpretation of our results. Although attribution of effects is unequivocal in the former, any differences between the CEE plus MPA and placebo groups seen during the postintervention phase could be attributable to factors associated with, but not inherent to the randomized treatment regimens. For example, health care–seeking behavior and cancer screening practices could have differed between the CEE plus MPA and placebo groups after the trial was stopped and the participants unblinded, although this possibility is unlikely to have influenced rates of fatal events. It should also be noted that annual mammography screenings continued during the postintervention phase and that completeness of follow-up was high and comparable for the 2 groups.

Chance could have contributed to some of our findings, consistent with the relatively small numbers of events available during the postintervention interval and the associated low precision for some of the estimates reported herein. Further, at this stage the cumulative hazards from time of randomization are predominantly influenced by the exposure time and event rates accrued during the trial phase. Conceivably, cessation of postmenopausal hormone therapy could have triggered adverse postintervention effects for one or another of the outcomes reported herein. Considering that newly diagnosed malignancies and cancer-related deaths are the main contributors to the overall unfavorable profile of postintervention health events, such an interpretation seems implausible. Instead, the trends over time in risks during the intervention and postintervention periods support the interpretation of the risks in the postintervention period as cumulative or delayed effects of the intervention.

The apparent excess mortality in the CEE plus MPA vs the placebo group observed during the postintervention phase was accounted for by deaths attributed to various cancers unrelated to the prespecified trial outcomes, most prominently lung cancers. Sex differences in lung cancer outcome have been reported, with women having decreased lung cancer survival compared with men, adjusted for smoking and comorbidities.[19,20] Estrogen receptors occur in non–small-cell lung cancer,[21] and although results are mixed,[22] menopausal hormone therapy use has been found to be associated with significantly decreased survival in women with lung cancer in one recent report[23] and high estradiol levels were associated with poor lung cancer survival in another.[24]

There are similarities between our results and the pattern of fatal and nonfatal noncardiovascular events reported by HERS II, the 2.7-year postintervention follow-up of the Heart and Estrogen/Progestin Replacement Study.[25] Compared with the intervention phase in the HERS study, the relative hazards of breast cancer and colon cancer during the follow-up converged toward the null, whereas the relative hazards of lung cancer and any cancer increased in magnitude (and away from the null). A qualitative difference between HERS II and the postintervention phase of this trial is the considerably higher use of CEE plus MPA during the 2.7 years of the HERS II follow-up (approximately 50% in those randomized to active treatment and approximately 6% for women randomized to placebo).[25] Hormone therapy use 8 to 12 months after stopping the WHI trial was low among the women who were actively taking study pills at trial termination: 4.3% in women formerly in the CEE plus MPA cohort and 1.2% in those formerly taking placebo.[26] The low frequency of hormone therapy use 1 year into the postintervention follow-up suggests that hormone use at this time did not influence the health risks and benefits observed after stopping the WHI CEE plus MPA trial to a meaningful degree.

Implications

This analysis of delayed and sustained health benefits and risks following randomized allocation to CEE plus MPA vs placebo adds new information to inform the optimal use of postmenopausal CEE plus MPA. Over the course of a mean 2.4 years from termination of intervention with CEE plus MPA, rapid changes in hormone therapy–related risks and benefits were observed, as well as trends that suggest that continued follow-up of the study participants of this trial will be informative as regards possible delayed effects of CEE plus MPA. During postintervention follow-up, the overall risk of cardiovascular events was comparable in those initially assigned to CEE plus MPA and to placebo, a greater risk of malignancies was observed in the CEE plus MPA compared with the placebo group, and no differences in the risk of fractures by treatment group

were seen. Following termination of use of CEE plus MPA of 3.5 to 8.5 years, clinical vigilance seems warranted with respect to a sustained higher risk of malignancies.

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REFERENCES

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
2. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349(6):523-534.
3. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289(20):2673-2684.
4. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1739-1748.
5. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243-3253.
6. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas*. 2006;55(2):103-115.
7. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C; Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350(10):991-1004.
8. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1729-1738.

9. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292(13):1573-1580.
10. LaCroix AZ. Estrogen with and without progestin: benefits and risks of short-term use. *Am J Med*. 2005;118(suppl 12b):79-87.
11. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297(13):1465-1477.
12. American College of Obstetricians and Gynecologists (ACOG) Task Force on Hormone Therapy. Hormone therapy. *Obstet Gynecol*. 2004;104(4)(4 suppl):1S-4S.
13. US Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the US Preventive Services Task Force. *Ann Intern Med*. 2005; 142(10):855-860.
14. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291 (1):47-53.
15. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1): 61-109.
16. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*. 2000;56(3):779-781.
17. Ravdin PM, Cronin KA, Howlader N, et al. The Decrease in Breast-Cancer Incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670-1674.
18. Breen N, Cronin KA, Meissner HI, et al. Reported drop in mammography. *Cancer*. 2007;109 (12):2405-2409.
19. Palomares MR, Sayre JW, Shekar KC, Lillington LM, Chlebowski RT. Gender influence on weight loss pattern and survival of non-small cell lung carcinoma patients. *Cancer*. 1996;78(10):2119-2126.
20. Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? *J Clin Oncol*. 2007;25(13):1705-1712.
21. Márquez-Garbán DC, Chen HW, Fishbein MC, Goodglick L, Pietras RJ. Estrogen receptor signaling pathways in human non-small cell lung cancer. *Steroids*. 2007;72(2):135-143.
22. Ettinger B, Friedman GD, Bush T, Quesenberry CP. Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol*. 1996; 87(1):6-12.
23. Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with lung cancer. *J Clin Oncol*. 2006;24(1):59-63.
24. Ross H, Bonomi P, Langer M, et al. Effect of gender on outcome in two randomized phase III trials of paclitaxel poliglumex (PPX) in chemonaive patients with advanced NSCLC and poor performance status (PS2) [abstract]. *J Clin Oncol*. 2007;24(184)(June 29 suppl): 7039.
25. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002; 288(1):58-66.
26. Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA*. 2005;294(2):183-193.

To be fertile in hypotheses is the first requisite [of creativity], and to be willing to throw them away the moment experience contradicts them is the next.
—William James (1842-1910)