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Original Contribution

Conjugated Equine Estrogens and Breast Cancer Risk in the Women's Health Initiative Clinical Trial and Observational Study

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The Women's Health Initiative randomized controlled trial found a trend ($p = 0.09$) toward a lower breast cancer risk among women assigned to daily 0.625-mg conjugated equine estrogens (CEEs) compared with placebo, in contrast to an observational literature that mostly reports a moderate increase in risk with estrogen-alone preparations. In 1993–2004 at 40 US clinical centers, breast cancer hazard ratio estimates for this CEE regimen were compared between the Women's Health Initiative clinical trial and observational study toward understanding this apparent discrepancy and refining hazard ratio estimates. After control for prior use of postmenopausal hormone therapy and for confounding factors, CEE hazard ratio estimates were higher from the observational study compared with the clinical trial by 43% ($p = 0.12$). However, after additional control for time from menopause to first use of postmenopausal hormone therapy, the hazard ratios agreed closely between the two cohorts ($p = 0.82$). For women who begin use soon after menopause, combined analyses of clinical trial and observational study data do not provide clear evidence of either an overall reduction or an increase in breast cancer risk with CEEs, although hazard ratios appeared to be relatively higher among women having certain breast cancer risk factors or a low body mass index.

breast neoplasms; clinical trial; cohort studies; estrogens; hormone replacement therapy; postmenopause

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; HT, postmenopausal hormone therapy; WHI, Women's Health Initiative.

Editor's note: *An invited commentary on this article is published on page 1416.*

The Women's Health Initiative (WHI) randomized controlled trial of daily use of 0.625 mg of conjugated equine

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estrogens (CEEs) by 10,739 posthysterectomy US women stopped early in 2004 primarily because of an elevation in stroke risk (1, 2). The trial yielded a nonsignificantly lower incidence of invasive breast cancer in the active hormone group (3), with a hazard ratio of 0.80 (95 percent confidence interval (CI): 0.62, 1.04; $p = 0.09$) over an average 7.1-year follow-up period. This hazard ratio estimate compares with generally higher hazard ratios from an extensive observational literature (4, 5).

For example, the UK Million Women Study (5) reported a hazard ratio of 1.30 (95 percent CI: 1.21, 1.40) for estrogen-alone regimens, with little evidence of hazard ratio variation among regimens involving differing estrogens. In the WHI CEE trial, much of the evidence for a possibly reduced breast cancer hazard ratio (3) arose from women who had not previously used postmenopausal hormone therapy (HT), many of whom were years past menopause at the time of trial enrollment. The hazard ratio was 0.65 (95 percent CI: 0.46, 0.92) among women without prior HT compared with 1.02 (95 percent CI: 0.70, 1.50) among women with prior HT ($p = 0.09$ for difference). In spite of only 237 incident cases, this trial was able to identify higher hazard ratios among subsets of women at comparatively high risk, including those with an elevated 5-year Gail model (6) risk score ($p = 0.01$), those having one or more first-degree relatives with breast cancer ($p = 0.01$), and those having a personal history of benign breast disease ($p = 0.005$).

Here, we compare results from the CEE trial with corresponding results from the WHI observational study with a goal of identifying reasons for any hazard ratio discrepancy. If results from the two cohorts are in good agreement following provision for differences in the characteristics and HT exposure patterns of participating women, then analysis of combined data from the two sources may help to clarify the breast cancer effects of CEE, especially among recently postmenopausal women.

The WHI observational study includes 93,676 postmenopausal women enrolled from the same populations as the WHI clinical trial (7) over essentially the same time period (1993–1998). Many elements of the protocol were common to the two WHI components, including baseline questionnaire and interview data collection and the major elements of outcome ascertainment.

MATERIALS AND METHODS

Study design and population

Detailed WHI recruitment methods and eligibility criteria have been published previously (8). Eligible women were 50–79 years of age at screening, were postmenopausal, had no medical condition associated with a predicted survival of less than 3 years, and were likely to be residing in the same geographic area for at least 3 years. Additional CEE trial exclusion criteria involved safety, adherence, and retention concerns and included a personal history of invasive or noninvasive breast cancer. Women ineligible for, or not interested in, the WHI clinical trial were given the opportunity to enroll in the observational study. The observational study was intended to provide risk factor information on major causes of morbidity and mortality and to serve as a secular control for the clinical trials. All women provided written informed consent for their respective WHI activities and supplied a baseline fasting blood specimen, a medications and dietary supplements inventory, and common core questionnaires (7, 9).

Information on lifetime hormone use was obtained from clinical trial and observational study women at baseline by a trained interviewer, assisted by a structured questionnaire and chart displaying color photographs of various hormone preparations. For HT, detailed information was obtained on the preparation, estrogen and progestin doses, schedule, and route of administration. The age at starting and stopping each preparation was recorded. Estrogen-alone use was defined as use of prescription oral or transdermal preparations for at least 3 months, whereas estrogen plus progestin use was defined similarly for estrogen plus oral progestin, including preparations used continuously or intermittently.

Women using HT at baseline were required to undergo a 3-month washout period prior to randomization in the CEE trial. Women without a uterus were potentially eligible for this trial of daily use of 0.625 mg of CEE or matched placebo. There were no restrictions on hormone therapy use for observational study participants.

This article is based on data from a clinical trial and an observational study subcohort of women enrolled at 40 US clinical centers. The ''gap time'' from menopause to first use of HT emerged in preliminary analyses as a useful factor for explaining hazard ratio patterns, so the clinical trial analyses presented here excluded women of an unknown age at menopause or having unknown prior HT information. Following this exclusion, 4,493 (84.6 percent) of the women assigned to CEE and 4,596 (84.7 percent) of the women assigned to placebo remained in the clinical trial subcohort used in this analysis.

The corresponding observational study subcohort comprised 17,437 women who were either using the same daily 0.625-mg CEE regimen (9,336 women) or were not using any HT (8,101 women) at the time of enrollment in the observational study. To enhance comparability with the clinical trial, observational study subcohort women were required to be posthysterectomy, to have no personal history of breast cancer, and to have had a mammogram within 2 years prior to enrollment. As with the clinical trial subcohort, women were also required to be of a known age at menopause and to have prior HT data. Finally, women in this observational study subcohort were required to have known values for a list of potential confounding factors described below (figure 1).

Follow-up and outcome ascertainment

Clinical outcomes were reported semiannually in the clinical trial and annually in the observational study. Initial reports of outcomes were ascertained by self-administered questionnaire. Breast cancer occurrences were confirmed by review of medical records and pathology reports by physician-adjudicators at the local clinical centers. All cases were subsequently classified (10) at the Clinical Coordinating Center by using the National Cancer Institute's

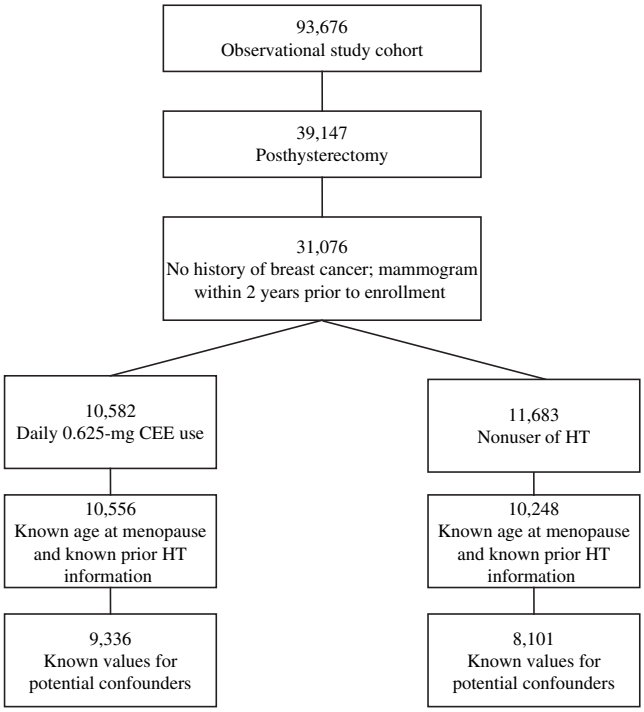

FIGURE 1. Numbers of US women in the Women's Health Initiative observational study meeting selection criteria, United States, 1993–2004. CEE, conjugated equine estrogen; HT, postmenopausal hormone therapy.

Surveillance, Epidemiology, and End Results coding system (www.seer.cancer.gov).

Yearly mammography and clinical breast examination were required in the CEE trial, and study medications were withheld if these procedures were not completed. Mammogram reports were obtained from performance sites and were reviewed locally and coded for recommendation. Mammograms with suspicious abnormalities or highly suggestive of malignancy required clearance before additional study medication was dispensed. In the observational study, annual data collection updated each woman's mammogram history, and the WHI did not intervene regarding the mammography practices of participating women.

Information on the use of HT was updated semiannually in the clinical trial and annually in the observational study.

Statistical methods

Age at menopause was defined as the age at which a woman last had menstrual bleeding, had a bilateral oophorectomy, or began using HT. Any such age greater than 60 years was recoded as 60 years. Age at first use of HT was defined both for women who had used any HT prior to WHI enrollment and for women whose first use of HT was the active treatment in the clinical trial. The gap time from menopause to (first) HT use was the difference between these two ages.

Primary data analyses used time-to-event methods based on the Cox regression procedure (11), with time from randomization in the clinical trial and time from enrollment in the observational study as the basic time variable. Incidence rates of invasive breast cancer during follow-up were stratified on baseline age in 5-year categories and on clinical trial or observational study cohort.

Disease events in the CEE trial were included through February 29, 2004, when women stopped taking study pills, giving an average 7.1 years of follow-up. Follow-up time in the observational study subcohort was included through December 15, 2004, to give an equivalent average follow-up time of 7.1 years.

Confounding in the observational study was addressed by including breast cancer risk factors, collected at baseline, in the Cox regression model. Because such factors are independent of treatment assignment, they were not included in clinical trial analyses.

Potential confounding factors in observational study analyses (in addition to stratification on baseline age) included age (linear), body mass index (<25, 25–29, 30–34, >34 kg/m^2, plus linear), education (high school or less, beyond high school, college degree), smoking (never, past, current), alcohol consumption (never, past, <1/week, 1–7/week, >7/week), general health (fair/poor, good/very good/excellent), physical activity in metabolic equivalent units/week (0–3.75, 3.76–8.75, 8.76–17.5, >17.5), family history of breast cancer (yes, no), 5-year Gail model (6) breast cancer risk percentage (<1.25, 1.25–1.74, >1.74, plus linear), and bilateral oophorectomy (yes, no). This rather extensive list aimed to control confounding as thoroughly as practical, without introducing sparse-data biases (12).

Cox model hazard ratio estimates were calculated separately for less than 2, 2–5, and more than 5 years from CEE initiation, with proportional hazards within these time periods. Time from CEE initiation was defined as time from randomization for women randomized to CEE in the clinical trial. Women who had not used any HT before randomization were classified as ''no prior HT,'' while all other clinical trial women were included in a ''prior HT'' group. Time from CEE initiation among CEE users in the observational study was defined as the sum of the duration of the ongoing daily 0.625-mg CEE episode at enrollment plus time since enrollment. A usage gap of 1 year or longer was required to define a new CEE episode. CEE users who had used any HT prior to the beginning of the CEE episode ongoing at observational study enrollment were classified as prior HT. Women in the nonuser group in the observational study were classified as prior HT if they had used any HT prior to observational study enrollment.

Disease incidence rates in the Cox model were also stratified on prior HT, and confounding factor coefficients (observational study only) were estimated separately for the prior HT and no prior HT groups. Additional potential confounding factors were included for the prior HT stratum as follows: prior estrogen-alone use in years (none vs. each of <5, 5–10, >10) and prior estrogen plus progestin use in years (none vs. each of <5, 5–10, >10).

A product term between a CEE and an observational study (vs. clinical trial) indicator variable in the log-hazard ratio

TABLE 1. Invasive breast cancer incidence rates in the US Women's Health Initiative CEE* clinical trial and corresponding observational study subcohort according to prior use of hormone therapy, 1993–2004

	Prior HT*,†				No prior HT†			
	Clinical trial		Observational study‡		Clinical trial		Observational study‡	
	Placebo	CEE†	Nonuser	CEE†	Placebo	CEE†	Nonuser	CEE†
No. of women	2,659	2,541	3,807	1,651	1,977	1,952	4,177	7,684
Mean age (years)	63.4	63.6	65.5	64.1	64.1	63.8	64.8	63.3
No. of events§	50	46	83	46	49	30	103	205
Age-adjusted annualized incidence (%)¶	0.27	0.26	0.36	0.40	0.37	0.22	0.39	0.43
CEE user to nonuser incidence ratio	0.95		1.11		0.61		1.09	

* CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy.

† Prior HT was defined relative to the baseline CEE episode for CEE users in the observational study and relative to Women's Health Initiative enrollment for other women.

‡ The observational study subcohort comprises women with a hysterectomy, without a prior breast cancer diagnosis, with a mammogram in the 2 years prior to observational study enrollment, and either using the daily 0.625-mg CEE regimen studied in the clinical trial or not using any HT at the time of enrollment.

§ Only invasive breast cancer diagnoses that occurred within 2 years of the most recent mammogram were included.

¶ Age adjusted to the 5-year age distribution in the clinical trial cohort.

enabled hazard ratios in the observational study to differ by a multiplicative factor from those in the clinical trial. Estimation of this ''CEE in the observational study/CEE in the clinical trial'' hazard ratio factor provides an overall test of agreement between CEE effects in the two cohorts, and the inclusion of this factor in data analysis provides for residual confounding in the observational study.

In both the clinical trial and observational study cohorts, hazard ratios were standardized for mammographic screening patterns during WHI follow-up by censoring the follow-up for a woman when she first exceeded 2 years without a mammogram.

In some analyses, hazard ratios among women who were adherent to CEE were estimated by censoring the follow-up period for a woman 6 months after she stopped taking CEE if in a user group or 6 months after initiating any HT if in a nonuser group. The 6-month period was included to avoid HT changes related to diagnostic work-up from inappropriately influencing analyses.

In this paper, nominal 95 percent confidence intervals are presented for hazard ratio parameters. In addition, two-sided significance tests (p values) are presented.

RESULTS

Table 1 shows the numbers of women, their mean ages, and the number of incident breast cancers in the clinical trial and observational study subcohorts, separately by prior HT status. The age-adjusted incidence rate ratios for CEE users compared with nonusers were similar from the clinical trial and observational study among women having prior HT but were lower in the clinical trial than in the observational study for women without prior HT.

Confounding in the observational study could have contributed to these patterns. In addition, hazard ratio comparisons between the clinical trial and observational study need to acknowledge the different durations of CEE use in the two cohorts, since most CEE users were some years into their baseline episode of CEE at the time of enrollment in the observational study. Table 2 includes the numbers of observational study women who developed breast cancer during follow-up in the time periods less than 2, 2–5, and more than 5 years from CEE initiation, along with corresponding numbers from the clinical trial. Much of the information from the observational study for assessing CEE effects pertains to the more than 5 years from initiation category, where the clinical trial information is comparatively limited, but the overlap in time from CEE initiation distributions between the two cohorts was sufficient to allow a meaningful comparison between corresponding hazard ratio estimates.

The hazard ratio estimates (and 95 percent confidence intervals) in table 2 arose from Cox model (11) analysis of combined clinical trial and observational study data that included confounding factors in the observational study (refer to the Materials and Methods section). These analyses also included a hazard ratio interaction between CEE and cohort that led to an overall ratio of the CEE hazard ratio in the observational study to the CEE hazard ratio in the clinical trial estimated at 1.43 (95 percent CI: 0.91, 2.26). This 43 percent larger hazard ratio estimate in the observational study compared with that in the clinical trial ($p = 0.12$) suggests that confounding factors and different distributions of time from CEE initiation may not fully explain differential hazard ratios for CEE use between the two cohorts.

Women without prior HT who enrolled in the CEE trial were often many years past menopause at the time of

TABLE 2. Breast cancer hazard ratio estimates for CEE* according to prior postmenopausal hormone therapy status and years from hormone therapy initiation for US women, 1993–2004†

No. of years from CEE initiation	Prior HT*,‡			No prior HT‡		
	HR*	95% CI*	No. of cases§	HR	95% CI	No. of cases§
<2	1.24	0.57, 2.68	12/1	0.72	0.30, 1.70	8/2
2–5	0.72	0.42, 1.24	17/4	0.75	0.46, 1.21	23/12
>5	0.83	0.52, 1.35	17/41	0.71	0.45, 1.12	14/191

* CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy; HR, hazard ratio; CI, confidence interval.

† CEE in the observational study/CEE in the clinical trial: HR = 1.43, 95% CI: 0.91, 2.26.

‡ Prior HT was defined relative to the baseline episode for CEE users in the observational study and relative to Women's Health Initiative enrollment otherwise. Confounding factors in the observational study were controlled separately in the prior HT and no prior HT groups and are listed in the Materials and Methods section of the text.

§ No. of cases among CEE users in the clinical trial/no. of cases among CEE users in the observational study that contribute to the hazard ratio estimate.

randomization, whereas many CEE users in the observational study were comparatively few years beyond menopause at the beginning of their baseline HT episode. Similarly, women with prior HT in either the clinical trial or the observational study mostly initiated HT within a few years following menopause. Table 3 shows the stark contrast between clinical trial women without prior HT and the other three groups regarding the distribution of gap time from menopause to first use of HT in the CEE user groups. Note, for example, that there were only four breast cancer cases among women without prior HT who were randomized to CEE within 5 years following menopause.

To examine the effect of gap time distribution on clinical trial results, the clinical trial data were analyzed with separate hazard ratios (for CEE use) according to prior HT and gap time from menopause to first use of HT (<5 vs. ≥5 years). These analyses (table 4) provided a suggestion ($p = 0.20$) of lower hazard ratios among women having longer (≥5 years) gap times as a possible explanation for lower hazard ratios among women without prior HT.

Gap time was next considered as a factor to explain apparent differences between hazard ratios in the observational study and in the clinical trial. To do so, a product term was included on the Cox model log-hazard ratio between a CEE indicator and gap time. To avoid an undue influence by some very long gap times, gap times of more than 15 years were recoded as 15 years. Table 5 shows estimated hazard ratios and 95 percent confidence intervals for women

TABLE 3. Distribution of gap time from menopause to first use of postmenopausal hormones among CEE* users in the clinical trial and observational study according to prior use of postmenopausal hormone therapy by US women, 1993–2004

	Gap time (years) from menopause to first use of HT*					
	No prior HT†			Prior HT†		
	<5	5–15	>15	<5	5–15	>15
Clinical trial participants						
% of women by prior HT use	10	32	58	84	12	4
No. of women‡	198	618	1,136	2,129	299	113
No. of breast cancer cases	4	5	21	40	4	2
Observational study participants						
% of women by prior HT use	76	17	7	87	11	2
No. of women‡	6,626	1,154	597	1,662	213	30
No. of breast cancer cases	188	36	11	46	5	0

* CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy.

† Prior HT was defined relative to the ongoing CEE episode at Women's Health Initiative enrollment in the observational study and relative to randomization to CEE in the clinical trial.

‡ Women were selected to have a known time from menopause to first use of HT (refer to the Materials and Methods section of the text).

TABLE 4. Invasive breast cancer hazard ratios for CEE* by years from menopause to first hormone therapy use in the Women's Health Initiative clinical trial, United States, 1993–2004

	No. of years from menopause to first HT* use			
	<5		≥5	
	HR*,†	95% CI*	HR†	95% CI
No prior HT‡	1.12	0.39, 3.21	0.58	0.36, 0.93
Prior HT‡	1.00	0.66, 1.51	0.77	0.33, 1.80

* CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy; HR, hazard ratio; CI, confidence interval.

† Hazard ratios (and 95% confidence intervals) from Cox model analyses that stratified on baseline age (5-year categories). Numbers of women and breast cancer cases contributing to each hazard ratio estimate are given in table 1.

‡ Prior HT was defined relative to enrollment in the clinical trial.

TABLE 5. Breast cancer hazard ratio estimates for CEE* according to prior postmenopausal hormone therapy and years from CEE initiation among US women who initiated CEE at menopause (gap time of 0), 1993–2004†

No. of years from CEE initiation	Prior HT*,‡		No prior HT‡	
	HR*	95% CI*	HR	95% CI
<2	1.63	0.68, 3.91	1.44	0.54, 3.84
2–5	0.82	0.42, 1.57	1.15	0.57, 2.32
>5	0.91	0.49, 1.69	1.00	0.54, 1.84

* CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy; HR, hazard ratio; CI, confidence interval.

† CEE in the observational study/CEE in the clinical trial: HR = 1.07, 95% CI: 0.60, 1.93.

‡ Prior HT was defined relative to the baseline episode for CEE users in the observational study and relative to Women's Health Initiative enrollment otherwise. Confounding factors in the observational study were controlled separately in the prior HT and no prior HT groups and are listed in the Materials and Methods section of the text. Refer to table 2 for numbers of breast cancer cases in the clinical trial and observational study in this table. Corresponding hazard ratio estimates for women who first initiate CEE following *x* years after menopause (up to 15) can be obtained by multiplying those in the table by $(0.967)^x$.

who began CEE use immediately following menopause (gap time of 0). The dependence of the CEE hazard ratio on this gap time variable was significant ($p = 0.03$) in these analyses. Corresponding hazard ratio estimates for women who initiated CEE, for example, 5 years following menopause, under this statistical model, would have been lower than those shown in table 5 by a factor of 0.85 (95 percent CI: 0.73, 0.98). The ratio of the hazard ratio for CEE use from the observational study to that from the clinical trial was 1.07 (95 percent CI: 0.60, 1.93; $p = 0.82$), indicating excellent agreement overall between the clinical trial and observational study after this accommodation of gap time. Further analyses applied this same hazard ratio model separately in the clinical trial and observational study, and no evidence was found for a difference between cohorts in either gap time coefficients ($p = 0.56$) or overall hazard ratio functions (likelihood ratio $p = 0.92$). The hazard ratio for CEE use also decreased with increasing gap time ($p = 0.03$) in a corresponding analysis of observational study data alone.

Some additional analyses were carried out to elucidate the interpretation of the gap time association with hazard ratio, as follows: An interaction of CEE with a linear term in years from CEE initiation was added to the analysis to allow for any residual duration effects beyond the categories given in table 5 and was found to not be significant ($p = 0.65$; hazard ratio = 1.00 for this factor, 95 percent CI: 0.98, 1.01). Similarly, age at WHI enrollment was not significant as a potential additional interaction factor ($p = 0.84$; hazard ratio = 1.00, 95 percent CI: 0.98, 1.02), nor was age at HT initiation ($p = 0.33$; hazard ratio = 1.01, 95 percent CI: 0.99, 1.03). In each of these analyses, time from menopause to HT initiation remained significantly associated with the CEE hazard ratio ($p < 0.005$) in the presence of the other factor, pointing to the value of gap time as a relevant time scale to characterize CEE effects on breast cancer risk.

The upper part of table 6 presents a more empirical, less model-dependent view of CEE hazard ratios among women without prior HT, with a separate hazard ratio estimate in each cell defined by gap years from menopause to CEE initiation and years from CEE initiation. The data are quite sparse in some cells, and confidence intervals may be inaccurate. Nevertheless, a pattern of lower hazard ratios among women whose gap time was greater than 5 years is evident. Hazard ratios among women whose gap times were less than 5 years did not suggest a breast cancer risk reduction with CEE. As shown in the lower part of table 6, these patterns persisted among women adherent to their CEE user or nonuser classification (refer to the Materials and Methods section).

Given the good agreement between clinical trial and observational study hazard ratios shown in table 5, it was of interest to use the combined clinical trial and observational study data to reexamine the previously mentioned interactions (3) of the CEE hazard ratio with other factors. Adding interaction factors one at a time to the table 5 analysis resulted in estimated hazard ratios that increased by a factor of 1.14 (95 percent CI: 1.01, 1.29; $p = 0.04$) with a one-unit increase in 5-year Gail model (6) breast cancer risk; increased by a factor of 1.42 (95 percent CI: 1.00, 2.02; $p = 0.05$) among women with a history of benign breast disease; increased by a factor of 1.27 (95 percent CI: 0.87, 1.84; $p = 0.21$) among women with a first-degree relative with breast cancer; and decreased by a factor of 0.97 (95 percent CI: 0.95, 1.00; $p = 0.03$) for a one-unit increase in body mass index.

DISCUSSION

Preliminary analysis of WHI observational study data on postmenopausal estrogen-alone regimens in relation to

TABLE 6. Breast cancer hazard ratios according to gap years from menopause to CEE* use, and years from CEE initiation among US women without prior postmenopausal hormone therapy, from combined analysis of clinical trial and observational study data, 1993–2004†

No. of years from CEE initiation	Gap time (years) from menopause to first use of CEE								
	<5			5–15			>15		
	HR*	95% CI*	No. of cases‡	HR	95% CI	No. of cases‡	HR	95% CI	No. of cases‡
Without nonadherence censoring									
<2	1.04	0.14, 8.01	1/0	0.53	0.12, 2.39	1/1	0.83	0.29, 2.36	4/1
2–5	1.30	0.58, 2.88	2/7	0.64	0.28, 1.45	3/4	0.67	0.35, 1.28	12/1
>5	0.86	0.52, 1.42	1/157	0.63	0.35, 1.13	1/26	0.60	0.30, 1.17	5/8
With nonadherence censoring									
<2	1.28	0.16, 10.02	1/0	0.70	0.15, 3.22	1/1	1.11	0.37, 3.29	4/1
2–5	1.53	0.62, 3.78	1/7	0.68	0.26, 1.83	1/4	0.56	0.23, 1.39	6/0
>5	0.97	0.53, 1.81	0/151	0.79	0.40, 1.57	1/26	0.79	0.35, 1.75	4/7

* CEE, conjugated equine estrogen; HR, hazard ratio; CI, confidence interval.

† No prior HT was defined relative to the beginning of the baseline CEE episode among CEE users in the observational study and relative to Women's Health Initiative enrollment otherwise. Confounding factors in the observational study are listed in the Materials and Methods section of the text.

‡ No. of breast cancer cases in the clinical trial/no. of breast cancer cases in the observational study that contribute to the hazard ratio estimate.

invasive breast cancer yielded a hazard ratio estimate of 1.28 for estrogen-alone users versus nonusers of HT after control for the set of confounding factors used in this presentation (refer to the Materials and Methods section). This hazard ratio estimate was 79 percent larger ($p < 0.01$) than the corresponding estimate (HR = 0.71) from the CEE trial. As shown in table 2, this discrepancy was reduced to 43 percent ($p = 0.12$) after control for mammographic screening patterns prior to and following WHI enrollment, restricting the estrogen-alone user group in the observational study to women using the same daily 0.625-mg CEE regimen studied in the clinical trial and controlling for time from CEE initiation. These factors, particularly mammographic screening patterns, should be carefully controlled in observational studies of hormone therapy effects on breast cancer. Gap time from menopause to first use of HT explains the residual discrepancy, with hazard ratios in the observational study estimated to be only 7 percent higher than those in the clinical trial ($p = 0.82$) following additional control for gap time (table 5).

Among women who initiate CEE use soon after menopause (e.g., <5 years), the women most likely to be making hormone therapy decisions in the future, WHI data do not provide clear evidence for either an overall reduction or an overall increase in breast cancer risk with CEE use (tables 5 and 6). Our interaction analyses suggest a relatively higher hazard ratio among women having such characteristics as low body mass index or high Gail model (6) breast cancer risk.

The clinical trial included very few women without prior HT and with short gap times. Hence, the hazard ratios shown in table 4 are not robust to gap time cutpoint choices (e.g., 5 vs. 10 years) or other analytic choices. Even when clinical trial and observational study data were combined, the hazard ratios reported in this article were not precisely determined. However, the analysis presented here suggests agreement between hazard ratios from the clinical trial and observational study after control for gap time, and they give results generally consistent with an extensive related observational literature (4, 5). Hence, observational studies would seem to be a reasonable source for more precise estimates of CEE effects. The fact that hazard ratios depended on gap time, as well as mammographic screening pattern and other factors (e.g., body mass index) in analysis of WHI data, suggests that these factors should be considered in observational study analysis and interpretation.

In a separate article (13), we present corresponding analyses for daily use of 0.625-mg CEE plus daily use of 2.5-mg medroxyprogesterone acetate from the WHI estrogen plus progestin trial (14, 15) and the corresponding observational study subset among women with a uterus at WHI enrollment. These analyses mutually reinforce those given here concerning gap time as a useful explanatory factor.

The present analyses suggest a possibly reduced breast cancer risk among women who initiate CEE some years (e.g., >5 years) following menopause. Although the biologic basis for any such reduction is unclear, preclinical studies indicate that breast cancers, when exposed to a period of estrogen deprivation, make adaptive changes (16, 17) that alter their susceptibility to proliferative stimulation by estrogen. In addition, lobular involution is associated with reduced breast cancer risk (18), and a longer time from menopause with resultant involution could decrease the number of epithelial breast cells potentially influenced by CEE.

In summary, with careful standardization and control, and with consideration of time from menopause to CEE initiation and time since CEE initiation, the hazard ratios from the WHI trial and cohort study agree concerning the breast cancer effects of CEE. Among hysterectomized women who initiate a daily 0.625 CEE regimen soon after menopause, there is little indication of a reduction in breast cancer risk.

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