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Original Contribution

Estrogen Plus Progestin Therapy and Breast Cancer in Recently Postmenopausal Women

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The Women's Health Initiative trial found a modestly increased risk of invasive breast cancer with daily 0.625-mg conjugated equine estrogens plus 2.5-mg medroxyprogesterone acetate, with most evidence among women who had previously received postmenopausal hormone therapy. In comparison, observational studies mostly report a larger risk increase. To explain these patterns, the authors examined the effects of this regimen in relation to both prior hormone therapy and time from menopause to first use of postmenopausal hormone therapy ("gap time") in the Women's Health Initiative trial and in a corresponding subset of the Women's Health Initiative observational study. Postmenopausal women with a uterus enrolled at 40 US clinical centers during 1993–1998. The authors found that hazard ratios agreed between the two cohorts at a specified gap time and time from hormone therapy initiation. Combined trial and observational study data support an adverse effect on breast cancer risk. Women who initiate use soon after menopause, and continue for many years, appear to be at particularly high risk. For example, for a woman who starts soon after menopause and adheres to this regimen, estimated hazard ratios are 1.64 (95% confidence interval: 1.00, 2.68) over a 5-year period of use and 2.19 (95% confidence interval: 1.56, 3.08) over a 10-year period of use.

breast neoplasms; clinical trials as topic; cohort studies; estrogens; hormone replacement therapy; postmenopause; progestins

Abbreviations: CI, confidence interval; E+P, estrogen plus progestin; HT, postmenopausal hormone therapy; WHI, Women's Health Initiative.

Use of estrogen plus progestin (E+P) in the Women's Health Initiative (WHI) randomized controlled trial increased invasive breast cancer risk (1, 2), with a hazard ratio of 1.24 (95 percent confidence interval (CI): 1.01,

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1.54) over a 5.6-year average intervention period. In contrast, observational studies mostly report a larger influence of combined postmenopausal hormone therapy (HT) on breast cancer risk. Although the Million Women Study (3) reported doubling of risk for combined HT (hazard ratio = 2.00, 95 percent CI: 1.88, 2.12), other observational studies report somewhat smaller hormone effects. However, in these reports, increased breast cancer risk is commonly found for longer durations of E+P use (4–6). In the WHI trial, an elevation in breast cancer risk with E+P was observed among women with prior use of HT (hazard ratio = 1.85, 95 percent CI: 1.18, 2.90) but not among those without HT exposure before enrollment (hazard ratio = 1.09, 95 percent CI: 0.86, 1.39; interaction $p = 0.04$). Risk in the WHI trial began to increase after about 2 years of E+P use (7), and a significant trend ($p = 0.01$) of an increased hazard ratio of breast cancer with years from randomization was identified.

To explain the interaction of prior HT with the magnitude of the E+P effect, and the apparent discrepancy with observational reports, we carried out preliminary analyses of E+P and breast cancer risk in the WHI observational study. This prospective cohort study includes 93,676 postmenopausal women enrolled from the same population base as the WHI clinical trial, over essentially the same time period. Many elements of the protocol were common to the clinical trial and observational study, including baseline questionnaire and interview data collection and the major elements of outcome ascertainment.

Initial analyses indicated that, in the observational study, E+P was associated with a nearly twofold increase in breast cancer risk for women both with and without prior HT. Clinical trial participants without prior hormone therapy were considerably older than observational study participants when they first used E+P, but age at randomization was not significantly related to the magnitude of the hormone effect in the WHI trial (2). After some deliberation, we identified time from menopause to first use of HT, hereafter referred to as ''gap time,'' as a possible explanatory factor. To investigate this issue, the clinical trial data were reanalyzed with gap time as a variable that may relate to the breast cancer hazard ratio. Subsequently, data from a comparable subset of observational study participants were used for confirmation, and combined data from the two cohorts were used to estimate breast cancer effects.

This paper reports on the first use of combined data from the E+P trial and the WHI observational study to assess E+P effects on breast cancer risk. The two data sources are complementary, with most information from the clinical trial pertaining to the first few years following randomization among women who may have been many years past menopause at randomization, and with most information from the observational study pertaining to time periods well after HT initiation among women who typically first used HT soon after menopause. There is, however, sufficient overlap in the distribution of both time from menopause to first use of hormone therapy and time from hormone therapy initiation to allow useful comparisons between the two cohorts.

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, and had no medical condition precluding 3 years of survival. For the E+P clinical trial, additional exclusion criteria involved safety, adherence, and retention concerns and included prior invasive breast cancer or hysterectomy. Women ineligible for, or not interested in, the clinical trials were given the opportunity to enroll in the observational study, which was intended to provide risk factor information on major causes of morbidity and mortality. All women provided written informed consent, supplied a baseline fasting blood specimen, and completed a medications and dietary supplements inventory as well as common core questionnaires (9, 10).

Information on lifetime hormone use was obtained at baseline by a trained interviewer, assisted by a structured questionnaire and chart displaying colored photographs of various hormone preparations. Information was obtained on the preparation, doses, schedule, route of administration, and therapy duration.

Women using hormone therapy at baseline were required to undergo a 3-month washout period prior to randomization in the hormone therapy trials. Women who had undergone hysterectomy were potentially eligible for a trial of daily 0.625-mg conjugated equine estrogen or matched placebo (11, 12), while women with a uterus were potentially eligible for the trial considered here of that same conjugated equine estrogen regimen plus daily 2.5-mg medroxyprogesterone acetate or matched placebo. There were no restrictions on hormone therapy use for observational study participants.

This paper is based on the cohort of 16,608 women enrolled in the E+P clinical trial and a corresponding observational study subcohort of 32,084 women with an intact uterus who either were not using hormone therapy (25,328 women) or were users at the time of enrollment of the same daily 0.625-mg conjugated equine estrogen plus 2.5-mg medroxyprogesterone acetate regimen studied in the clinical trial (6,756 women). Women enrolled at any of 40 participating US clinical centers during 1993–1998. To enhance comparability with the clinical trial cohort, women in this observational study subcohort were also required to have had a mammogram within 2 years prior to WHI enrollment and not to have had a prior invasive or noninvasive breast cancer diagnosis.

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 medical record and pathology report review by physician-adjudicators at the local clinical centers. All cases of disease were subsequently classified (13) at the clinical coordinating center by using the National Cancer Institute's

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

Yearly mammography and clinical breast examination were required in the hormone therapy trials, and study medications were withheld if these tests were not completed. Mammogram reports were reviewed locally and were 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.

Statistical methods

Age at menopause was defined as the lesser of 60 years or the age at which a woman last had menstrual bleeding, had bilateral oophorectomy, or began using hormone therapy. Detailed histories of hormone therapy exposure enabled an age at first use of hormone therapy to be defined, both for women who had used any hormone therapy prior to WHI enrollment and for women whose first use of hormones was that assigned in the E+P trial. The gap time from menopause to first hormone therapy use was the difference between these two ages. Women whose age at menopause was determined by the use of hormone therapy were assigned a gap time of zero. A total of 827 (10 percent) women assigned to E+P and 642 (8 percent) women assigned to placebo were excluded from analysis because of missing data on age at menopause or age at first use of HT. In the observational study, users and nonusers of E+P were selected to have the corresponding data available.

Time-to-event methods based on the Cox regression procedure (14) were used for primary data analyses, with time from randomization in the clinical trial and time from enrollment in the observational study as the basic time variable. Invasive breast cancer incidence rates during follow-up were stratified on baseline age in 5-year categories. Combined clinical trial and observational study analyses also stratified on cohort (clinical trial or observational study) as well as on prior HT status, as defined below. Hence, the comparison group for E+P users comprised all nonusers in the same baseline 5-year age category and, in combined clinical trial and observational study analyses, the same cohort and the same prior HT status.

Follow-up in the clinical trial was included through July 7, 2002, when study medications were discontinued, giving an average 5.6 years of follow-up; and it was included in the observational study through February 28, 2003, giving a comparable 5.5 years of follow-up. To control confounding, standard breast cancer risk factors were included in the Cox regression model in observational study analyses.

Dependence of the (Cox model) hazard ratio on years from initiation of the current episode of hormone therapy was accommodated by including distinct hazard ratios for less than 2, 2–5, and more than 5 years, with proportional hazards within these time periods. These categories represent early, middle, and late follow-up periods in the clinical trial and have been used previously in combined clinical trial and observational study analyses of hormone therapy in relation to cardiovascular disease (15, 16). These analyses involve time-dependent variables in the regression model, as women in the E+P groups move from one time-from-initiation period to the next during follow-up. Time from initiation was defined as time from randomization in the clinical trial, and as the sum of time from enrollment and duration of the ongoing E+P use identified at baseline in the observational study, with a usage gap of a year or more defining a new episode. Observational study participants who had used HT prior to the earlier of WHI enrollment or their baseline episode of hormone therapy were classified as having prior hormone therapy, as were clinical trial participants who had used HT prior to WHI enrollment.

Hazard ratios were standardized for mammographic screening patterns during follow-up by censoring the follow-up for a woman, in either the clinical trial or the observational study, when she first exceeded 2 years without a mammogram. Hazard ratios for women who were E+P adherent were estimated by censoring the follow-up period 6 months after a woman stopped taking the HT used at baseline, if an E+P user, or 6 months after initiating any HT, if a nonuser. The 6-month period was chosen to keep changes in HT use during diagnostic workup from inappropriately affecting results.

Hazard ratios, controlled for gap time and time from E+P initiation, were compared by using a likelihood ratio test that simultaneously contrasts seven parameters: three time-from-initiation hazard ratio parameters (<2, 2–5, >5 years) among women without prior HT, a corresponding three hazard ratio parameters among women with prior HT, and a gap-time interaction parameter that is linear in the log–hazard ratio. More specialized tests were also conducted to examine 1) evidence for an overall higher or lower hazard ratio in the observational study compared with the clinical trial by including a product term between an observational study indicator variable and an E+P indicator variable in the log–hazard ratio model and 2) whether gap-time interaction effects differ between the clinical trial and observational study, by contrasting corresponding log–hazard ratio coefficients.

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

RESULTS

Table 1 shows the number of women in the clinical trial and observational study, their mean ages, the number diagnosed with invasive breast cancer, and the annualized incidence rates separately according to prior hormone therapy use. These analyses show breast cancer incidence rate ratios for E+P users versus nonusers adjusted to the 5-year age distribution of the clinical trial. These ratios were close to 2 (1.86–2.20) for all groups except clinical trial participants without prior HT use, where a much smaller ratio (1.13) was found.

Table 2 shows the distribution of gap time from menopause to the first use of hormone therapy in these cohorts,

TABLE 1. Incidence rates of invasive breast cancer in the US Women's Health Initiative clinical trial and observational study cohorts (enrollment, 1993–1998), according to E+P* use and prior use of postmenopausal hormone therapy†

	No prior hormone therapy		Prior hormone therapy	
	Placebo	E+P	Placebo	E+P
Clinical trial of E+P				
Women (no.)	6,020	6,277	2,082	2,229
Mean age (years)	63.4	63.4	63.0	62.6
Breast cancer cases (no.)	116	138	28	58
Annualized incidence (%)‡	0.35	0.40	0.25	0.47
Incidence ratio	1.13		1.86	
	Nonusers	E+P	Nonusers	E+P
Observational study				
Women (no.)	19,668	5,710	5,660	1,046
Mean age (years)	64.7	61.0	64.8	64.3
Breast cancer cases (no.)	312	199	110	43
Annualized incidence (%)‡	0.35	0.72	0.38	0.79
Incidence ratio	2.20		2.07	

* E+P, estrogen plus progestin.

† Prior postmenopausal hormone therapy was defined relative to the beginning of the ongoing E+P episode at Women's Health Initiative enrollment for E+P users in the observational study and relative to Women's Health Initiative enrollment for other women.

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

TABLE 2. Distribution of gap time from menopause to first use of postmenopausal hormones among E+P* users in the US Women's Health Initiative clinical trial and observational study (enrollment, 1993–1998), according to prior use of postmenopausal hormone therapy†

	Gap time (years)					
	No prior hormone therapy			Prior hormone therapy		
	<5	5–15	>15	<5	5–15	>15
Clinical trial						
% of women by prior hormone use	17	43	40	84	14	3
No. of women‡	952	2,338	2,160	1,864	302	63
Breast cancer cases (no.)	22	46	46	51	6	1
Observational study						
% of women by prior hormone use	75	20	6	88	11	2
No. of women‡	4,257	1,115	338	916	113	17
Breast cancer cases (no.)	160	34	5	40	3	0

* E+P, estrogen plus progestin.

† Prior postmenopausal hormone therapy was defined relative to the ongoing E+P episode at Women's Health Initiative enrollment in the observational study and relative to Women's Health Initiative enrollment for women randomized to E+P use in the clinical trial.

‡ Excluded women for whom a gap-time value was missing.

along with the corresponding numbers of women and breast cancer cases. Clinical trial participants without prior HT tended to have large gap times, with 40 percent having a gap time in excess of 15 years, whereas most women in the other three groups had gap times of less than 5 years.

Estimated clinical trial breast cancer hazard ratios for E+P use were somewhat larger (table 3) for women who initiated E+P within 5 years of menopause than those for women with gap times of 5 or more years. The E+P hazard ratio depended significantly ($p = 0.02$) on gap time (<5 vs. ≥ 5 years) after controlling for prior hormone therapy status but did not depend significantly on prior hormone therapy status after controlling for gap time ($p = 0.53$).

A more refined analysis of the clinical trial data was carried out that enabled the E+P hazard ratio to depend quantitatively on both gap time and time from E+P initiation. Specifically, the Cox model log–hazard ratio included indicator variables for less than 2, 2–5, and more than 5 years from E+P initiation, separately for women with and without prior HT, along with the linear gap-time variable. To avoid undue influence by some long gap times, times greater than 15 years were recoded as 15 years in defining this gap-time variable. Estimated hazard ratios (table 4) for women who began hormone therapy immediately following menopause (gap time of zero) were elevated after the first 2 years of E+P use. The E+P hazard ratio was estimated to decrease by a factor of 0.84 (95 percent CI: 0.69, 1.03; $p = 0.09$) with a 5-year increment in gap time.

Table 4 also shows corresponding hazard ratio estimates from the observational study. These estimates were imprecise for the first 2 years of E+P use because there were few recent E+P initiators at the time of enrollment in the observational study. The hazard ratio estimates were similar to those from the clinical trial for longer-term use. The E+P hazard ratio depended ($p = 0.01$) on gap time and was estimated to decrease by a factor of 0.79 (95 percent CI: 0.66, 0.96; $p = 0.01$) with a 5-year increment in gap time.

A test of equality of the six hazard ratios for E+P shown in table 4 and the hazard ratio gap-time factor between the clinical trial and observational study did not provide evidence of a difference ($p = 0.49$), supporting use of the combined clinical trial and observational study data (table 4) for more precise hazard ratio estimation. The hazard ratio depended strongly ($p < 0.001$) on gap time in these combined cohort analyses and decreased by a factor of 0.81 (95 percent CI: 0.71, 0.91) with a 5-year gap-time increment. Also note the strong hazard ratio dependence on years from E+P initiation in these analyses for women both without ($p < 0.001$) and with ($p = 0.03$) prior hormone therapy use. These combined clinical trial and observational study analyses enabled the E+P hazard ratio to differ by a multiplicative factor between the two cohorts. This factor of E+P in the observational study divided by E+P in the clinical trial was estimated as 1.03 (95 percent CI: 0.69, 1.53), attesting to the good overall agreement between hazard ratios in the two cohorts. Likewise, there was no evidence that the magnitude of the gap-time interaction effect differed between the two cohorts ($p = 0.67$).

TABLE 3. Hazard ratios for invasive breast cancer for E+P* use by years from menopause to first use of postmenopausal hormones (gap time) and prior hormone therapy use in the US Women's Health Initiative clinical trial (enrollment, 1993–1998)

	Gap time (years)†				HR* for interaction with gap time (<5 vs. ≥5 years) (*p* value)‡
	<5		≥5		
	HR	95% CI*	HR	95% CI	
No prior hormone therapy§	1.77	1.07, 2.93	0.99	0.74, 1.31	0.02
Prior hormone therapy§	2.06	1.30, 3.27	1.30	0.57, 2.99	
HR for interaction with prior hormone therapy (no vs. yes) (*p* value)¶		0.53			

* E+P, estrogen plus progestin; HR, hazard ratio; CI, confidence interval.

† HRs and 95% CIs were derived from Cox model analyses that stratified on baseline age (5-year categories) and included prior hormone therapy as a breast cancer risk factor.

‡ Controlled for HR dependence on prior hormone therapy.

§ Prior (postmenopausal) hormone therapy status was defined relative to enrollment in the Women's Health Initiative clinical trial.

¶ Controlled for HR dependence on gap time (<5 vs. ≥5 years).

To examine whether the gap-time interaction could be attributed to confounding by duration of E+P use, the analysis on the right side of table 4 was repeated by adding a product term between E+P and a linear term in years from E+P initiation in the log–hazard ratio model. The hazard ratio factor for a 5-year gap-time increase was 0.83 (95 percent CI: 0.73, 0.95; $p = 0.005$) even though a modest interaction of the hazard ratio with years from E+P initiation ($p = 0.04$) was observed. The same analysis, but with follow-up times censored 6 months after a change from user or nonuser group status, gave a 5-year gap-time hazard ratio factor of 0.81 (95 percent CI: 0.70, 0.94; $p = 0.005$), whereas the interaction with duration of E+P use was nonsignificant ($p = 0.41$). Interactions of the E+P hazard ratio with several other factors were also considered, including the Gail et al. model (17) 5-year risk percentage, body mass index, family history of breast cancer, and prior diagnosis of benign breast disease. Of these factors, none showed evidence of association with the E+P hazard ratio ($p > 0.4$), with the possible exception of a lower hazard ratio for women having a relatively high body mass index ($p = 0.11$). The gap-time interaction was essentially unchanged when hazard ratio interactions were included with these other factors ($p < 0.002$ in each case). In addition, E+P hazard ratios were modestly higher ($p = 0.03$) among women who were older at WHI enrollment and among women having lengthy times from menopause to WHI enrollment ($p = 0.02$), but gap-time hazard ratio associations remained highly significant ($p < 0.001$) in the presence of these other interactions.

Additional analyses were carried out to ensure that the assumed form of the hazard ratio dependence on gap time (linear in log–hazard ratio) was not unduly affecting results. Figure 1 shows hazard ratio estimates from a further analysis of data from the combined cohorts. This analysis classified gap time into <5-, 5–15-, and >15-year categories and excluded women with prior hormone therapy. The data were rather sparse for long gap times and for short times from hormone therapy initiation, but elevations in breast cancer risk became evident after about 2 years from E+P initiation among women who started E+P within 5 years of menopause.

The lower part of figure 1 presents corresponding hazard ratio estimates with follow-up times censored 6 months after a change in E+P user or nonuser status. Among adherent women who initiated E+P within 5 years of menopause, there was limited evidence for a hazard ratio increase within the first 2 years of use, whereas hazard ratios were substantially elevated after the first 2 years.

From the combined clinical trial and observational study analyses shown in the lower part of figure 1, women who initiated E+P within 5 years of menopause experienced a breast cancer risk that was elevated ($p < 0.001$) and increased with duration of use ($p < 0.001$). The "average" hazard ratio over 5 years of E+P use was 1.64 (95 percent CI: 1.00, 2.68). The corresponding hazard ratio over a 10-year period of use was 2.19 (95 percent CI: 1.56, 3.08).

DISCUSSION

The negative association between E+P hazard ratio and time from menopause to first use of HT provides a possible explanation for a comparatively lower hazard ratio among women without prior HT in the clinical trial, since these women had much longer gap times.

Breast cancer hazard ratios in the observational study were in agreement with those from the clinical trial after controlling for both years from menopause to hormone therapy initiation and years since hormone therapy initiation (i.e., duration of E+P use for adherent women). For women who initiated E+P within 5 years of menopause—the group most likely making hormone therapy decisions in the future—the two data sources combined (figure 1) to give hazard ratios of 1.85 (95 percent CI: 1.03, 3.34) for 2–5 years of use and 2.75 (95 percent CI: 1.73, 4.39) for more than 5 years of use. These analyses project an increase from

TABLE 4. Hazard ratios for invasive breast cancer for E+P* use, in relation to prior hormone therapy and years from E+P therapy initiation, for women who began hormone therapy at menopause (gap time of zero) in the US Women's Health Initiative clinical trial and observational study (enrollment, 1993–1998)

No. of years from E+P initiation†	Clinical trial‡		Observational study‡,§		Combined studies‡,¶	
	HR*	95% CI*	HR	95% CI	HR	95% CI
No prior hormone therapy#						
<2	0.79	0.40, 1.57	1.69	0.60, 4.77	0.98	0.56, 1.72
2–5	1.97	1.11, 3.50	1.85	1.13, 3.02	2.01	1.41, 2.86
>5	1.99	0.92, 4.29	2.94	2.33, 3.69	2.85	2.29, 3.54
Prior hormone therapy#						
<2	1.11	0.54, 2.25	2.63	0.61, 11.29	1.28	0.66, 2.51
2–5	3.42	1.68, 6.95	1.64	0.63, 4.25	2.56	1.54, 4.24
>5	2.42	0.64, 9.17	3.32	1.79, 6.13	3.30	1.90, 5.73
Factor for 5-year increase in gap time	0.84	0.69, 1.03	0.79	0.66, 0.96	0.81	0.71, 0.91

* E+P, estrogen plus progestin; HR, hazard ratio; CI, confidence interval.

† Time from E+P initiation was defined as time from enrollment for women assigned to E+P in the clinical trial and as the sum of this time plus duration of the ongoing E+P episode at the time of enrollment in the observational study. The number of invasive breast cancer cases among E+P users in the <2, 2–5, and >5 years from E+P initiation were, respectively, 6, 41, and 15 for the clinical trial no prior hormone therapy group; 14, 12, and 5 for the clinical trial prior hormone therapy group; 4, 22, and 156 for the observational study no prior therapy group; and 2, 6, and 25 for the observational study prior hormone therapy group.

‡ HRs and 95% CIs were derived from Cox models that stratified baseline rates on age (5-year categories) and prior hormone therapy status and cohort (clinical trial or observational study). Women for whom age at menopause or age at first use of hormone therapy was missing were omitted, leaving data on 15,139 (91.2%) of the clinical trial women available for analysis.

§ HR estimates in the observational study controlled for confounding factors separately in the prior hormone therapy and no prior hormone therapy groups and included age (linear), body mass index (<25, 25–29, 30–34, >34 kg/m^2, and linear), education (high school or less, beyond high school, college degree), smoking (never, past, current), alcohol intake (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 et al. (17) model breast cancer risk % (<1.25, 1.25–1.74, >1.74, and linear), and bilateral oophorectomy (yes, no). For women with prior hormone therapy, confounding factors also included prior E+P use in years (none, <5, 5–10, >10) and prior estrogen-alone use in years (none, <5, 5–10, >10). Women for whom confounding-factor data, age at menopause, or age at first use of hormone therapy was missing were omitted, leaving data on 27,954 women (87.1% of the observational study subcohort) for analysis.

¶ HR estimates from combined study analyses used the same statistical model as those used in separate clinical trial and observational study analyses but restricted the hazard ratios to be common in the two cohorts up to a multiplicative factor (to control for residual confounding in the observational study). That factor was estimated as 1.03 (95% CI: 0.69, 1.53), indicating excellent overall agreement between hazard ratios in the two cohorts.

Prior (postmenopausal) hormone therapy was defined relative to the baseline E+P episode for E+P users in the observational study and relative to Women's Health Initiative enrollment otherwise.

28 cases of invasive breast cancer per 10,000 person-years among nonusers of E+P, to 46 cases (attributable risk, 39 percent) over the first 5 years of use, to 61 cases (attributable risk, 54 percent) over the first 10 years of E+P use among women with gap times of less than 5 years.

Several biologic events could mediate a differential effect of E+P on breast cancer risk depending on time from menopause to initiation of HT. Preclinical studies indicate that breast cancers, when exposed to a period of estrogen deprivation, make adaptive changes (18, 19) that decrease their susceptibility to proliferative stimulation by estrogen (20). In addition, combined hormone therapy increases mammographic density (21, 22) and slows the change from a dense pattern to a more fatty pattern, thought to represent lobular involution with reduction in the number of breast epithelial and stromal cells (23). Because lobular involution is associated with reduced breast cancer risk (24), a longer time from menopause with resultant lobular involution could

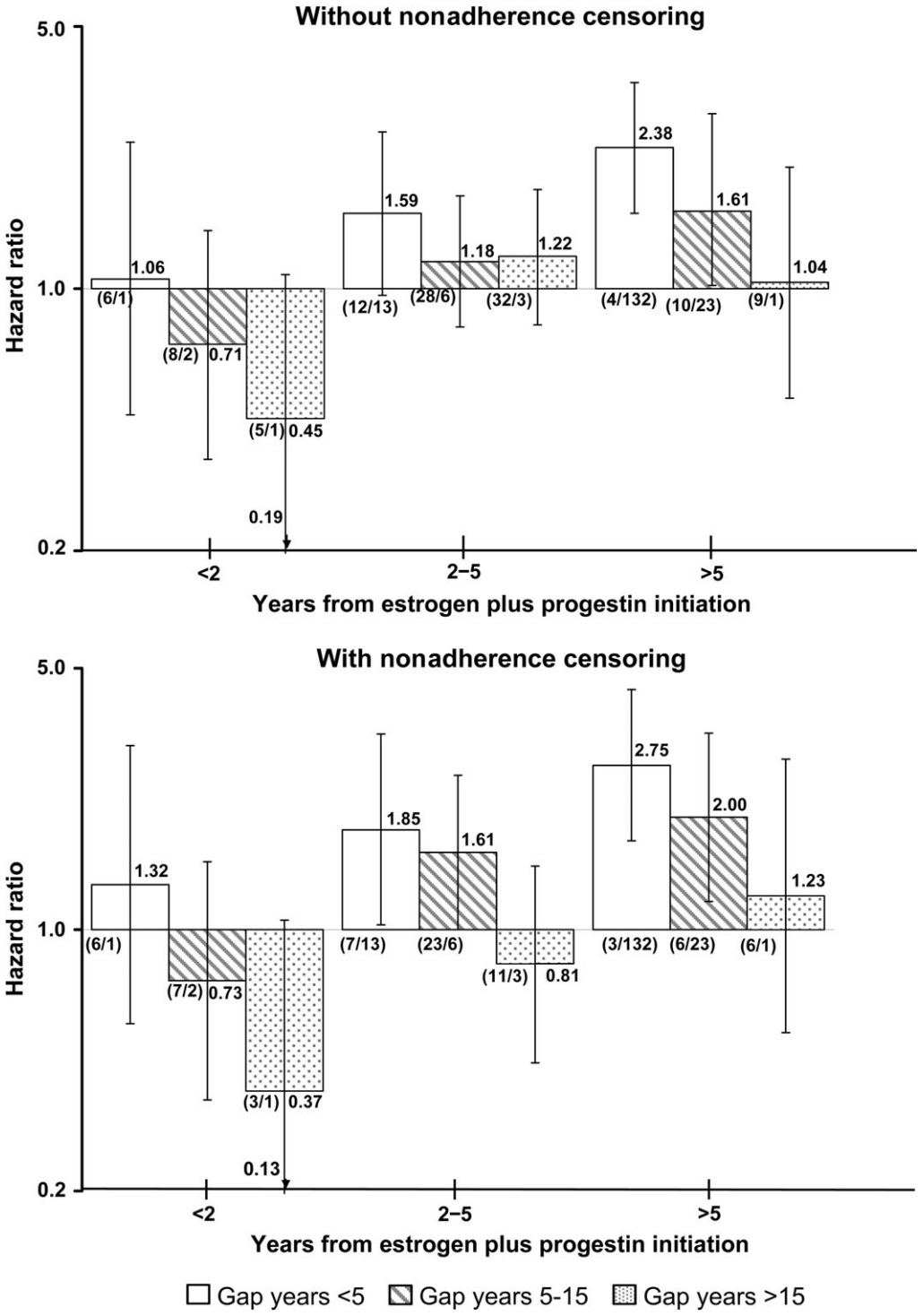

FIGURE 1. Hazard ratios for invasive breast cancer according to gap years from menopause to first use of estrogen plus progestin, and years from estrogen plus progestin initiation, among women without prior postmenopausal hormone therapy, obtained from combined analyses of the Women's Health Initiative clinical trial and observational study data (women enrolled at any of 40 participating US clinical centers during 1993–1998). Hazard ratios and 95% confidence intervals (plotted on a logarithmic scale) are from Cox model analyses that stratified on baseline age (5-year categories) and cohort (clinical trial vs. observational study). Refer to the fourth footnote of table 4 for confounding factor control in the observational study. These analyses also enabled hazard ratios in the observational study to differ from those in the clinical trial by a multiplicative factor to control for possible residual confounding in the observational study. Values in parentheses, number of breast cancer cases among estrogen plus progestin users in the clinical trial/number of breast cancer cases among estrogen plus progestin users in the observational study. The lower part of the figure was derived by censoring follow-up times 6 months after a change in estrogen plus progestin user/nonuser status.

decrease the number of epithelial breast cells potentially influenced by estrogen and progestin. Biologic inferences about E+P effects on breast cancer are somewhat limited by potential influence of these hormones on mammographic interpretation and breast cancer detection (2, 25).

Concerning data analysis methods, time from enrollment is the natural, basic time variable in Cox regression analysis of clinical trial data, but other choices may be of interest for cohort data analyses, including study subject age. Here, we defined time from enrollment as the basic time variable for both the clinical trial and observational study while stratifying breast cancer rates on baseline age. Doing so implies that hormone therapy hazard ratios derive from comparisons between E+P users and nonusers who are the same length of time from WHI enrollment and are also close in age. As such, these hazard ratios can be expected to be very similar to those that would derive from corresponding analyses that define age as the basic time variable (both clinical trial and observational study) that also stratify on baseline age (so that women of a given age during follow-up are also a similar time from enrollment and covariate ascertainment, within strata). For example, under this alternative modeling strategy, the E+P hazard ratios corresponding to the combined clinical trial and observational study analyses on the right side of table 4 are, respectively, 0.99 (95 percent CI: 0.56, 1.73), 2.05 (95 percent CI: 1.44, 2.92), and 2.96 (95 percent CI: 2.37, 3.68) for women without prior HT and 1.36 (95 percent CI: 0.70, 2.66), 2.44 (95 percent CI: 1.47, 4.07), and 3.33 (95 percent CI: 1.92, 5.79) for women with prior HT, while the hazard ratio factor for a 5-year gap-time increase is 0.81 (95 percent CI: 0.71, 0.91), in close agreement with those shown in table 4.

Furthermore, the rather complex definition of prior HT status in the observational study may benefit from some elaboration. With an average baseline age of 63 years, there were few HT initiators during observational study follow-up, so that E+P user and nonuser groups were necessarily defined according to E+P use at enrollment. Women in the E+P user group had often used the study regimen for some years prior to observational study enrollment. Any use of another HT regimen prior to this ongoing baseline episode caused a woman to be classified as having prior HT. In addition, a woman who used the study regimen only prior to enrollment, but had a usage gap of 1 year or longer in this prior HT history, was classified as having prior HT. For such women, the duration of the ongoing baseline episode was the time from enrollment to the first usage gap of 1 year or longer encountered, going back in time.

The strengths of this study include the randomized controlled design of the clinical trial, with findings independently tested in the well-characterized observational study cohort. The two cohorts were drawn from the same populations; both received personal interviews regarding their history of hormone therapy use and had serial assessment of mammography use, common breast cancer risk factor assessment procedures, and very similar breast cancer ascertainment procedures. Study limitations include potential reliability issues associated with the retrospective assessment of both prior hormone therapy use (26, 27) and age at menopause (28, 29), especially among women who were many years past menopause at WHI enrollment. In addition, relief of vasomotor symptoms or risk of osteoporosis were likely reasons for observational study women to be using E+P at enrollment, whereas clinical trial women agreed to be randomly assigned to E+P or placebo. However, the good agreement between hazard ratios from the two cohorts suggests little, if any, hazard ratio confounding (i.e., effect modification) by this factor.

Another limitation relates to the few clinical trial women without prior HT having short gap times. This limitation implies that corresponding breast cancer hazard ratios from clinical trial analyses may be sensitive to modeling assumptions. For example, analyses of the type shown in table 3, but with a 10-year gap-time cutpoint, do not provide evidence of a hazard ratio dependence on gap time. The figure 1 analyses provide an examination of hazard ratios among women without prior HT that is rather robust to modeling assumptions, but some cells involved a small number of breast cancer cases, and most cases derived from the observational study in some cells. It will be valuable for the hazard ratio associations examined here to be considered in other studies, especially those that include many recent E+P initiators without prior HT, and that can estimate gap time and duration of E+P use with precision.

In summary, the WHI clinical trial and observational study each support an adverse effect of daily 0.625-mg conjugated equine estrogen plus 2.5-mg medroxyprogesterone acetate on breast cancer. Women who initiate treatment soon after menopause and continue for many years appear to be at particularly high risk.

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A list of key investigators involved in this research follows. A full listing of WHI investigators can be found at the following website: http://www.whi.org.

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