Original Investigation

Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone

Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials

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Editorial page 283

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IMPORTANCE The use of menopausal hormone therapy (HT) continues in clinical practice, but reports are conflicting concerning the longer-term breast cancer effects of relatively short-term use.

OBJECTIVE To report the longer-term influence of menopausal HT on breast cancer incidence in the 2 Women's Health Initiative (WHI) randomized clinical trials.

DESIGN, SETTING, AND PARTICIPANTS A total of 27 347 postmenopausal women aged 50 to 79 years were enrolled at 40 US centers from 1993 to 1998 and followed up for a median of 13 years through September 2010.

INTERVENTIONS A total of 16 608 women with a uterus were randomized to conjugated equine estrogens (0.625 mg/d [estrogen]) plus medroxyprogesterone acetate (2.5 mg/d [progestin]) (E + P) or placebo with a median intervention duration of 5.6 years, and 10 739 women with prior hysterectomy were randomized to conjugated equine estrogens alone (0.625 mg/d) or placebo with a median intervention duration of 7.2 years.

MAIN OUTCOMES AND MEASURES Time-specific invasive breast cancer incidence rates and exploratory analyses of breast cancer characteristics by intervention and postintervention phases in the 2 HT trials.

RESULTS In the E + P trial, hazard ratios (HRs) for the influence of combined HT on breast cancer were lower than 1 for 2 years (HR, 0.71; 95% CI, 0.47-1.08) and steadily increased throughout intervention, becoming significantly increased for the entire intervention phase (HR, 1.24; 95% CI, 1.01-1.53). In the early postintervention phase (within 2.75 years from intervention), there was a sharp decrease in breast cancer incidence in the combined HT group, though the HR remained higher than 1 (HR, 1.23; 95% CI, 0.90-1.70). During the late postintervention phase (requiring patient re-consent), the HR for breast cancer risk remained higher than 1 through 5.5 years (median) of additional follow-up (HR, 1.37; 95% CI, 1.06-1.77). In the estrogen alone trial, the HR for invasive breast cancer risk was lower than 1 throughout the intervention phase (HR, 0.79; 95% CI, 0.61-1.02) and remained lower than 1 in the early postintervention phase (HR, 0.55; 95% CI, 0.34-0.89), but risk reduction was not observed during the late postintervention follow-up (HR, 1.17; 95% CI, 0.73-1.87). Characteristics of breast cancers diagnosed during early and late postintervention phases differed in both trials.

CONCLUSIONS AND RELEVANCE In the E + P trial, the higher breast cancer risk seen during intervention was followed by a substantial drop in risk in the early postintervention phase, but a higher breast cancer risk remained during the late postintervention follow-up. In the estrogen alone trial, the lower breast cancer risk seen during intervention was sustained in the early postintervention phase but was not evident during the late postintervention follow-up.

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After reports of increased breast cancer risk with estrogen plus progestin from the Women's Health Initiative (WHI) randomized clinical trial (clinicaltrials.gov identifier: NCT000000611)[1,2] followed by the Million Women Study observational analysis,[3] use of menopausal hormone therapy dramatically decreased.[4-6] A substantial population-based decrease in breast cancer incidence followed, which was attributed to the decrease in hormone therapy use.[7,8] While this relationship has been supported by analyses in US[9,10] and international populations,[11] the rapid nature of the decrease and the potential influence of changes in mammography use[12] raised interpretation questions. Over the short term, these issues were addressed in the WHI estrogen plus progestin trial, where nearly all participants discontinued study medication at one time as instructed.[13] In that setting, breast cancer risk rapidly decreased after combined hormone therapy ended, while mammography use remained closely comparable in placebo and active therapy groups.[14]

With a longer postintervention follow-up of 8.2 years, breast cancer risk with estrogen plus progestin use appeared to be similarly increased in the intervention and postintervention phases.[15] These findings are in contrast to the preponderance of observational studies, in which limited or no breast cancer risk was seen after only a few years after stopping therapy.[3,16] However, recent results from the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort suggested residual increases in breast cancer risk for long-term (>5 year) hormone therapy users.[17]

Following the initial WHI reports, decreases in both combined estrogen plus progestin use as well as in estrogen alone use were seen.[4,5] However, in the WHI randomized trials, while estrogen plus progestin increased breast cancer incidence and breast cancer deaths,[2,18] estrogen alone in women with prior hysterectomy significantly reduced breast cancer incidence and breast cancer deaths.[19] Such results raised questions regarding the short- and long-term postintervention effects of these 2 regimens on breast cancer. Therefore, we examined early and late postintervention effects on breast cancer in the 2 WHI hormone therapy trials with a current median follow-up of 13 years.

At a Glance

- We examined influences of menopausal hormone therapy on breast cancer incidence during intervention and early and late postintervention phases in the Women's Health Initiative trials (13 years of follow-up).
- Estrogen plus progestin use significantly increased breast cancer incidence while patients were receiving the agents, but the hazard ratio (HR) decreased when the therapy was discontinued.
- An elevated HR persisted (HR, 1.37; 95% CI, 1.06-1.77) years after stopping combined hormone therapy.
- Use of estrogen alone significantly reduced breast cancer incidence.
- For estrogen alone, the reduction of breast cancer incidence persisted throughout the early postintervention phase (HR, 0.55; 95% CI, 0.34-0.89) but was lost during the late postintervention phase (HR, 1.17; 95% CI, 0.73-1.87) (P = .03).

Methods

Details of the WHI hormone therapy trials have been described.[1,20] Postmenopausal women aged between 50 and 79 years with no previous breast cancer and anticipated survival of greater than 3 years were eligible and were enrolled from 40 clinical centers in the United States from 1993 through 1998. Both trials were approved by institutional review boards at the clinical centers and participants provided written informed consent.

A total of 16 608 women with a uterus were randomized to oral conjugated equine estrogens (CEE) (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d [progestin]) (Prempro; Pfizer) or placebo, and 10 729 women with prior hysterectomy were randomized to CEE (0.625 mg/d) alone (Premarin; Pfizer) or placebo. The primary efficacy outcome in both trials was coronary heart disease, and the primary safety outcome was invasive breast cancer[21]; the sample size was based on these end points. Clinical outcome information was collected at 6-month intervals, with breast cancers confirmed by medical record review by local physician adjudicators. Final adjudication occurred at the Clinical Coordinating Center. Mammograms and breast examinations were required annually through the originally specified completion date in both trials (March 31, 2005).

The intervention phase of the estrogen plus progestin trial ended on July 7, 2002, after 5.6 years (median) when an unfavorable risk to benefit ratio emerged.[1] The intervention phase of the estrogen alone trial ended on February 29, 2004, after 7.2 years (median) owing to increased stroke risk and no overall favorable risk to benefit ratio.[20] In both trials, participants were instructed by letter, sent to coincide with the publication of the trial results, to stop study pill (active or placebo) use. After intervention, participants were followed up and annual mammograms were recommended.

In the estrogen plus progestin trial, there was 2.75 years between the end of intervention and the planned trial completion date (March 31, 2005). After this date, additional written informed consent was required for continued follow-up, which was obtained in 81.1% of the surviving participants.[15] To examine time trends, analyses were conducted for 3 phases: intervention, early postintervention (within 2.75 years after stopping the intervention), and late postintervention. In the estrogen alone trial, the intervention ended a little more than a year before the trial completion date. To have comparable periods, early postintervention was defined similarly as 2.75 years after the intervention ended. Participant flow in both trials is described in CONSORT diagrams (eFigure in the Supplement).[15]

Invasive breast cancer incidence in the intervention, early postintervention, and late postintervention phases were the primary study end points. The incidence results were assessed with time-to-event methods based on the intention-to-treat principle. Incidence rate comparisons are presented as hazard ratios (HRs) and 95% CIs from Cox proportional hazard models stratified by age and randomization group in the WHI Dietary Modification Trial.[22] To investigate time trends,

time-varying linear HRs were calculated for the intervention and the entire postintervention phase. To provide further detail, the postintervention phase was further subdivided, and HRs were estimated separately for the early and late postintervention phases. Comparisons were made between the 2 postintervention phases and between the intervention and an overall "average postintervention"; for brevity, summary statistics for the overall postintervention phase are not shown. To show the reasonableness of fit for the linear time-varying HR, biennial hazard ratios and 95% CIs were overlaid

Sensitivity analyses for adherence were conducted after censoring for events that occurred 6 months after a woman became nonadherent (using <80% of study pills). Women adherent through 5.6 years in the estrogen plus progestin trial and through 7.2 years in the estrogen alone trial did not have their outcomes censored. Time-varying weights, inversely proportional to the estimated probability of continued adherence, were used in the proportional hazards models to maintain the distribution of the sample characteristics during follow-up.

In exploratory analyses, HRs were estimated across tumor types and also compared between study periods, with statistical significance ($P < .05$) based on a test of interaction. Analyses of breast cancer subtypes incorporated censoring at diagnosis of any other breast cancer subtype.[23]

All analyses were conducted using SAS version 9.3 (SAS Institute) statistical software. Figures were created using R-2.15 software (R Development Core Team). All *P* values are 2 sided.

Results

In the estrogen plus progestin and the estrogen alone trials, risk factors for breast cancer were balanced between the 2 randomized groups (**Table**). As previously reported, the risk of invasive breast cancer was higher in the combined hormone therapy group during intervention (**Figure 1**).[2] The time-varying HRs used to calculate estrogen plus progestin influence on breast cancer risk were lower than 1 during the first 2 years. Subsequently, breast cancer risk increased throughout the intervention phase and became statistically significant.

During early postintervention phase, there was a sharp decrease in breast cancer risk in the combined hormone therapy group, and the difference in the HR slope for the estrogen plus progestin effect on breast cancer risk during intervention compared with the slope during the entire postintervention period was statistically significant ($P = .04$) (Figure 1). The lower breast cancer risk seen during early postintervention follow-up was not sustained because during the late postintervention period the HR for combined hormone therapy influence on breast cancer risk remained greater than 1, with no evidence of modulation of risk over time ($P = .96$).

In the estrogen alone trial in women with prior hysterectomy, the invasive breast cancer risk was lower than 1 throughout the 7.2-year intervention phase, approaching but not crossing 1 over time (**Figure 2**). In the early postintervention phase, the HR for the influence of estrogen alone on breast cancer risk was substantially lower than during the intervention phase but became attenuated over time. The HR during early postintervention phase was 0.55 (95% CI, 0.34-0.89) compared with 1.17 (95% CI, 0.73-1.87) during the late postintervention phase, with the HR crossing 1 after approximately 4.5 years (Figure 2).

Mammography use rates (annualized percentage) were balanced between randomization groups during and after intervention in both trials. Adjustment for mammogram use as a time-dependent variable did not appreciably affect the analytic results.

Breast cancer characteristics and corresponding risk estimates for hormone therapy by randomization group and therapy phase from exploratory analyses are outlined in **Figure 3** and **Figure 4**. Complete findings are included as eTables 1 and 2 in the Supplement. Competing risk analyses suggest different risk profiles between the early and late postintervention periods. Specifically, with estrogen plus progestin there were more large tumors (HR, 2.67; 95% CI, 1.19-6.00; compared with HR, 0.97; 95% CI, 0.57-1.65 [$P = .04$]), more progesterone receptor–negative tumors (HR, 2.67; 95% CI, 1.25-5.73; compared with HR, 0.93; 95% CI, 0.54-1.59 [$P = .004$]), and somewhat more triple-negative tumors during early vs late postintervention. With estrogen alone, there were more *HER2*-positive (HR, 1.79; 95% CI, 0.43-7.49; compared with HR, 0.25; 95% CI, 0.03-2.23 [$P = .007$]) and fewer moderately differentiated (HR, 0.24; 95% CI, 0.10-0.59; compared with HR, 1.99; 95% CI, 0.96-4.10 [$P = .008$]) tumors during early vs late postintervention. For both hormone therapy trials, risk profiles did not differ between the intervention and overall postintervention periods for any of the tumor types.

Discussion

With longer postintervention follow-up, complex patterns of hormone therapy influence on breast cancer risk emerged in the 2 WHI trials. In the estrogen plus progestin trial, the increasing breast cancer risk seen during intervention was followed by a substantial drop in risk in the early postintervention period but with a sustained higher breast cancer risk during the late postintervention phase. In the estrogen alone trial, the lower breast cancer risk seen during intervention was sustained in the early postintervention phase but was lost during the late postintervention follow-up.

During intervention in the estrogen plus progestin trial, the initial HRs below 1 during the first 2 years reflects the negative influence of combined hormone therapy on mammogram diagnostic performance.[24] During this period, breast cancer diagnosis was delayed, leading to more advanced-stage cancers and larger tumors[2] and to the emergence of a year-to-year increase in breast cancer risk throughout the intervention phase.[14]

In the early postintervention phase, a rapid decrease in the breast cancer incidence rate in the estrogen plus progestin group was seen. This likely represents a therapeutic influence of change in hormone environment on preclinical breast cancers similar to that seen with adjuvant aromatase inhibitor or tamoxifen use in early-stage breast cancer.[25,26] In this regard, Santen and colleagues[27] developed a breast cancer growth kinetic model based on clinical findings and

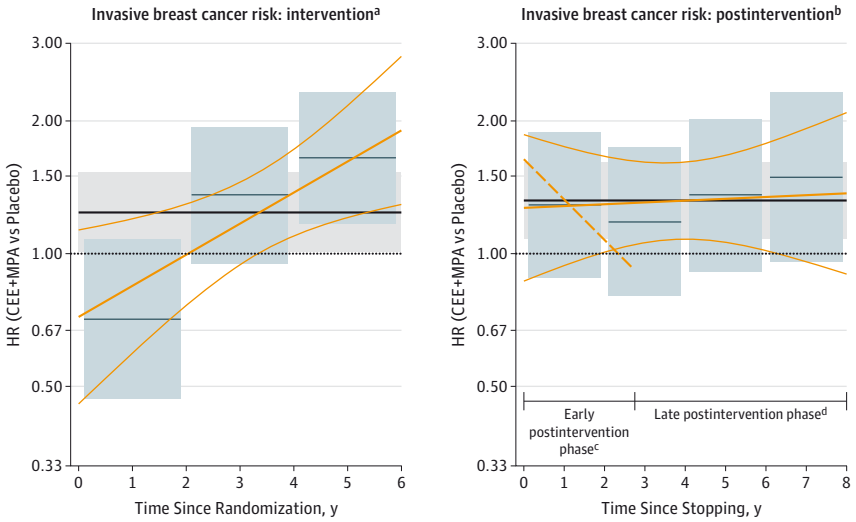
Table. Baseline Characteristics of Participants in the Women's Health Initiative Trials of Postmenopausal Hormone Therapy

Characteristic	Trials, No. (%)			
	CEE + MPA		CEE Alone	
	Active (n = 8506)	Placebo (n = 8102)	Active (n = 5310)	Placebo (n = 5429)
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	63.6 (7.3)	63.6 (7.3)
Age group at screening, y				
50-59	2837 (33.4)	2683 (33.1)	1639 (30.9)	1674 (30.8)
60-69	3854 (45.3)	3655 (45.1)	2386 (44.9)	2465 (45.4)
70-79	1815 (21.3)	1764 (21.8)	1285 (24.2)	1290 (23.8)
Race/ethnicity				
White	7141 (84.0)	6805 (84.0)	4009 (75.5)	4075 (75.1)
Black	548 (6.4)	574 (7.1)	781 (14.7)	835 (15.4)
Hispanic	471 (5.5)	415 (5.1)	319 (6.0)	332 (6.1)
American Indian	25 (0.3)	30 (0.4)	41 (0.8)	34 (0.6)
Asian/Pacific Islander	194 (2.3)	169 (2.1)	86 (1.6)	78 (1.4)
Unknown	127 (1.5)	109 (1.3)	74 (1.4)	75 (1.4)
College degree or higher	2915 (34.4)	2839 (35.3)	1217 (23.2)	1327 (24.6)
BMI				
<25	2579 (30.4)	2479 (30.8)	1110 (21.0)	1096 (20.3)
25-29	2992 (35.3)	2835 (35.2)	1798 (34.0)	1915 (35.5)
≥30	2899 (34.2)	2737 (34.0)	2375 (45.0)	2385 (44.2)
Smoking				
Never	4178 (49.6)	3999 (50.0)	2723 (51.9)	2705 (50.4)
Past	3362 (39.9)	3157 (39.5)	1986 (37.8)	2090 (38.9)
Current	880 (10.5)	838 (10.5)	542 (10.3)	571 (10.6)
Age at menarche, y				
≤11	1725 (20.3)	1670 (20.7)	1215 (23.0)	1280 (23.7)
12-13	4578 (54.0)	4334 (53.7)	2805 (53.1)	2853 (52.8)
≥14	2182 (25.7)	2061 (25.6)	1259 (23.8)	1274 (23.6)
Age at first birth, y				
Never pregnant/no term pregnancies	860 (11.2)	833 (11.5)	491 (10.4)	463 (9.5)
<20	1124 (14.6)	1117 (15.4)	1193 (25.2)	1234 (25.3)
20-29	4996 (64.8)	4698 (64.6)	2846 (60.0)	2914 (59.8)
>30	727 (9.4)	624 (8.6)	210 (4.4)	260 (5.3)
Benign breast disease				
No	6340 (83.6)	6278 (83.3)	3894 (80.8)	3787 (78.4)
Yes, 1 biopsy	956 (12.6)	972 (12.9)	678 (14.1)	748 (15.5)
Yes, ≥2 biopsies	290 (3.8)	288 (3.8)	250 (5.2)	295 (6.1)
First-degree female relatives with breast cancer	1009 (12.7)	895 (11.8)	696 (14.2)	685 (13.6)
Gail 5-y risk score				
<1.25	2806 (33.0)	2717 (33.5)	2129 (40.1)	2149 (39.6)
1.25-<1.75	2859 (33.6)	2703 (33.4)	1620 (30.5)	1688 (31.1)
≥1.75	2841 (33.4)	2682 (33.1)	1561 (29.4)	1592 (29.3)
Bilateral oophorectomy	29 (0.3)	24 (0.3)	1938 (39.5)	2111 (42.0)
Years since menopause				
<10	2780 (36.2)	2711 (36.1)	827 (18.4)	817 (17.6)
10-<20	3049 (39.7)	2992 (39.9)	1438 (32.0)	1500 (32.4)
≥20	1850 (24.1)	1805 (24.0)	2230 (49.6)	2319 (50.0)
Menopausal hormone therapy status				
Never used	6277 (73.8)	6022 (74.4)	2769 (52.2)	2769 (51.0)
Past user	1671 (19.7)	1587 (19.6)	1871 (35.2)	1947 (35.9)
Current user[a]	554 (6.5)	490 (6.1)	669 (12.6)	709 (13.1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

[a] Required 3-month washout before entry.

Figure 1. Effects Over Time of Estrogen Plus Progestin on the Incidence of Breast Cancer in the Women's Health Initiative Clinical Trial



Overall hazard ratio (HR) and 95% CI (black line and gray-shaded region, respectively) are shown for the effect of conjugated equine estrogens plus medroxyprogesterone acetate (CEE + MPA) on the risk of invasive breast cancer compared with placebo during the intervention period (left panel) and the overall postintervention phase (right panel). A reference line (dotted black) at unity corresponds to no differential risk between randomization groups. Hashmarks (bottom of right panel) indicate the early and late postintervention periods. Time-varying linear HR and 95% CI (orange lines) are also displayed for the intervention period (left panel) and overall postintervention period (right panel), as well as a time-varying linear HR for the early postintervention phase (dashed orange line). Biennial HRs and 95%CIs (solid blue lines and blue-shaded regions, respectively) are presented as an alternate description for time-varying risk. The biennial HR (95% CI) were 0.71 (0.47-1.08), 1.36 (0.95-1.94), 1.65 (1.17-2.32) during the intervention, and 1.29 (0.88-1.88), 1.18 (0.80-1.74), 1.36 (0.91-2.02), and 1.49 (0.96-2.33) for the postintervention phase. Significance tests of the time-varying linear HR for the primary (adherence adjusted) analysis were conducted and yielded $P = .008$ (.007) for linear trend during the intervention; $P = .28$ (.04) for linear trend during the early postintervention phase; $P = .07$ (.006) for difference between linear trends of intervention and early postintervention phase; $P = .86$ (.65) for linear trend during the overall postintervention phase; and $P = .04$ (.02) for difference between linear trends of intervention and overall postintervention phase. Time-varying linear HR is not shown for the late postintervention phase because significance test results were not suggestive of a trend: $P = .96$ (.55) for a linear trend during the late postintervention phase.

[a] HR, 1.24 (95% CI, 1.01-1.53).

[b] HR, 1.32 (95% CI, 1.08-1.61).

[c] HR, 1.23 (95% CI, 0.90-1.70).

[d] HR, 1.37 (95% CI, 1.06-1.77).

estimated that 94% of the breast cancers during intervention in the WHI estrogen plus progestin trial were present when the trial began.[27] Thus, the early postintervention effects represent the influence of the rapid lowering of estrogen and progestin levels on preclinical cancers.

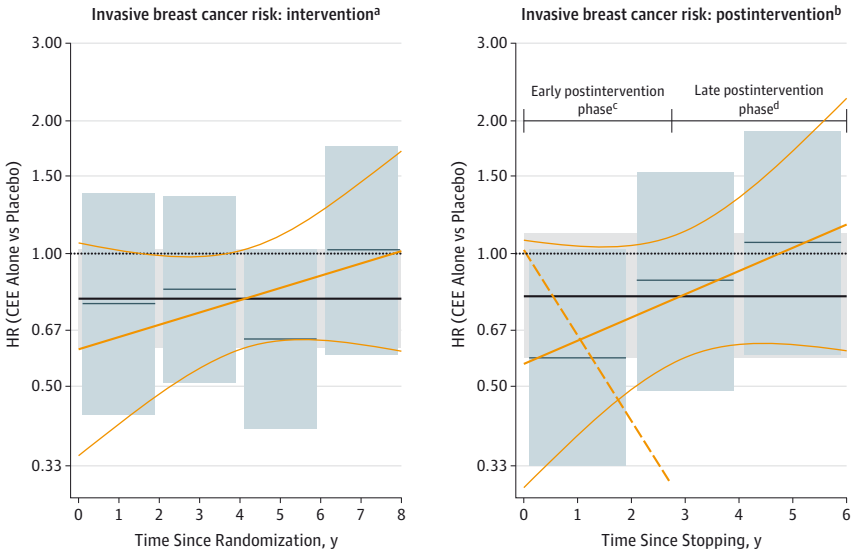
In the late postintervention phase, a relatively constant HR of higher than 1 for estrogen plus progestin influence on breast cancer risk persists. As a result, estrogen plus progestin increased breast cancer risk throughout cumulative follow-up.[15] The persistent elevation in risk years after discontinuation of hormone use could represent a rebound effect if the rapid lowering of hormone levels did not completely eliminate all preclinical cancers that could subsequently grow and emerge later. Such a finding would be congruent with the adjuvant breast cancer experience, where long-term (10 years compared with 5 years) tamoxifen use is needed to maximize cancer recurrence reduction.[28,29] The finding of a cumulative sustained increase in breast cancer after stopping combined hormone therapy, with no differential mammography use between randomization groups, indicates that breast cancer risk with estrogen plus progestin use is greater than previously described.[2]

While the cumulative mean HRs are similar in the intervention and the entire postintervention period, the intervention phase HR reflects an increase to a higher risk (HR >1.5) at the end of intervention and a subsequent decreasing year-to-year risk after intervention.

The breast cancer findings in the 2 hormone therapy trials differ. With estrogen alone, the HR for breast cancer risk remained lower than 1 throughout intervention. Because estrogen alone does not substantially interfere mammographic breast cancer detection,[30] this finding represents an actual lowering of the breast cancer incidence. In early postintervention phase, the HR was lower than at any time during the intervention, with subsequent late postintervention attenuation such that no longer-term lowering is seen beyond approximately 4.5 years. Nonetheless, use of estrogen alone reduced breast cancer risk throughout the cumulative follow-up.[15]

The initial lower breast cancer risk seen with the use of estrogen alone could reflect a treatment effect on preclinical breast cancers because estrogen receptor–positive cancers respond to sudden lowering of estrogen exposure with tumor reduction. This effect would not be seen in the placebo group because no change in their estrogen environment occurred after intervention. A favorable effect of estrogen alone on breast cancer incidence continuing for several years in late postintervention phase may reflect an influence of estrogen on pre-

Figure 2. Effects Over Time of Estrogen-Alone on the Incidence of Breast Cancer in the Women's Health Initiative Clinical Trial



Overall hazard ratio (HR) and 95% CI (black line and gray-shaded region, respectively) are shown for the effect of conjugated equine estrogens (CEE) alone on the risk of invasive breast cancer compared with placebo during the intervention period (left panel) and the overall postintervention phase (right panel). A reference line (dotted black) at unity corresponds to no differential risk between randomization groups. Hashmarks (top of right panel) indicate the early and late postintervention periods. Time-varying linear HR and 95% CI (orange lines) are also displayed for the intervention period (left panel) and overall postintervention period (right panel), as well as a time-varying linear HR for the early postintervention phase (dashed orange line). Biennial HRs and 95% CIs (solid blue lines and blue-shaded regions, respectively) are presented as an alternate description for time-varying risk. Significance tests of the time-varying linear HR for the primary (adherence adjusted) analysis were conducted and yielded $P = .29$ (.97) for linear trend during the intervention; $P = .14$ (.63) for linear trend during the early postintervention phase; $P = .10$ (.64) for difference in these linear trends; $P = .20$ (.27) for linear trend during the overall postintervention phase; and $P = .61$ (.34) for the difference between linear trends of intervention and overall postintervention phase. Time-varying linear HR is not shown for the late postintervention phase because significance test results were not suggestive of a trend: $P = .62$ (.46) for a linear trend during the late postintervention phase.

[a] HR, 0.79 (95% CI, 0.61-1.02).

[b] HR, 0.80 (95% CI, 0.58-1.11).

[c] HR, 0.55 (95% CI, 0.34-0.89).

[d] HR, 1.17 (95% CI, 0.73-1.87).

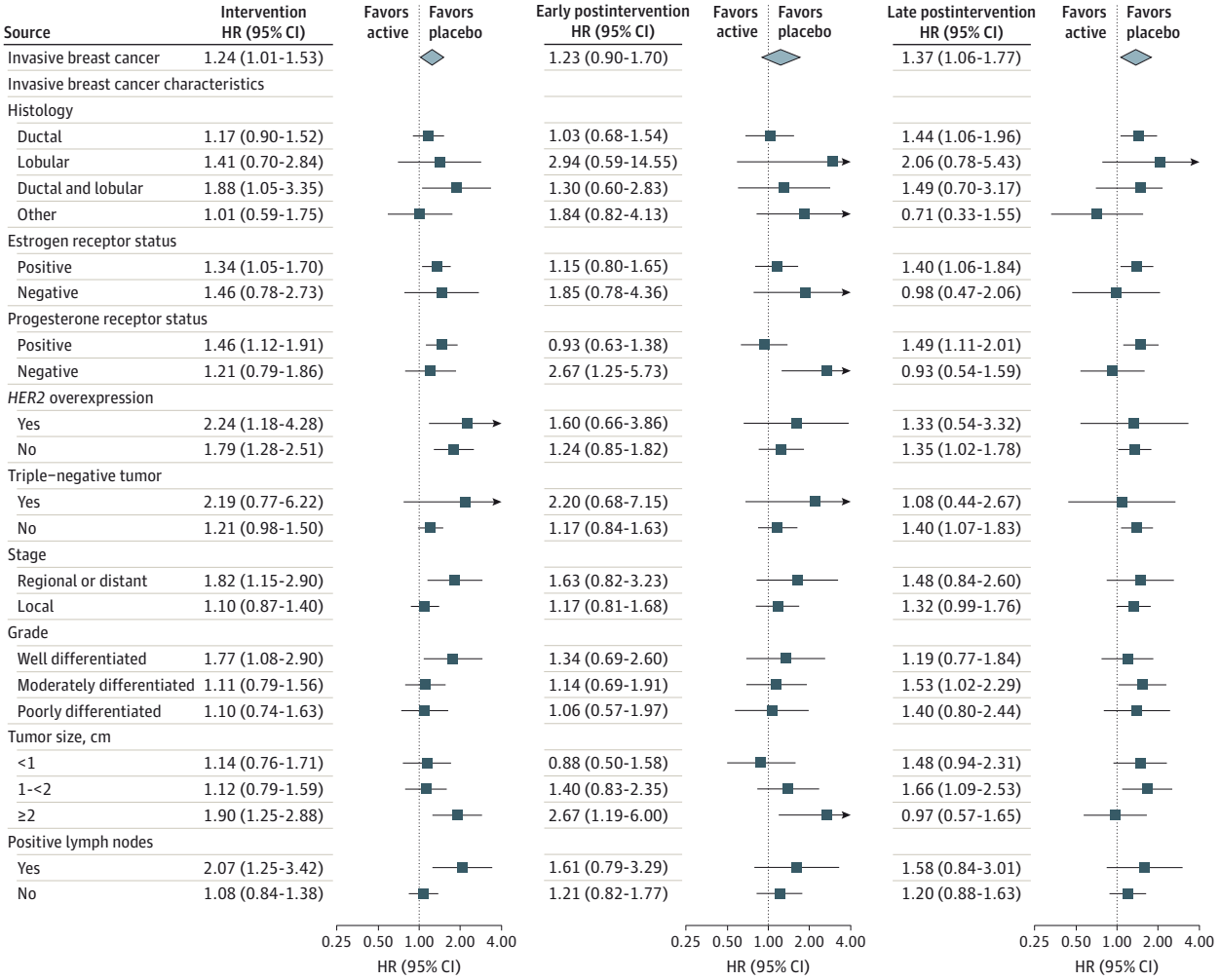
clinical breast cancers that would otherwise have become clinically manifest later. After that pool of exogenous estrogen-exposed tumors are depleted, no further estrogen benefit would be seen.

In both trials, exploratory analyses identified some changes in the characteristics of breast cancers diagnosed in the early postintervention compared with the late postintervention periods. Limited subgroup numbers preclude definitive conclusions. One possibility is that a sudden change in estrogen exposure mainly influences hormone receptor–positive, low-grade tumors, with a higher percentage of unfavorable cancers seen in both trials in the early postintervention phase (more large and receptor-negative tumors with estrogen plus progestin and more *HER2*-positive tumors and fewer moderately differentiated tumors with estrogen alone) compared with the late postintervention phase. Breast cancer characteristics did not differ between the intervention and overall postintervention periods.

Results from the Surveillance, Epidemiology, and End Results (SEER) program parallel our postintervention findings. In the early 1990s to 2002, year-to-year moderate increases in breast cancer incidence were seen reflecting increases in mammography screening, rates of obesity, and menopausal hormone therapy use.[31,32] In SEER, a substantial drop in breast cancer in 2003 was coincident with the decrease in menopausal hormone therapy in the United States[4,5] and elsewhere.[6,11] After 2003, the annual breast cancer incidence rates stabilized at a lower level than in 2002, with no further year-to-year reduction seen.[32] These findings are consistent with the WHI results, where the lack of a continued steep decline in breast cancer incidence rate after the early postintervention phase suggests depletion of incident preclinical breast cancers exposed to exogenous estrogen plus progestin. The subsequent sustained HRs, while greater than 1, were lower than the HR in the final intervention year (Figure 1).

Observational studies consistently report little or no increase in breast cancer risk in previous hormone therapy users, sometimes combining results from estrogen alone and estrogen plus progestin use.[16,33] However, in most older studies, mammography frequency was not determined, and, in that era, women receiving menopausal hormone therapy were substantially more likely to have screening mammography compared with women not receiving hormone therapy.[34] Given the recent emphasis on early breast cancer detection, at present, hormone therapy use has less influence on a woman's decision regarding screening mammography. In the WHI trials there was no differential mammography use by randomization group in either study.

Figure 3. Associations Between Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate and Breast Cancer Incidence

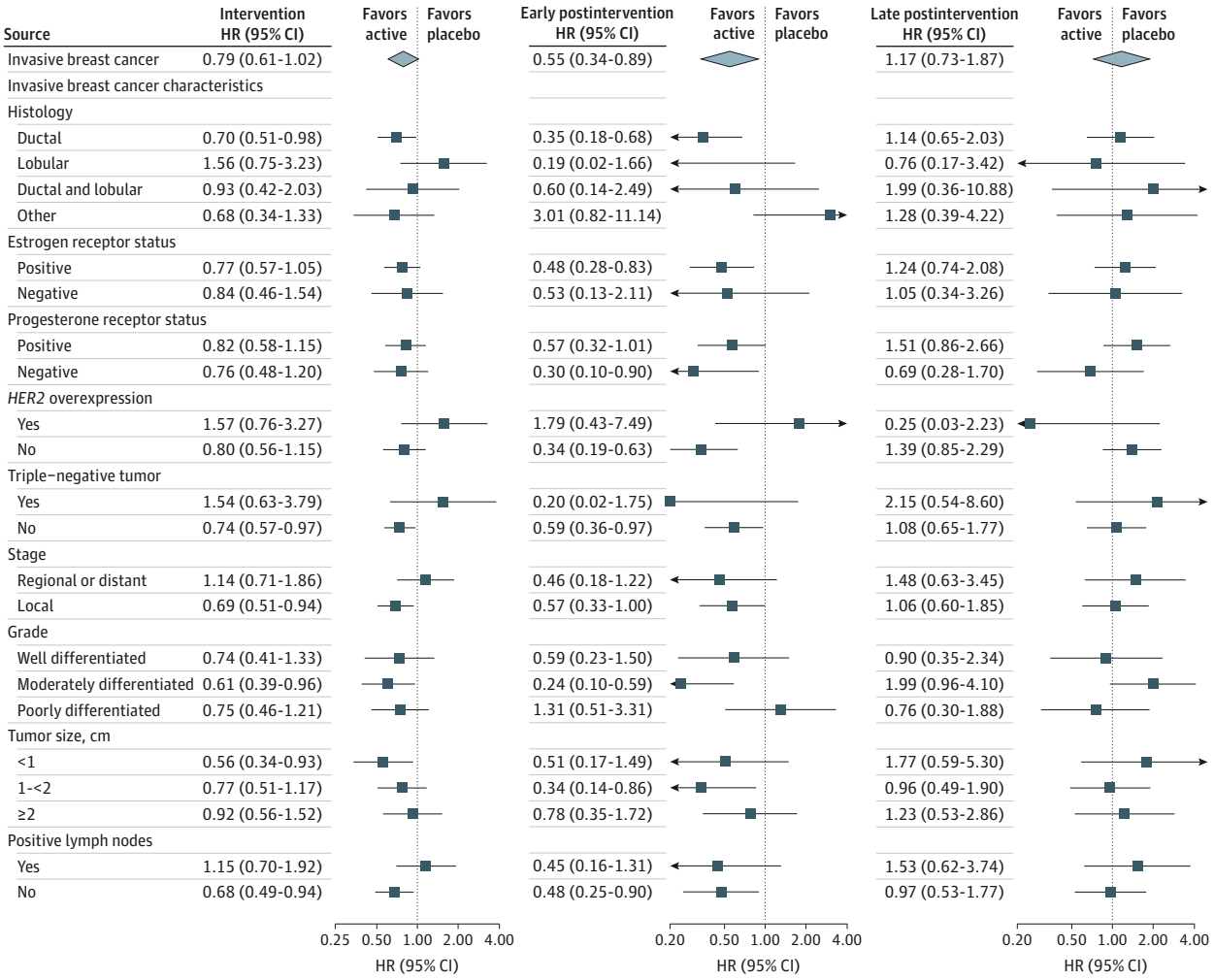


A test of interaction between the hazard ratio (HR) for early postintervention phase vs HR for late postintervention phase (ie, 1.23 vs 1.37) yields a *P* value of .61. A test of interaction between the HR for intervention vs a pooled esimate of the postintervention phase (ie, 1.24 vs 1.32) yields a *P* value of .69.

Most recently, Fournier and colleagues[17] addressed the issue of breast cancer risk after stopping menopausal hormone therapy in the large E3N cohort. Long-term (>5 years) users of estrogen plus progestin (other than progesterone or dydrogesterone) had a residual increase in breast cancer risk through approximately 10 years after intervention. This finding is similar to the WHI randomized trial result. However, in the E3N cohort, as in the preponderance of observational studies,[3,16] use of estrogen alone was associated with a statistically significantly higher breast cancer incidence compared with nonuse, which was sustained even after stopping therapy,[17] a finding opposite from the WHI randomized trial result.

The higher breast cancer risk seen in most observational studies with estrogen alone cannot be easily reconciled with the opposite findings in the WHI randomized trial. The statistically significant decrease in deaths from breast cancer with estrogen alone[19] and the lower risk sustained throughout the postintervention period supports the reliability of the finding. Time-from-menopause (gap time) to hormone therapy initiation could reconcile some of these differences because there is less evidence for estrogen use to influence on breast cancer risk when therapy is begun closer to menopause.[35,36] While women in the WHI trial began therapy further from menopause than in usual clinical practice, there was no statistically significant interaction between time-from-menopause and influence of estrogen alone on breast cancer.[19] A lower breast cancer risk with estrogen alone has received support from other randomized trials. In the Estrogen for the Prevention of Re-Infarction Trial (ESPRIT) in 1017 women, after 14 years follow-up there were fewer breast cancers in the unopposed estrogen (estradiol valerate, 2 mg/d) group (7 vs 15 [HR, 0.47; 95% CI, 0.19-1.15]).[37] Similarly, in a smaller randomized trial in Denmark, in 192 women there were fewer breast cancers in the estrogen alone (17β-estradiol, 2 mg/d) group (10 vs 17 [HR, 0.58; 95% CI, 0.27-1.29]).[38]

Figure 4. Associations Between Conjugated Equine Estrogen and Breast Cancer Incidence



A test of interaction between the HR for the early postintervention phase vs the HR for the late postintervention phase (ie, 0.55 vs 1.17) yields a *P* value of .03. A test of interaction between the HR for intervention vs a pooled estimate of the postintervention phase (ie, 0.79 vs 0.80) yields a *P* value of .94.

A biological rationale supports an anticancer effect of exogenous estrogen.[39] While mediating mechanisms are not completely understood, breast tumor cells adapt to grow in the prevailing estrogen environment and may not tolerate substantial change in exposure.[40] Furthermore, in preclinical models, after some period of estrogen deprivation, tumor gene expression profile changes, making tumors susceptible to estrogen-induced apoptosis.[41] Furthermore, in the WHI trials, strong breast cancer risk profiles associated with baseline serum estrogen levels were lost following estrogen plus progestin use but remained following use of estrogen alone, suggesting important differences between these preparations on ductal epithelial cell proliferation.[42]

Study strengths include the randomized, placebo-controlled study designs, the large sample sizes, mammogram clearance before entry and serial mammography, verification of invasive breast cancers, and a clear study drug stopping point in both trials. Study limitations include the need for re-consent for late postintervention follow-up and unblinded reporting of breast cancers after intervention. Only 1 hormone regimen was evaluated in each trial, either conjugated equine estrogen alone or with medroxyprogesterone acetate. Whether these findings apply to lower doses or other regimens is unknown.

Conclusions

With longer follow-up of the 2 WHI hormone therapy trials, a complex pattern of changing year-to-year influences on breast cancer was observed. The ongoing influences on breast cancer after stopping hormone therapy in the WHI trials require recalibration of breast cancer risk and benefit calculation for both regimens, with greater adverse influence for estrogen and progestin use and somewhat greater benefit for use of estrogen alone.

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