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Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women

Rowan T. Chlebowski, MD, PhD
Garnet L. Anderson, PhD
Margery Gass, MD
Dorothy S. Lane, MD
Aaron K. Aragaki, MS
Lewis H. Kuller, MD
JoAnn E. Manson, MD, DrPH
Marcia L. Stefanick, PhD
Judith Ockene, MD
Gloria E. Sarto, MD
Karen C. Johnson, MD, MPH
Jean Wactawski-Wende, PhD
Peter M. Ravdin, MD, PhD
Robert Schenken, MD
Susan L. Hendrix, DO
Aleksandar Rajkovic, MD, PhD
Thomas E. Rohan, PhD
Shagufta Yasmeen, MD
Ross L. Prentice, PhD
for the WHI Investigators

Context In the Women's Health Initiative randomized, placebo-controlled trial of estrogen plus progestin, after a mean intervention time of 5.6 (SD, 1.3) years (range, 3.7-8.6 years) and a mean follow-up of 7.9 (SD, 1.4) years, breast cancer incidence was increased among women who received combined hormone therapy. Breast cancer mortality among participants in the trial has not been previously reported.

Objective To determine the effects of therapy with estrogen plus progestin on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (SD, 2.7) years, through August 14, 2009.

Design, Setting, and Participants A total of 16 608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo pill. After the original trial completion date (March 31, 2005), reconsent was required for continued follow-up for breast cancer incidence and was obtained from 12 788 (83%) of the surviving participants.

Main Outcome Measures Invasive breast cancer incidence and breast cancer mortality.

Results In intention-to-treat analyses including all randomized participants and censoring those not consenting to additional follow-up on March 31, 2005, estrogen plus progestin was associated with more invasive breast cancers compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year]; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P=.004$). Breast cancers in the estrogen-plus-progestin group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] vs 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; $P=.03$). There were more deaths directly attributed to breast cancer (25 deaths [0.03% per year] vs 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00-4.04; $P=.049$) as well as more deaths from all causes occurring after a breast cancer diagnosis (51 deaths [0.05% per year] vs 31 deaths [0.03% per year]; HR, 1.57; 95% CI, 1.01-2.48; $P=.045$) among women who received estrogen plus progestin compared with women in the placebo group.

Conclusions Estrogen plus progestin was associated with greater breast cancer incidence, and the cancers are more commonly node-positive. Breast cancer mortality also appears to be increased with combined use of estrogen plus progestin.

Trial Registration clinicaltrials.gov Identifier: NCT00000611

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THE WOMEN'S HEALTH INITIATIVE (WHI) randomized trial evaluating estrogen plus progestin compared with placebo in postmenopausal women was stopped after a mean of 5.6 (SD, 1.3) years when health risks exceeded benefits for combined hormone therapy,[1] including an increased risk of invasive breast cancers[1,2] and delayed breast cancer diagnoses resulting in more advanced-stage cancers.[2,3] Assessment of breast cancer outcomes after a mean

For editorial comment see p 1719.

CME available online at www.jamaarchivescme.com and questions on p 1730.

Author Affiliations: Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California (Dr Chlebowski); Fred Hutchinson Cancer Research Center, Seattle, Washington (Drs Anderson and Prentice and Mr Aragaki); University of Cincinnati, Cincinnati, Ohio (Dr Gass); State University of New York at Stony Brook (Dr Lane); University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Kuller); Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Dr Manson); Stanford Prevention Research Center, Stanford, California (Dr Stefanick); University of Massachusetts/Fallon Clinic, Worcester (Dr Ockene); University of Wisconsin, Madison (Dr Sarto); University of Tennessee Health Science Center, Memphis (Dr Johnson); University at Buffalo, Buffalo, New York (Dr Wactawski-Wende); Cancer Therapy and Research Center (Dr Ravdin) and University of Texas Health Science Center (Dr Schenken), San Antonio; Wayne State School of Medicine and Hurtzel Hosptial, Detroit, Michigan (Dr Hendrix); Baylor College of Medicine, Houston, Texas (Dr Rajkovic); Albert Einstein College of Medicine, New York, New York (Dr Rohan); and University of California at Davis, Sacramento (Dr Yasmeen).
A list of the WHI Investigators appears at the end of this article.
Corresponding Author: Rowan T. Chlebowski, MD, PhD, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W Carson St, Torrance, CA 90502 (rchlebowski@gmail.com).

follow-up of 7.9 (SD, 1.4) years revealed that the increased risk of breast cancer associated with combined hormone therapy declined soon after discontinuation of hormones.[4] Nonetheless, questions of clinical relevance remain, including the cumulative, long-term effect of estrogen plus progestin on breast cancer incidence and whether breast cancer mortality is increased by combined hormone therapy use.

Most[5-7] but not all[8,9] observational studies have suggested that breast cancers associated with combined postmenopausal hormone therapy have favorable characteristics,[5-7] less advanced stage,[5,10] and less mortality risk.[7,10,11] Because the influence of estrogen plus progestin on breast cancer mortality has not been addressed in a randomized trial setting, we report updated information on breast cancer incidence and, for the first time, information on breast cancer mortality related to combined hormone therapy use in the WHI trial.

METHODS

The WHI trial of estrogen plus progestin has been previously described[1,12,13] and used a study design approved by the institutional review boards at the participating clinical centers.[12,14] Briefly, women were eligible if they were aged 50 to 79 years, were postmenopausal, and provided written informed consent. Excluded were women with prior hysterectomy, prior breast cancer, or conditions precluding 3-year survival. Women using postmenopausal hormones were eligible after a 3-month washout period. Baseline mammograms and clinical breast examinations with results not suggestive of cancer were required. Information on demographic characteristics, medical history, lifestyle, and breast cancer risk factors were collected with standardized self-report instruments. Medication use was assessed by interviewer-administered questionnaire. Time since menopause was defined as the interval from onset of menopause to first hormone therapy or placebo use.[15] Adherence to study medication was assessed by dispensing history and serial pill counts by weighing returned pills.

Participants were randomized to receive conjugated equine estrogens, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d, in a single tablet (Prempro; Wyeth Ayerst, Collegeville, Pennsylvania) or an identical-appearing placebo pill. Randomization by permuted-block algorithm, stratified by clinical center and age group,[14] was determined at the WHI Clinical Coordinating Center and implemented at local clinical centers using a bar-code dispensing procedure for staff and participant blinding. Participants were contacted at 6-month intervals to collect clinical outcome information and attended annual clinic visits. Yearly mammograms and clinical breast examinations were required during the intervention phase, and study drugs were withheld until completion and clearance of abnormal findings. After the active intervention ended, annual mammograms and breast examinations were encouraged and information on their frequency was collected annually.

The total study population included 16 608 women with initial randomization beginning on November 15, 1993. The study intervention phase ended on July 7, 2002, after net harm for combined hormone therapy use was identified[1] and participants were instructed to stop taking their assigned study medication. In the postintervention phase beginning on July 8, 2002, clinical visits and follow-up continued per protocol through March 31, 2005, the original trial completion date. In the study extension phase beginning April 1, 2005, through August 14, 2009, subsequent follow-up for additional breast cancer incidence results required reconsent (which was obtained from 12 788 [83%] of 15 408 surviving participants).

Breast cancers were verified by centrally trained, locally based physician adjudicators after medical record and pathology report review.[16] Final adjudication and coding of histology, hormone receptor status (positive or negative), and *ERBB2 (HER2)* status (overexpression or not) based on pathology report review was performed at the WHI Clinical Coordinating Center using the Surveillance, Epidemiology, and End Results coding system.[17] Attribution of cause of death was based on medical record review by physician adjudicators, blinded to randomization allocation at the local clinical centers, with central final adjudication.[16] The National Death Index was cross-checked with all clinical trial participants at 2- to 3-year intervals.

Prior reports of breast cancer cases include 349 cases identified during the intervention phase with mean follow-up of 5.6 (SD, 1.3) years (median, 5.6 years; range, 4.6-8.6 years)[2] and 488 cases identified through the original trial completion date with mean follow-up of 7.9 (SD, 1.4) years.[4] The current report, based on a preplanned analysis of breast cancer incidence and associated mortality, includes 678 cases identified through August 14, 2009, with a mean follow-up of 11.0 (SD, 2.7) years.

For the WHI estrogen and progestin clinical trial, a target sample size of 15 125 participants was calculated primarily based on coronary heart disease considerations. As a result, power to detect a 15% increase in breast cancer was 55% after 9 years and 87% after 14 years of follow-up.[12]

Comparisons of breast cancer characteristics were based on Fisher exact tests and *t* tests. Age at menopause was defined as previously described,[15] largely by age at last menstrual bleeding, bilateral oophorectomy date, or date postmenopausal hormone therapy was initiated.

Results for invasive breast cancer incidence and deaths from breast cancer were assessed with time-to-event methods based on the intention-to-treat principle. Analyses included all 16 608 randomized participants. Annualized percentages were calculated by dividing the total number of events by total

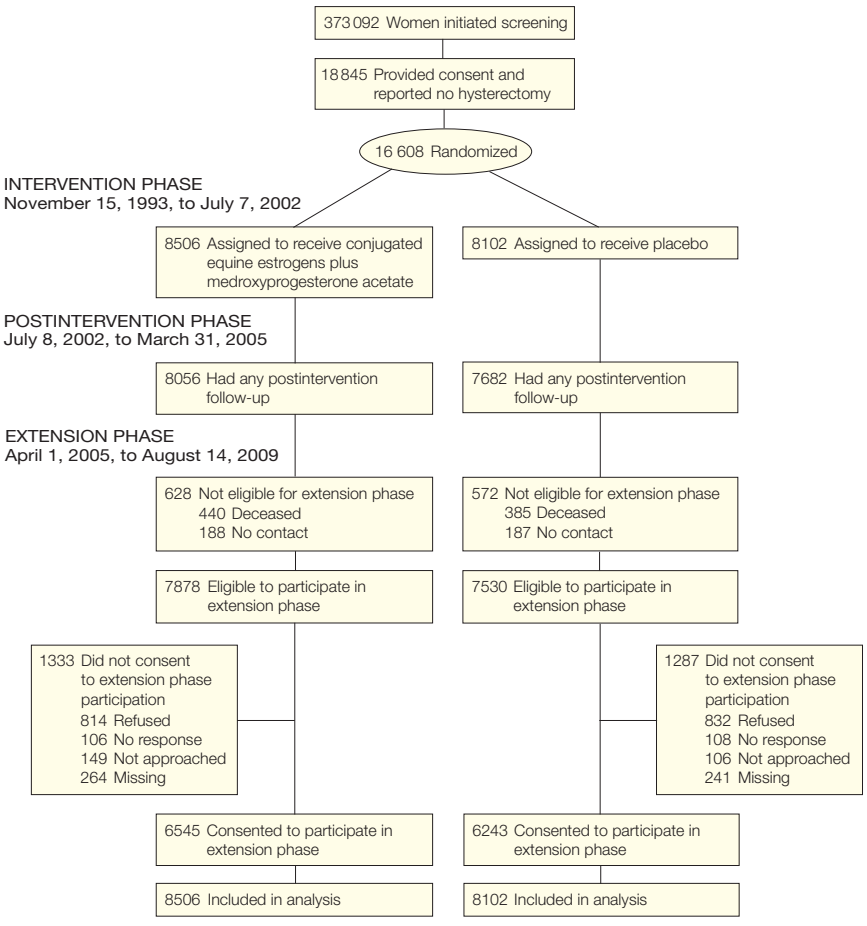
follow-up time in years. Hazard ratios (HRs) were estimated from Cox regression models stratified by baseline 5-year age groups and randomization status in the WHI dietary modification trial. No distinction was made between the intervention phase and the postintervention phase. In both phases, the breast cancer risk for use of estrogen plus progestin was greater than 1 and was approximately equal. The summary (Cox model) HRs represent the mean over the entire study period. In addition, the null hypothesis tests for breast cancer incidence and mortality do not assume proportionality. Event times were defined relative to the date of randomization, with censoring defined by end of follow-up, loss to follow-up, or death from causes other than breast cancer. Kaplan-Meier curves describe cumulative breast cancer hazard ratios over time. Competing risk curves were also computed and were nearly identical to the Kaplan-Meier estimates.

For breast cancer incidence analyses, women who did not consent to active follow-up after March 31, 2005, were censored as of that date. The original consent permitted continued follow-up for vital status. Analyses for deaths due to breast cancer among women who did not reconsent were censored on December 31, 2005, early in the reconsent period, because mortality data in this group may be incomplete at more recent times. Additional mortality analyses censored women not reconsenting on March 31, 2005.

To examine the potential effect of censoring women who did not reconsent to follow-up after March 31, 2005, several secondary analyses were performed, including comparison of reconsent rates by baseline characteristics and randomization assignment and adjusted HR analyses using both inverse probability weighting and multiple imputation. The inverse probability weighting analyses developed a logistic regression model for reconsenting using baseline factors and randomization assignment. For the multiple imputation method, invasive breast cancer events or censoring times were imputed for the 2620 eligible participants who did not reconsent (1333 in the intervention and 1287 in the placebo groups) beginning on March 31, 2005. Cox regression models were then fit for each of 25 imputed data sets and the resulting regression parameter estimates were averaged. Adherence sensitivity analyses for breast cancer mortality were conducted by censoring follow-up 6 months after a participant became nonadherent (defined as using <80% of study pills or starting nonprotocol hormone therapy). Six subgroups of clinical interest were identified post hoc and examined for breast cancer HR variation. Less than 1 subgroup would be expected to be positive by chance alone.

All analyses were conducted using SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina). All statistical tests were 2-sided and $P<.05$ was considered statistically significant.

Figure 1. Flow of Study Participants



The intervention phase ran from November 15, 1993, to July 7, 2002. The postintervention phase began on July 8, 2002, the day after participants were instructed to stop study medication use (conjugated equine estrogens plus medroxyprogesterone acetate or placebo) and continued through the original trial completion date (March 31, 2005). The extension phase began on April 1, 2005, and includes follow-up for participants who reconsented (83% of those eligible) through August 14, 2009.

RESULTS

The flow of participants through the study is outlined in FIGURE 1. Baseline characteristics for the initially randomized 16 608 participants have been previously published (eTable 1; available at http://www.jama.com).[1,2] Participant characteristics in the 2 ran-

domization groups were closely comparable in both the initial and reconsenting populations (eTable 2 and eTable 3). Those reconsenting were slightly younger and more likely to be white compared with those not reconsenting. During the active intervention, study drugs were stopped at some time by 42% in the combined hormone group and 38% in the placebo group.[1]

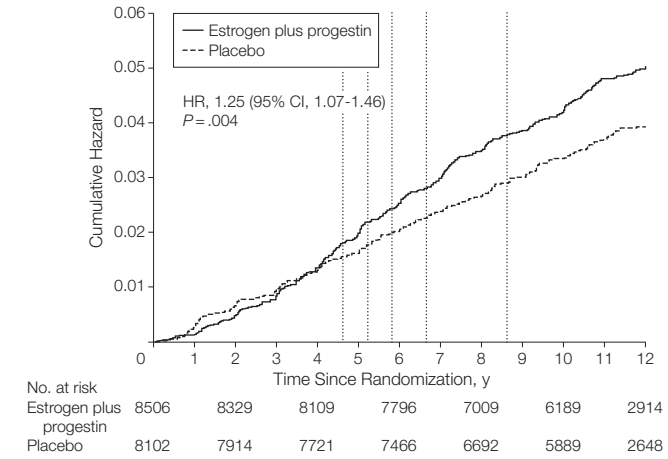
Mammography frequency was comparable in the 2 randomization groups during the original trial period through March 31, 2005 (annualized percentage, 80% for hormone vs 80% for placebo). In the reconsenting population of 15 408 women in the extension phase, the percentages of women with 1 or more mammograms were also comparable in the 2 groups (86% for hormone vs 86% placebo).

Mean follow-up in the intervention plus postintervention periods was 11.0 (SD, 2.7) years, with a range of 0.1 to 15.3 years, representing a total of 170 166 person-years of follow-up.

In intention-to-treat analysis, estrogen plus progestin compared with placebo increased the incidence of invasive breast cancer (385 cases [0.42% per year] vs 293 cases [0.34% per year], respectively; HR, 1.25; 95% confidence interval [CI], 1.07-1.46; $P = .004$). FIGURE 2 also shows quintiles of duration of study intervention based on time of participant entry into study and cessation of study intervention.

A significantly larger fraction of breast cancers presented with positive lymph nodes in the combined hormone therapy group compared with the placebo group (81 [23.7%] vs 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; $P = .03$). There was no evidence of a differential effect of combined hormone therapy on receptor-positive vs receptor-negative tumors. Somewhat more tumors overexpressed *ERBB2 (HER2)* and were triple-negative in the hormone therapy group compared with the placebo group (TABLE). However, because determination of *ERBB2 (HER2)* status was not routinely obtained in community medical practices until 1998, it was not un-

Figure 2. Incidence of Invasive Breast Cancer in the WHI Clinical Trial



Intention-to-treat Kaplan-Meier cumulative hazard curves for incidence of invasive breast cancer by study group and time since randomization. The hazard ratio (HR), 95% confidence interval (CI), and *P* value are from Cox regression models, stratified by 5-year age intervals and randomization assignment in the Women's Health Initiative (WHI) dietary modification trial. All women stopped the intervention by 8.6 years. Quintiles of duration of follow-up are indicated by the dotted lines.

Table. Characteristics of Invasive Breast Cancers by Study Group

Characteristics	No. (%) of Invasive Breast Cancers[a] Estrogen Plus Progestin (n = 385)	Placebo (n = 293)	*P* Value[b]
Tumor size			
No tumor found/no primary mass	1 (0.3)	2 (0.7)	
Microscopic focus or foci, cm	9 (2.5)	15 (5.5)	
≤0.5	38 (10.5)	27 (9.9)	.34
>0.5 to 1	92 (25.3)	84 (30.7)	
>1 to 2	146 (40.2)	98 (35.8)	
>2	77 (21.2)	48 (17.5)	
Mean (SD) size, cm	1.7 (1.3)	1.5 (1.1)	.11
Lymph nodes examined			
No	39 (10.3)	28 (9.6)	.80
Yes[c]	341 (89.7)	263 (90.4)	
No. of positive lymph nodes			
0	258 (76.3)	218 (83.8)	.06
1-3	60 (17.8)	34 (13.1)	
>3	20 (5.9)	8 (3.1)	
Positive lymph nodes			
No	258 (76.1)	218 (83.5)	.03
Yes[d]	81 (23.9)	43 (16.5)	
SEER stage			
Localized	288 (75.2)	238 (81.2)	.05
Regional	86 (22.5)	46 (15.7)	
Distant	5 (1.3)	7 (2.4)	
Regional/distant			
No	288 (76.0)	238 (81.8)	.07
Yes	91 (24.0)	53 (18.2)	
Unknown	4 (1.0)	2 (0.7)	
Histology			
Ductal	238 (62.1)	195 (66.6)	.41
Lobular	36 (9.4)	20 (6.8)	
Ductal and lobular	57 (14.9)	35 (11.9)	
Tubular	13 (3.4)	9 (3.1)	
Other	39 (10.2)	34 (11.6)	

(continued)

Table. Characteristics of Invasive Breast Cancers by Study Group (continued)

Characteristics	No. (%) of Invasive Breast Cancers[a]		*P* Value[b]
	Estrogen Plus Progestin (n = 385)	Placebo (n = 293)	
Grade			
Well differentiated	100 (26.1)	67 (22.9)	.51
Moderately differentiated	140 (36.6)	116 (39.6)	
Poorly differentiated/anaplastic	92 (24.0)	77 (26.3)	
Unknown	51 (13.3)	33 (11.3)	
Estrogen receptor status			
Positive	308 (80.0)	230 (78.5)	.81
Negative	48 (12.5)	33 (11.3)	
Borderline	0 (0.0)	1 (0.3)	
Unknown/not evaluated/missing data	29 (7.5)	29 (9.9)	
Progesterone receptor status			
Positive	262 (68.1)	194 (66.2)	.92
Negative	86 (22.3)	62 (21.2)	
Borderline	5 (1.3)	3 (1.0)	
Unknown/not evaluated/missing data	32 (8.3)	34 (11.6)	
ERBB2 (HER2) overexpression			
Yes	54 (14.0)	26 (8.9)	.17
No	233 (60.5)	161 (54.9)	
Borderline	3 (0.8)	1 (0.3)	
Unknown/not evaluated/missing data	95 (24.7)	105 (35.8)	
Triple-negative tumor status			
Estrogen receptor/progesterone receptor/*ERBB2 (HER2)* triple-negative	26 (6.8)	14 (4.8)	.61
Other, including borderline	259 (67.3)	173 (59.0)	
Unknown/missing all or some data	100 (26.0)	106 (36.2)	

Abbreviation: SEER, Surveillance, Epidemiology, and End Results program.
[a] Data are presented as No. (%) of invasive breast cancers unless otherwise indicated.
[b] *P* values are based on Fisher exact test of association.
[c] Ten instances (5 estrogen plus progestin and 5 placebo) occurred in which lymph nodes were examined but number examined was not specified.
[d] Two instances (1 estrogen plus progestin and 1 placebo) occurred in which positive nodes were determined but number of positive nodes were not specified.

common for information on *ERBB2 (HER2)* status to be missing.

In subgroup analyses, no significant interactions were observed among combined hormone therapy use and breast cancer incidence with age, body mass index, and Gail risk score (FIGURE 3). For women entering the study with no prior use of estrogen plus progestin, the HR for breast cancer incidence was 1.16 (95% CI, 0.98-1.37) compared with an HR of 1.85 (95% CI, 1.25-2.80) for women with prior combined hormone therapy use ($P = .03$ for interaction). The HR for breast cancer incidence among women with 1 year or less of prior combined hormone therapy use was 2.16 (95% CI, 1.15-4.24) (Figure 3). Women who first used hormone therapy closer to menopause (<5 years) were at somewhat greater risk of developing breast cancer in the combined hormone therapy group, but the interaction term was not significant ($P = .08$).

More women died of breast cancer in the combined hormone therapy group compared with the placebo group (25 deaths [0.03% per year] vs 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00-4.04; $P = .049$) (FIGURE 4A), representing 2.6 vs 1.3 deaths per 10 000 women per year, respectively. Censoring of follow-up time on March 31, 2005, for women not reconsenting did not alter the results for death due to breast cancer (HR, 1.96; 95% CI, 1.01-4.05; $P = .048$). Consideration of all-cause mortality after breast cancer diagnosis provided similar results; among women in the combined hormone therapy group, there were 51 deaths [0.05% per year] compared with 31 deaths [0.03% per year] among women in the placebo group; HR, 1.57; 95% CI, 1.01-2.48; $P = .045$) (Figure 4B), representing 5.3 vs 3.4 deaths per 10 000 women per year, respectively.

Sensitivity analyses also suggested an adverse effect of combined hormone therapy compared with placebo on breast cancer mortality when follow-up time for each woman was censored at nonadherence (14 vs 5 deaths, respectively; HR, 2.96; 95% CI, 1.00-8.77; $P = .053$). Inverse probability weighting and multiple imputation analyses to address potential imbalance associated with reconsent supported the primary analyses, suggesting an increase in deaths due to breast cancer with estrogen plus progestin (inverse probability weighting summary HR, 2.22; 95% CI, 1.07-4.59; multiple imputation summary HR, 2.12; 95% CI, 1.02-4.40).

COMMENT

In the WHI randomized, placebo-controlled trial, conjugated equine estrogen plus medroxyprogesterone acetate increased invasive breast cancer incidence, and the cancers were more commonly node-positive. There were more deaths attributed to breast cancer (2.6 vs 1.3 per 10 000 women per year) and more deaths due to all causes following a diagnosis of breast cancer (5.3 vs 3.4 per 10 000 women per year) in the combined hormone therapy group vs the placebo group.

With some exceptions,[8,9] the preponderance of observational studies have associated combined hormone therapy use with an increase in breast cancers that have favorable characteristics,[7] lower stage,[5,10] and longer survival compared with breast cancers diagnosed in nonusers of hormone therapy.[7,10] However, in the WHI randomized trial, combined hormone therapy increased breast cancer risk and interfered with breast cancer detection, leading to cancers being diagnosed at more advanced stages.[2,3] Now, with longer follow-up results available, there remains a cumulative, statistically significant increase in breast cancers in the combined hormone

therapy group, and the cancers more commonly had lymph node involvement. The observed adverse influence on breast cancer mortality of combined hormone therapy can reasonably be explained by the influence on breast cancer incidence and stage.

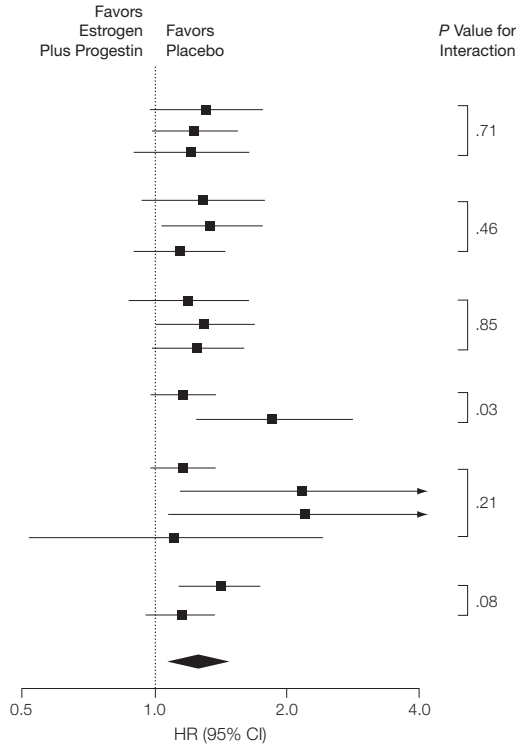
The discrepancy between the current randomized clinical trial findings and observational studies with respect to breast cancer mortality likely are related to potential confounding in observational analyses. Observational studies that begin analyses at breast cancer diagnosis and adjust for stage[7,18] potentially adjust away unfavorable consequences of estrogen-plus-progestin use. Postmenopausal hormone therapy users have mammograms at more regular intervals than nonusers,[19,20] likely because of breast cancer concerns. Studies that are unable to control for mammography can be confounded by differences between screening-detected and non–screening-detected breast cancers. Screening more commonly identifies slow-growing, favorable-grade, hormone receptor–positive breast cancers, and diagnosis is made at an earlier stage.[21-23] Our findings are consistent with the observational Million Women Study, in which all women had mammograms and breast cancer mortality analyses began at cohort entry rather than at the time of breast cancer diagnosis. In the Million Women Study, combined hormone therapy use was associated with higher breast cancer mortality (HR, 1.22; 95% CI, 1.00-1.48; $P=.05$).[10]

Following the initial report of results from the WHI trial,[1] a substantial decrease in breast cancer incidence occurred in the United States, which was attributed[24,25] to the marked decrease in postmenopausal hormone therapy use that occurred after publication of the trial results.[26] The adverse influence of estrogen plus progestin on breast cancer mortality suggests that a future reduction in breast cancer mortality in the United States may be anticipated as well.

Accurate determination of cause of death after a breast cancer diagnosis is problematic given the potential interaction between common comorbidities and cancer treatments.[27] Thus, the actual mortality risk related to breast cancer likely lies somewhere between the medical record attributed risk and consideration of all mortality following breast cancer diagnoses.

Figure 3. Invasive Breast Cancer Incidence by Baseline Characteristics and Study Group

Characteristics	Estrogen Plus Progestin, No. (Annualized %)	Placebo, No. (Annualized %)	HR (95% CI)	*P* Value for Interaction
Age, y				
50-59	111 (0.35)	79 (0.26)	1.31 (0.98-1.76)	.71
60-69	178 (0.43)	137 (0.35)	1.23 (0.99-1.54)	
70-79	96 (0.53)	77 (0.44)	1.21 (0.90-1.64)	
Body mass index				
Normal (<25)	91 (0.33)	69 (0.26)	1.29 (0.94-1.77)	.46
Overweight (25 to <30)	137 (0.43)	97 (0.32)	1.34 (1.04-1.75)	
Obese (≥30)	156 (0.50)	125 (0.44)	1.14 (0.90-1.44)	
Gail risk score				
<1.25	90 (0.29)	75 (0.26)	1.19 (0.88-1.63)	.85
1.25 to <1.75	134 (0.44)	97 (0.33)	1.29 (1.00-1.69)	
≥1.75	161 (0.53)	121 (0.43)	1.25 (0.99-1.59)	
Estrogen plus progestin use				
No	312 (0.42)	257 (0.36)	1.16 (0.98-1.37)	.03
Yes (past/current)	73 (0.44)	36 (0.23)	1.85 (1.25-2.80)	
Prior estrogen plus progestin duration, y				
None	312 (0.42)	257 (0.36)	1.16 (0.98-1.37)	.21
≤1	29 (0.50)	14 (0.25)	2.16 (1.15-4.24)	
>1 to <5	27 (0.40)	10 (0.16)	2.19 (1.08-4.80)	
≥5	17 (0.41)	12 (0.34)	1.10 (0.52-2.40)	
Time since menopause, y				
<5	130 (0.42)	293 (0.34)[a]	1.41 (1.14-1.74)	.08
≥5	209 (0.41)	293 (0.34)[a]	1.15 (0.96-1.37)	
Main effect	385 (0.42)	293 (0.34)	1.25 (1.07-1.46)	



Hazard ratios (HRs; estrogen plus progestin vs placebo) with 95% confidence intervals (CIs) are from Cox regression models stratified by age and randomization assignment in the dietary modification trial. For subgroup analyses, HRs are allowed to vary by subgroup, and Cox regression models are stratified by age, randomization assignment in the Women's Health Initiative dietary modification trial, and subgroup. *P* values are from Cox regression models for a 1-degree-of-freedom test for trend. Current use refers to those reporting estrogen plus progestin use at time of initial evaluation. A 3-month washout was required before study entry. The time-since-menopause variable was defined as the interval from the onset of menopause until first menopausal hormone therapy use or first study medication use (estrogen plus progestin or placebo).

[a] Events in both subsets of the estrogen plus progestin group are compared with all events in the placebo group.

The relative influence of combined hormone therapy on both the breast cancer mortality reported herein and lung cancer mortality[28] was greater than its influence on cancer incidence. Reproductive hormones,[29,30] especially progestin,[31,32] are potent stimulators of angiogenesis. Because increased angiogenesis increases both lung[33] and breast cancer metastases,[34] these findings suggest that angiogenesis stimulation by combined hormone therapy may facilitate growth and metastatic spread of already-established cancers. Unless the mortality risks of lung cancer and breast cancer can be mitigated, use of combined hormone therapy—other than short-term therapy in women with climacteric symptoms not ameliorated by other therapies—seems unwarranted.

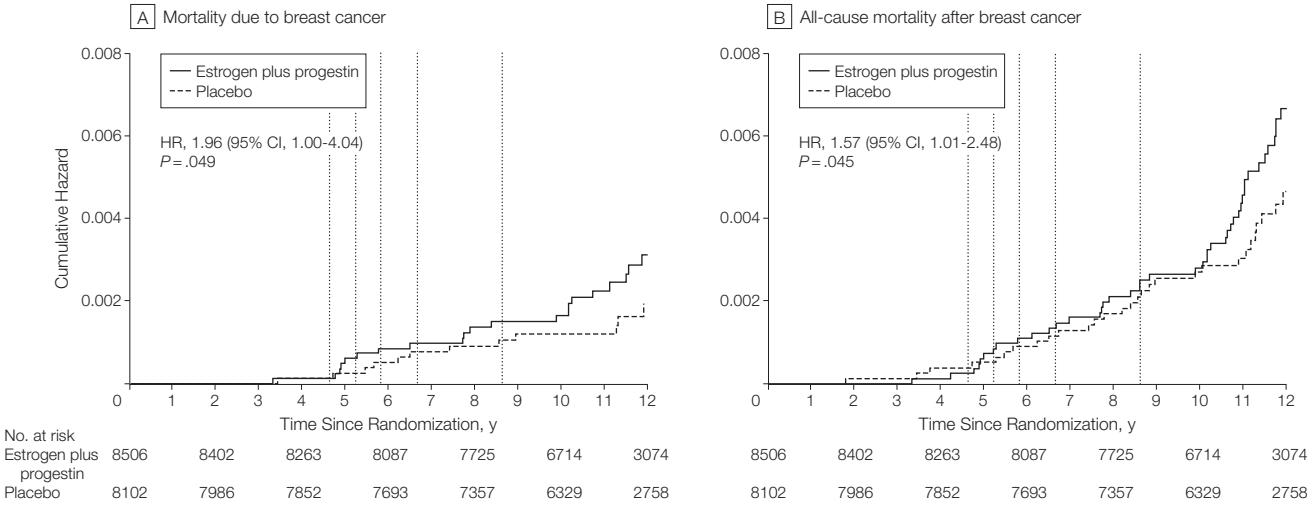
The WHI trial results evaluating estrogen plus progestin have been generally accepted by health regulatory agencies. However, some clinicians continue to question the applicability of the results to current clinical practice,[35,36] emphasizing potential differences in coronary heart disease risk when hormone therapy is begun shortly after menopause.[15,37] However, both prior analyses[38] and the current analysis reflecting longer follow-up of the study participants suggest a somewhat greater adverse hormonal effect on breast cancer incidence among women randomized closer to menopause, with similar findings seen in the French E3N observational cohort.[39] Additionally, current analyses support our prior suggestion that durations of use only slightly longer than those in the trial are associated with increases in breast cancer risk.[40] Given these findings and the effect of combined hormone therapy to delay breast cancer diagnosis,[2,3] from a breast cancer perspective, a safe interval for combined hormone therapy use cannot be reliably defined.

Strengths of this study include the randomized, double-blind design, a large and ethnically diverse study population, serial assessment of mammography and clinical breast examinations, central adjudication of breast cancers, and the long follow-up period. The lack of breast cancer therapy information and the modest number of deaths in women diagnosed as having breast cancer are limitations, as is the difficulty in attributing cause of death in breast cancer patients. For the breast cancer mortality analyses, the wide CIs with lower limits close to 1.0 imply some caution in interpretation. The relatively modest duration of study estrogen-plus-progestin use was limited by the net adverse effect of combined hormone therapy on clinical outcomes.

Some might consider a study limitation to be the necessity of reconsent for follow-up of disease incidence beyond the original trial completion date. The fact that 17% of women did not reconsent may have influenced estimation of the effect of combined hormone therapy on breast cancer. However, in both the original randomized group and in the reconsenting group, baseline characteristics were comparable in the hormone therapy and placebo groups. In addition, inverse probability weighting and multiple imputation analyses to address this concern resulted in similar findings regarding use of estrogen plus progestin and deaths due to breast cancer.

In conclusion, use of estrogen plus progestin increases the incidence of breast cancer, and the cancers are more

Figure 4. Deaths After Breast Cancer in the WHI Clinical Trial



Kaplan-Meier cumulative hazard curves for (A) mortality directly attributed to breast cancer, by study group and time since randomization and (B) mortality due to all causes following a breast cancer diagnosis, by study group and time in the trial. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values are from Cox regression models, stratified by 5-year age intervals and randomization assignment in the Women's Health Initiative (WHI) dietary modification trial. All women stopped the intervention by 8.6 years.

commonly node-positive. Mortality data analyses suggest that breast cancer mortality may also be increased.

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Study concept and design: Chlebowski, Manson, Wactawski-Wende, Hendrix, Prentice.
Acquisition of data: Chlebowski, Gass, Lane, Kuller, Manson, Stefanick, Ockene, Sarto, Johnson, Wactawski-Wende, Hendrix, Yasmeen.
Analysis and interpretation of data: Chlebowski, Anderson, Aragaki, Manson, Johnson, Wactawski-Wende, Ravdin, Schenken, Hendrix, Rajkovic, Rohan, Prentice.
Drafting of the manuscript: Chlebowski, Aragaki, Prentice.
Critical revision of the manuscript for important intellectual content: Chlebowski, Anderson, Gass, Lane, Aragaki, Kuller, Manson, Stefanick, Ockene, Sarto, Johnson, Wactawski-Wende, Ravdin, Schenken, Hendrix, Rajkovic, Rohan, Prentice.
Statistical analysis: Aragaki, Yasmeen, Prentice.
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WHI Investigators: *Program Office:* National Heart, Lung, and Blood Institute, Bethesda, MD (Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Joan McGowan, Nancy Geller, Leslie Ford). *Clinical Coordinating Center:* Fred Hutchinson Cancer Research Center, Seattle, WA (Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth Patterson, Anne McTiernan, Barbara Cochrane, Julie Hunt, Lesley Tinker, Charles Kooperberg, Martin McIntosh, C. Y. Wang, Chu Chen, Deborah Bowen, Alan Kristal, Janet Stanford, Nicole Urban, Noel Weiss, Emily White); Medical Research Laboratories, Highland Heights, KY (Evan Stein, Peter Laskarzewski); San Francisco Coordinating Center, San Francisco, CA (Steven R. Cummings, Michael Nevitt, Lisa Palermo); University of Minnesota, Minneapolis (Lisa Harnack); Fisher BioServices, Rockville, MD (Frank Cammarata, Steve Lindenfelser); University of Washington, Seattle (Bruce Psaty, Susan Heckbert). *Clinical Centers:* Albert Einstein College of Medicine, Bronx, NY (Sylvia Wassertheil-Smoller, William Frishman, Judith Wylie-Rosett, David Barad, Ruth Freeman); Baylor College of Medicine, Houston, TX (Aleksandar Rajkovic, Jennifer Hays, Ronald Young, Haleh Sangi-Haghpeykar); Brigham and Women's Hospital, Harvard Medical School, Boston, MA (JoAnn E. Manson, Kathryn M. Rexrode, Brian Walsh, J. Michael Gaziano, Maria Bueche); Brown University, Providence, RI (Charles B. Eaton, Michele Cyr, Gretchen Sloane); Emory University, Atlanta, GA (Lawrence Phillips, Vicki Butler, Vivian Porter); Fred Hutchinson Cancer Research Center, Seattle, WA (Shirley A. A. Beresford, Vicky M. Taylor, Nancy F. Woods, Maureen Henderson, Robyn Andersen); George Washington University, Washington, DC (Lisa Martin, Judith Hsia, Nancy Gaba, Richard Katz); Los Angeles Biomedical Research Institute at Harbor-UCLA Research and Education Institute, Torrance, CA (Rowan Chlebowski, Robert Detrano, Anita Nelson, Michele Geller); Kaiser Permanente Center for Health Research, Portland, OR (Yvonne Michael, Evelyn Whitlock, Victor Stevens, Njeri Karanja); Kaiser Permanente Division of Research, Oakland, CA (Bette Caan, Stephen Sidney, Geri Bailey Jane Hirata); Medical College of Wisconsin, Milwaukee (Jane Morley Kotchen, Vanessa Barnabei, Theodore A. Kotchen, Mary Ann C. Gilligan, Joan Neuner); MedStar Research Institute/Howard University, Washington, DC (Barbara V. Howard, Lucile Adams-Campbell, Lawrence Lessin, Cheryl Iglesia, Linda K Mickel); Northwestern University, Chicago/Evanston, IL (Linda Van Horn, Philip Greenland, Janardan Khandekar, Kiang Liu, Carol Rosenberg); Rush University Medical Center, Chicago, IL (Henry Black, Lynda Powell, Ellen Mason, Martha Gulati); Stanford Prevention Research Center, Stanford, CA (Marcia L. Stefanick, Mark A. Hlatky, Bertha Chen, Randall S. Stafford, Sally Mackey); State University of New York at Stony Brook (Dorothy Lane, Iris Granek, William Lawson, Catherine Messina, Gabriel San Roman); Ohio State University, Columbus (Rebecca Jackson, Randall Harris, Electra Paskett, W. Jerry Mysiw, Michael Blumenfeld); University of Alabama at Birmingham (Cora E. Lewis, Albert Oberman, James M. Shikany, Monika Safford); University of Arizona, Tucson/Phoenix (Cynthia A. Thomson, Tamsen Bassford, Cheryl Ritenbaugh, Zhao Chen, Marcia Ko); University at Buffalo, Buffalo, NY (Jean Wactawski-Wende, Maurizio Trevisan, Ellen Smit, Susan Graham, June Chang); University of California at Davis, Sacramento (John Robbins, S. Yasmeen); University of California at Irvine (F. Allan Hubbell, Gail Frank, Nathan Wong, Nancy Greep, Bradley Monk); University of California at Los Angeles (Lauren Nathan, David Heber, Robert Elashoff, Simin Liu); University of California at San Diego, LaJolla/Chula Vista (Robert D. Langer, Michael H. Criqui, Gregory T. Talavera, Cedric F. Garland, Matthew A. Allison); University of Cincinnati, Cincinnati, OH (Margery Gass, Nelson Watts); University of Florida, Gainesville/Jacksonville (Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson); University of Hawaii, Honolulu (J. David Curb, Helen Petrovitch, Beatriz Rodriguez, Kamal Masaki, Patricia Blanchette); University of Iowa, Iowa City/Davenport (Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar, Jennifer Robinson); University of Massachusetts/Fallon Clinic, Worcester (Judith Ockene, Milagros Rosal, Ira Ockene, Robert Yood, Patricia Aronson); University of Medicine and Dentistry of New Jersey, Newark (Norman Lasser, Baljinder Singh, Vera Lasser, John Kostis, Peter McGovern); University of Miami, Miami, FL (Mary Jo O'Sullivan, Linda Parker, JoNell Potter, Diann Fernandez, Pat Caralis); University of Minnesota, Minneapolis (Karen L. Margolis, Richard H. Grimm, Mary F. Perron, Cynthia Bjerk, Sarah Kempainen); University of Nevada, Reno (Robert Brunner, William Graettinger, Vicki Oujevolk, Michael Bloch); University of North Carolina, Chapel Hill (Gerardo Heiss, Pamela Haines, David Ontjes, Carla Sueta, Ellen Wells); University of Pittsburgh, Pittsburgh, PA (Lewis Kuller, Jane Cauley, N. Carole Milas); University of Tennessee Health Science Center, Memphis (Karen C. Johnson, Suzanne Satterfield, Rongling Li, Stephanie Connelly, Fran Tylavsky); University of Texas Health Science Center, San Antonio (Robert Brzyski, Robert Schenken); University of Wisconsin, Madison (Gloria E. Sarto, Douglas Laube, Patrick McBride, Julie Mares, Barbara Loevinger); Wake Forest University School of Medicine, Winston-Salem, NC (Mara Vitolins, Greg Burke, Robin Crouse, Scott Washburn); Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI (Michael Simon). *Women's Health Initiative Memory Study:* Wake Forest University School of Medicine, Winston-Salem, NC (Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker). *Former Principal Investigators and Project Officers:* Baylor College of Medicine, Houston, TX (Jennifer Hays, John Foreyt); Brown University, Providence, RI (Annlouise R. Assaf); Emory University, Atlanta, GA (Dallas Hall); George Washington University, Washington, DC (Valery Miller); Kaiser Permanente Center for Health Research, Portland, OR (Barbara Valanis); Kaiser Permanente Division of Research, Oakland, CA (Robert Hiatt); National Cancer Institute, Bethesda, MD (Carolyn Clifford†); National Heart, Lung, and Blood Institute, Bethesda, MD (Linda Pottern); University of California at Irvine (Frank Meyskens Jr); University of California at Los Angeles (Howard Judd†); University of Cincinnati, Cincinnati, OH (James Liu, Nelson Watts); University of Miami, Miami, FL (Marianna Baum); University of Minnesota, Minneapolis (Richard Grimm); University of Nevada, Reno (Sandra Daugherty†); University of North Carolina, Chapel Hill (David Sheps, Barbara Hulka); University of Tennessee Health Science Center, Memphis (William Applegate); University of Wisconsin, Madison (Catherine Allen†); Wake Forest University School of Medicine, Winston-Salem, NC (Denise Bonds).
†Deceased.
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