

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

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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.



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and questions on p 1730.

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), re-consent 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.

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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.

Most⁵⁻⁷ 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 identified¹ 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 random-

ization, 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 re-consent were censored on December 31, 2005, early

in the re-consent period, because mortality data in this group may be incomplete at more recent times. Additional mortality analyses censored women not re-consenting on March 31, 2005.

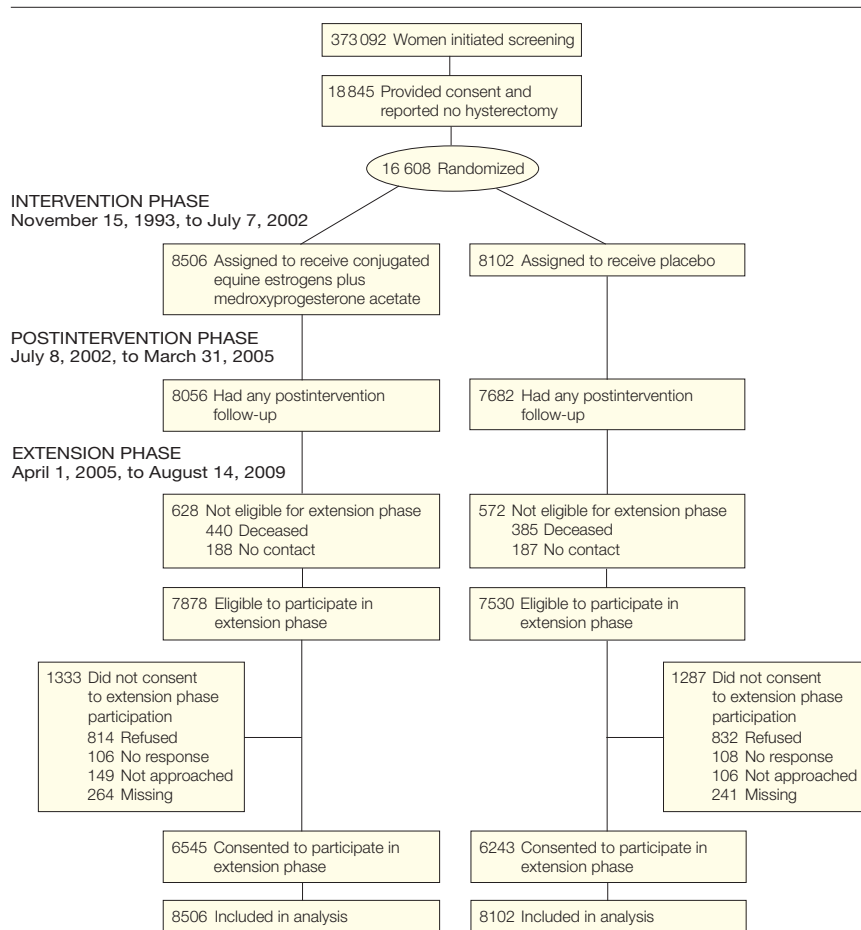
To examine the potential effect of censoring women who did not re-consent to follow-up after March 31, 2005, several secondary analyses were performed, including comparison of re-consent rates by baseline characteristics and randomization assignment and adjusted HR analyses using both inverse probability weighting and multiple imputation. The inverse probability weighting analyses developed a logistic regression model for re-consenting 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 re-consent (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 non-protocol 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.

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-

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 re-consented (83% of those eligible) through August 14, 2009.

domization groups were closely comparable in both the initial and re-consenting populations (eTable 2 and eTable 3). Those re-consenting were slightly younger and more likely to be white compared with those not re-consenting. 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

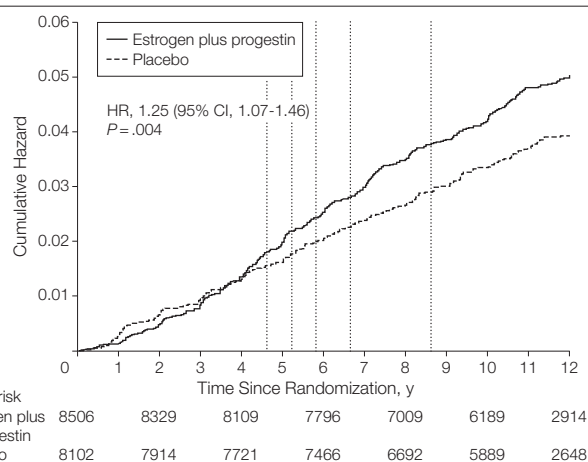
Mammography frequency was comparable in the 2 randomization groups during the original trial period through March 31, 2005 (annualized percentage, 80% for hormone vs 80% for placebo). In the re-consenting population of 15 408 women in the extension phase, the percentages of women with 1 or more mammograms 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		P Value ^b
	Estrogen Plus Progestin (n = 385)	Placebo (n = 293)	
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)	
<i>ERBB2</i> (<i>HER2</i>) 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/ <i>ERBB2</i> (<i>HER2</i>) 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.

^aData are presented as No. (%) of invasive breast cancers unless otherwise indicated.

^bP values are based on Fisher exact test of association.

^cTen instances (5 estrogen plus progestin and 5 placebo) occurred in which lymph nodes were examined but number examined was not specified.

^dTwo 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 com-

bined 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 consenting 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 recontact 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. Stud-

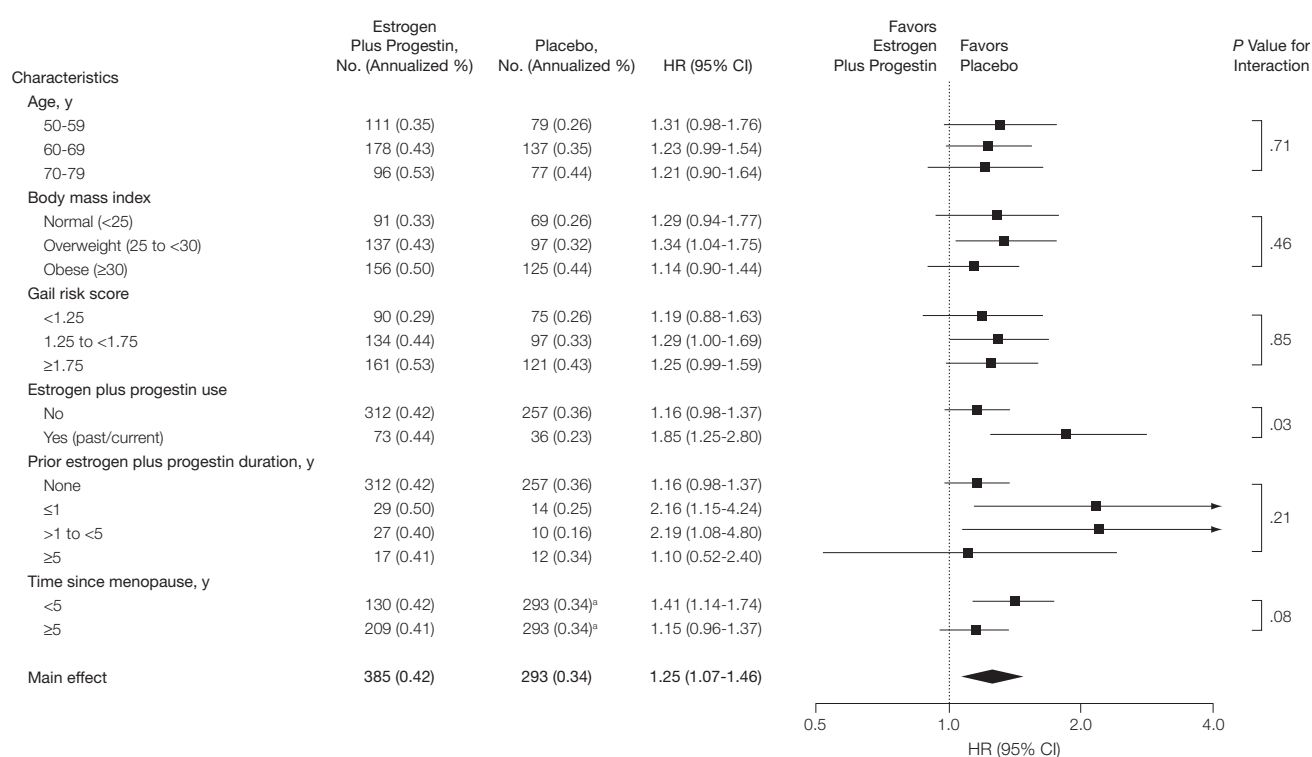
ies that are unable to control for mammography can be confounded by differences between screening-detected and non-screening-detected breast cancers. Screening more commonly identifies slow-growing, favorable-grade, hormone receptor-positive breast cancers, and diagnosis is made at an earlier stage.²¹⁻²³ 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 substan-

tial 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



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).

^aEvents 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 mortality²⁸ was greater than its influence on cancer incidence. Reproductive hormones,^{29,30} especially progesterin,^{31,32} are potent stimulators of angiogenesis. Because increased angiogenesis increases both lung³³ 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 progesterin 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

analyses³⁸ 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.

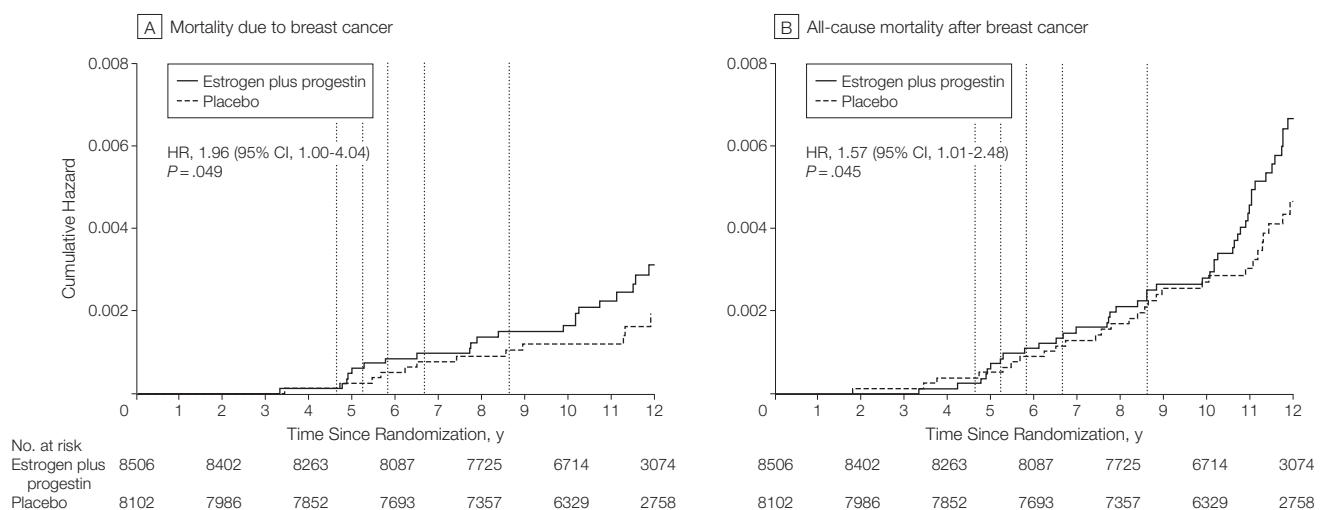
Strengths of this study include the randomized, double-blind design, a large and ethnically diverse study population, serial assessment of mammography and clinical breast examinations, central adjudication of breast cancers, and the long follow-up period. The lack of breast cancer therapy information 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-progesterin 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 re-consent for follow-up of disease incidence beyond the original trial completion date. The fact that 17% of women did not re-consent may have influenced estimation of the effect of combined hormone therapy on breast cancer. However, in both the original randomized group and in the re-consenting 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 progesterin and deaths due to breast cancer.

In conclusion, use of estrogen plus progesterin 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.

Author Contributions: Dr Chlebowski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chlebowski, Manson, Wactawski-Wende, Hendrix, Prentice.

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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.

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REFERENCES

- Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
- Chlebowski RT, Hendrix SL, Langer RD, et al; WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA*. 2003;289(24):3243-3253.
- Chlebowski RT, Anderson GL, Pettinger M, et al; Women's Health Initiative Investigators. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. *Arch Intern Med*. 2008;168(4):370-377.
- Chlebowski RT, Kuller LH, Prentice RL, et al; WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med*. 2009;360(6):573-587.
- Holli K, Isola J, Cuzick J. Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. *J Clin Oncol*. 1998;16(9):3115-3120.

6. Chen WY, Hankinson SE, Schnitt SJ, Rosner BA, Holmes MD, Colditz GA. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer*. 2004;101(7):1490-1500.
7. Rosenberg LU, Granath F, Dickman PW, et al. Menopausal hormone therapy in relation to breast cancer characteristics and prognosis: a cohort study. *Breast Cancer Res*. 2008;10(5):R78.
8. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419-427.
9. Kerlikowske K, Miglioretti DL, Ballard-Barbash R, et al. Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. *J Clin Oncol*. 2003;21(23):4314-4321.
10. Newcomb PA, Egan KM, Trentham-Dietz A, et al. Prediagnostic use of hormone therapy and mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(4):864-871.
11. Christante D, Pommier S, Garreau J, Muller P, LaFleur B, Pommier R. Improved breast cancer survival among hormone replacement therapy users is durable after 5 years of additional follow-up. *Am J Surg*. 2008;196(4):505-511.
12. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61-109.
13. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9)(suppl):S18-S77.
14. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9)(suppl):S5-S17.
15. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297(13):1465-1477.
16. Curb JD, McTiernan A, Heckbert SR, et al; WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9)(suppl):S122-S128.
17. National Cancer Institute. Surveillance, Epidemiology, and End Results program. <http://seer.cancer.gov/>. Accessed September 24, 2009.
18. Sener SF, Winchester DJ, Winchester DP, et al. The effects of hormone replacement therapy on postmenopausal breast cancer biology and survival. *Am J Surg*. 2009;197(3):403-407.
19. Heiss G, Wallace R, Anderson GL, et al; WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299(9):1036-1045.
20. Joffe MM, Byrne C, Colditz GA. Postmenopausal hormone use, screening, and breast cancer: characterization and control of a bias. *Epidemiology*. 2001;12(4):429-438.
21. Shen Y, Yang Y, Inoue LYT, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst*. 2005;97(16):1195-1203.
22. Sihto H, Lundin J, Lehtimäki T, et al. Molecular subtypes of breast cancers detected in mammography screening and outside of screening. *Clin Cancer Res*. 2008;14(13):4103-4110.
23. Dong W, Berry DA, Bevers TB, et al. Prognostic role of detection method and its relationship with tumor biomarkers in breast cancer: the University of Texas M. D. Anderson Cancer Center experience. *Cancer Epidemiol Biomarkers Prev*. 2008;17(5):1096-1103.
24. Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol*. 2006;24(33):e49-e50.
25. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670-1674.
26. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291(1):47-53.
27. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007;25(25):3808-3815.
28. Chlebowski RT, Schwartz AG, Wakelee H, et al; Women's Health Initiative Investigators. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet*. 2009;374(9697):1243-1251.
29. Losordo DW, Isner JM. Estrogen and angiogenesis: a review. *Arterioscler Thromb Vasc Biol*. 2001;21(1):6-12.
30. Dobrzycka B, Kinalski M, Piechocka D, Terlikowski SJ. The role of estrogens in angiogenesis in the female reproductive system [in Polish]. *Endokrynol Pol*. 2009;60(3):210-214.
31. Liang Y, Besch-Williford C, Brekken RA, Hyder SM. Progesterone-dependent progression of human breast tumor xenografts: a novel model for evaluating anti-tumor therapeutics. *Cancer Res*. 2007;67(20):9929-9936.
32. Hyder SM, Murthy L, Stancel GM. Progesterone regulation of vascular endothelial growth factor in human breast cancer cells. *Cancer Res*. 1998;58(3):392-395.
33. Calvo A, Catena R, Noble MS, et al. Identification of VEGF-regulated genes associated with increased lung metastatic potential: functional involvement of tenascin-C in tumor growth and lung metastasis. *Oncogene*. 2008;27(40):5373-5384.
34. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis: correlation in invasive breast carcinoma. *N Engl J Med*. 1991;324(1):1-8.
35. Power ML, Anderson BL, Schulkin J. Attitudes of obstetrician-gynecologists toward the evidence from the Women's Health Initiative hormone therapy trials remain generally skeptical. *Menopause*. 2009;16(3):500-508.
36. Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of HRT. *Atherosclerosis*. 2009;207(2):336-340.
37. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? a randomized trial. *Ann Intern Med*. 2010;152(4):211-217.
38. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol*. 2008;167(10):1207-1216.
39. Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol*. 2009;27(31):5138-5143.
40. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas*. 2006;55(2):103-115.