Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women

The Women's Health Initiative Randomized Trial

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Context The Women's Health Initiative trial of combined estrogen plus progestin was stopped early when overall health risks, including invasive breast cancer, exceeded benefits. Outstanding issues not previously addressed include characteristics of breast cancers observed among women using hormones and whether diagnosis may be influenced by hormone effects on mammography.

Objective To determine the relationship among estrogen plus progestin use, breast cancer characteristics, and mammography recommendations.

Design, Setting, and Participants Following a comprehensive breast cancer risk assessment, 16608 postmenopausal women aged 50 to 79 years with an intact uterus were randomly assigned to receive combined conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo from 1993 to 1998 at 40 clinical centers. Screening mammography and clinical breast examinations were performed at baseline and yearly thereafter.

Main Outcome Measures Breast cancer number and characteristics, and frequency of abnormal mammograms by estrogen plus progestin exposure.

Results In intent-to-treat analyses, estrogen plus progestin increased total (245 vs 185 cases; hazard ratio [HR], 1.24; weighted $P<.001$) and invasive (199 vs 150 cases; HR, 1.24; weighted $P=.003$) breast cancers compared with placebo. The invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology and grade but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; $P=.04$) and were at more advanced stage (regional/metastatic 25.4% vs 16.0%, respectively; $P=.04$) compared with those diagnosed in the placebo group. After 1 year, the percentage of women with abnormal mammograms was substantially greater in the estrogen plus progestin group (716 [9.4%] of 7656) compared with placebo group (398 [5.4%] of 7310; $P<.001$), a pattern which continued for the study duration.

Conclusions Relatively short-term combined estrogen plus progestin use increases incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and also substantially increases the percentage of women with abnormal mammograms. These results suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis.

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BREAST CANCER IS THE MOST common invasive cancer in US women and its etiology is not fully defined.[1,2] Despite observational studies suggesting increased breast cancer risk with estrogen[3] and especially long-duration combined hormone use,[4,5] the magnitude of breast cancer risk associated with menopausal hormone therapy is controversial.[6,7]

On July 9, 2002, the Women's Health Initiative (WHI) reported results from the randomized controlled trial of 16608 postmenopausal women comparing effects of estrogen plus progestin with placebo on chronic disease risk and confirmed that combined estro-

See also pp 3254 and 3304.

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Table 1. Descriptive Characteristics of Participants at Baseline by Treatment Group*

Characteristic	No. (%) Estrogen + Progestin (n = 8506)†	No. (%) Placebo (n = 8102)
Age at screening, y		
50-59	2839 (33.4)	2683 (33.1)
60-69	3853 (45.3)	3657 (45.1)
70-79	1814 (21.3)	1762 (21.7)
Ethnicity		
White	7140 (83.9)	6805 (84.0)
Black	549 (6.5)	575 (7.1)
Hispanic	472 (5.5)	416 (5.1)
American Indian	26 (0.3)	30 (0.4)
Asian/Pacific Islander	194 (2.3)	169 (2.1)
Unknown	125 (1.5)	107 (1.3)
Education		
0-8 y	202 (2.4)	177 (2.2)
Some high school	373 (4.4)	362 (4.5)
High school diploma/GED	1614 (19.1)	1608 (20.0)
School after high school	3356 (39.7)	3059 (38.0)
College degree or higher	2915 (34.5)	2838 (35.3)
Gail Risk Assessment, % per 5 y		
<1.25	2806 (33.0)	2717 (33.5)
1.25-1.74	2859 (33.6)	2703 (33.4)
≥1.75	2841 (33.4)	2682 (33.1)
Age at menarche, y		
<11	1725 (20.3)	1670 (20.7)
12-13	4578 (54.0)	4334 (53.7)
≥14	2182 (25.7)	2061 (25.6)
No. of term pregnancies		
Never pregnant	655 (7.7)	633 (7.8)
Never had term pregnancy	201 (2.4)	199 (2.5)
1	690 (8.2)	661 (8.2)
2	1908 (22.5)	1708 (21.2)
3	2020 (23.9)	1952 (24.2)
4	1416 (16.7)	1412 (17.5)
≥5	1575 (18.6)	1500 (18.6)
Age at first birth, y		
Never pregnant/no term pregnancy	860 (11.2)	833 (11.5)
<20	1124 (14.6)	1117 (15.4)
20-29	4996 (64.8)	4698 (64.6)
≥30	727 (9.4)	624 (8.6)
No. of children breastfed		
None	3813 (45.3)	3669 (45.7)
1-2	2606 (31.0)	2485 (31.0)
≥3	2001 (23.8)	1867 (23.3)
Oral contraceptive use, y		
No	4811 (56.6)	4655 (57.5)
Yes	3693 (43.4)	3444 (42.5)
<5	1982 (23.3)	1781 (22.0)
5 to <10	825 (9.7)	808 (10.0)
≥10	886 (10.4)	855 (10.6)
Prior estrogen only use, y		
No	7603 (89.4)	7237 (89.3)
Yes	903 (10.6)	864 (10.7)
<5	677 (8.0)	659 (8.1)
5 to <10	134 (1.6)	109 (1.3)
≥10	92 (1.1)	96 (1.2)
Prior estrogen plus progestin use, y		
No	6990 (82.2)	6706 (82.8)
Yes	1516 (17.8)	1396 (17.2)
<5	1050 (12.3)	997 (12.3)
5 to <10	315 (3.7)	258 (3.2)
≥10	151 (1.8)	141 (1.7)
Recency of hormone use, y		
Nonuser	6277 (73.8)	6020 (74.3)
Past <5	727 (8.6)	679 (8.4)
Past 5 to <10	335 (3.9)	310 (3.8)
Past >10	609 (7.2)	599 (7.4)
Current	554 (6.5)	491 (6.1)

(continued)

gen plus progestin use increases the risk of invasive breast cancer.[8] To better understand the relationship between breast cancer and exposure to estrogen plus progestin, a detailed analysis of the breast cancers that developed among women receiving active treatment compared with those receiving placebo was performed.

METHODS

Study Design

The WHI combined estrogen plus progestin randomized clinical trial enrolled 16 608 postmenopausal women with no prior hysterectomy from 1993 to 1998 at 40 clinical centers following a previously described design.[8,9] The study was approved by human subjects committees at each institution. Women who were recruited by mass mailings and media were eligible if they were between 50 and 79 years of age at study entry, postmenopausal, and provided written informed consent. Women with prior hysterectomy, breast cancer, or those with medical conditions likely to result in death within 3 years were excluded. Prior menopausal hormone use required a 3-month wash out period before baseline testing. All women had baseline mammogram and clinical breast examinations; abnormal findings required clearance before study entry.

Women were randomly assigned to receive estrogen plus progestin taken as a single daily tablet containing conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) (Prempro, Wyeth Ayerst, Philadelphia, Pa) or to receive an identical-appearing placebo. Randomization by the WHI clinical coordinating center was implemented locally by using a distributed study database and study medication bottles with unique bar codes for blinded dispensing. Descriptive characteristics for the 2 groups were assessed at baseline (TABLE 1).

Study medication was discontinued for development of breast cancer; endometrial pathology (hyperplasia not responsive to treatment, atypia, or cancer); deep-vein thrombosis or pul-

monary emboli; malignant melanoma; meningeoma; triglyceride level of more than 1000 mg/dL (11.3 mmol/L); or use of any nonstudy estrogen, progestin, androgen, tamoxifen, or raloxifene. Comprehensive breast cancer risk was assessed at baseline by interview (lifetime hormone use) or by self-report (other covariates) by using standardized questionnaires.

Follow-up Procedures

Participants were contacted after 6 weeks to assess symptoms and promote adherence, at 6-month intervals for clinical outcome, and annually for clinic visits. Yearly mammography and clinical breast examination were required, and study medications were withheld if they were not completed. Participants were followed for clinical outcomes regardless of medication adherence.

Initial reports of outcomes were ascertained by self-administered questionnaires. Breast cancer end points were confirmed by review of medical records and pathology reports (available in 98.2% of participants) by physician adjudicators at the local clinics. Women with in situ breast cancers, which at a later date were diagnosed with a new invasive breast cancer, were considered to have 2 separate breast cancer events (3 cases). All cases were subsequently centrally adjudicated using the Surveillance, Epidemiology, and End Results coding system. Invasive cancers originally classified as mixed ductal and lobular underwent additional blinded review by an oncologist (R.T.C.).

With the exception of these trial conduct procedures, the WHI clinical centers did not provide comprehensive health care. Mammograms in the WHI were performed at more than 3000 clinics, hospitals, and practice settings. Medical decisions regarding workup of breast findings were directed by community physicians.

Mammogram reports were obtained from performance sites and were reviewed locally and coded for recommendation (negative, benign finding-negative, short interval follow-up suggested, suspicious abnormality, and highly suggestive of malignancy). Mammograms with suspicious abnormalities or highly suggestive of malignancy required clearance before dispensing additional study medication.

Table 1. Descriptive Characteristics of Participants at Baseline by Treatment Group* (cont)

Characteristic	No. (%) Estrogen + Progestin (n = 8506)†	No. (%) Placebo (n = 8102)
No. of first-degree relatives with breast cancer		
None	6954 (87.3)	6676 (88.2)
1	927 (11.6)	816 (10.8)
≥2	82 (1.0)	79 (1.0)
No. of second-degree relatives with breast cancer‡		
None	7184 (95.8)	6880 (96.0)
1	304 (4.1)	282 (3.9)
≥2	13 (0.2)	3 (<0.1)
Benign breast disease		
No	6340 (83.5)	6278 (83.2)
Yes, 1 biopsy	967 (12.7)	981 (13.0)
Yes, ≥2 biopsies	290 (3.8)	288 (3.8)
BMI		
<25	2579 (30.4)	2479 (30.8)
25-30	2992 (35.3)	2834 (35.2)
>30	2899 (34.2)	2737 (34.0)
Dietary energy, kcal		
≤1119	1630 (19.8)	1575 (20.1)
>1119-1414.5	1632 (19.9)	1583 (20.2)
>1414.5-1715	1601 (19.5)	1611 (20.6)
>1715-2129.5	1689 (20.6)	1518 (19.4)
>2129.5	1661 (20.2)	1549 (19.8)
% Energy from fat		
≤27	1620 (19.7)	1539 (19.6)
>27-32.5	1601 (19.5)	1600 (20.4)
>32.5-37	1754 (21.4)	1660 (21.2)
>37-41.5	1590 (19.4)	1504 (19.2)
>41.5	1648 (20.1)	1533 (19.6)
Physical activity, metabolic equivalents/wk		
None	1427 (18.6)	1356 (17.9)
>0-3.75	1501 (19.6)	1519 (20.0)
>3.75-8.75	1355 (17.7)	1352 (17.8)
>8.75-17.5	1648 (21.5)	1634 (21.5)
>17.5	1739 (22.7)	1735 (22.8)
Alcohol use		
Nondrinker	972 (11.5)	938 (11.7)
Past drinker	1427 (16.9)	1380 (17.2)
<1 drink/mo	1174 (13.9)	1117 (13.9)
<1 drink/wk	1710 (20.3)	1513 (18.8)
1 to <7 drinks/wk	2113 (25.0)	2038 (25.4)
≥7 drinks/wk	1047 (12.4)	1049 (13.1)
Smoking		
Never	4178 (49.6)	3999 (50.0)
Past	3362 (39.9)	3157 (39.5)
Current	880 (10.5)	838 (10.5)
NSAID medication use		
No	8112 (95.4)	7715 (95.2)
Yes	394 (4.6)	387 (4.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); GED, general equivalency diploma; NSAID, nonsteroidal anti-inflammatory drug.

*Because of rounding, percentages may not all total 100. Not all characteristics sum to total number of participants for either estrogen plus progestin or placebo because of missing values for some participants. Mean (SD) for estrogen plus progestin vs placebo was 63.2 years (7.1) and 63.3 years (7.1), respectively, for age at screening; 28.5 (5.8) and 28.5 (5.9), respectively, for BMI; 1554.7 kcal (599.1) and 1544.8 kcal (588.2), respectively, for dietary energy; and 34.4 (8.4) and 34.3 (8.4), respectively, for percentage energy from fat.

†Includes 331 women previously randomized to an estrogen alone group who were reassigned to the estrogen plus progestin group following a protocol change as previously described.[8]

‡$P = .051$ by χ^2 test.

Study Termination

The study sample size was based on the estimated influence of estrogen plus progestin on coronary heart disease. For monitoring purposes, a global index of

benefit and risk was defined to include coronary heart disease, stroke, colorectal cancer, endometrial cancer, pulmonary embolus, hip fracture, and death due to other causes as well as invasive breast cancer.

After a mean (SD) follow-up of 5.2 years (1.3) (including end points through April 2002), the WHI data and safety monitoring board recommended stopping the trial based on the breast cancer comparison exceeding the predefined stopping boundary and overall risks exceeding benefits as measured by the global index. At that time, 290 locally adjudicated invasive breast cancers were described and the in situ breast cancers were not quantitated.[8] This report provides an updated analysis based on a mean (SD) follow-up of 5.6 years (1.3) with detailed analyses of the centrally adjudicated breast cancers (349 invasive and 84 in situ) diagnosed before July 8, 2002, the date participants were instructed to stop their study pills.

Statistical Analysis

A major hypothesis of the current analysis was that invasive breast cancer characteristics in the estrogen plus progestin group differed from the placebo group. In addition, given the influence of menopausal hormones on breast density[10-12] and the suggestion that hormones can complicate mammographic interpretation,[13] associations among estrogen plus progestin use, mammographic results, and breast cancer diagnoses were explored.

Primary results are assessed with time-to-event methods, based on the intent-to-treat principle. Hazard ratios (HRs) are reported from unweighted Cox proportional hazards regression analyses. *P* values from Wald Z statistics are reported from weighted Cox proportional hazards regression analyses stratified by age and randomization status in the dietary modification trial of the WHI. This weighting was specified in the trial design and motivated by observational reports suggesting lag to full effect of hormone on breast cancer incidence. The weighting, reflecting this hypothesis, varied linearly from zero at time of randomization to a maximum of 1 beginning at follow-up year 10.

Nominal confidence intervals (CIs) for inference regarding invasive breast cancer are used as these are considered final trial results for the primary safety outcome. The multiple testing over time is acknowledged in adjusted CIs derived from the monitoring plan, as previously described.[8] The fact that this outcome was a key factor in the early stopping of the trial could lead to some anticonservatism in the reported HR estimates.

Hazard ratios by time since randomization were calculated by using unweighted Cox proportional hazards regression models for all women and separately for women who had either received or not received menopausal hormone therapy before entering the study. Tests of trends with time were performed in an unweighted Cox proportional hazards regression model incorporating a linear time interaction term. Kaplan-Meier method plots describe breast cancer event rates over time. Sensitivity analyses examining the effect of nonadherence were conducted by repeating these analyses after censoring events that occurred 6 months after a woman became nonadherent (prospectively defined for adherence monitoring purposes as consuming <80% of study pills or starting hormone therapy during most recent study interval).

Comparisons of participant baseline and breast cancer tumor characteristics were based on χ^2, Fisher exact, or *t* tests. Interactions between baseline characteristics and randomization assignment were assessed in Cox proportional hazards regression models (weighted and unweighted) that included both the risk factor (where applicable as a continuous variable for computing the test statistic and *P* value) and randomization assignment as main effects. *P* values for assessing possible interactions were computed from likelihood ratio tests by comparing models with and without the interaction term. Women with missing values for a risk factor were omitted from these analyses. Twenty-three subgroup comparisons were tested and, accordingly, 1 test would be expected to be significant at the .05 level by chance alone. Ten comparisons are presented.

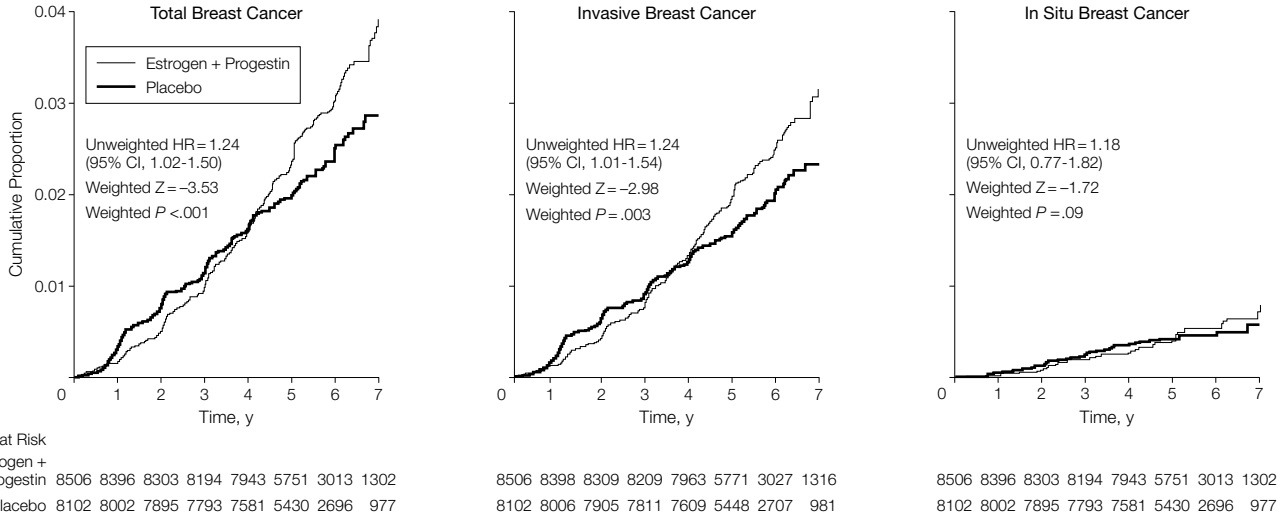
Calculated variables included (1) Gail Risk Assessment[14] that incorporated age, history of benign breast disease (atypia status unknown in WHI), age at menarche, age at first live birth, race/ethnicity, and numbers of mothers and sisters with breast cancer; (2) duration and recency of menopausal hormone therapy and oral contraceptive use; (3) body mass index (calculated as weight in kilograms divided by the square of height in meters); (4) dietary variables, including energy, percentage energy from fat, and alcohol use; and (5) physical activity (metabolic equivalent–hours per week of activity). Analyses were performed by using SAS version 8.02 (SAS Institute Inc, Cary, NC); $P<.05$ was considered significant.

RESULTS

Breast cancer risk characteristics were closely comparable in the 2 study groups including factors related to prior hormonal exposure, family history, dietary intake, education, ethnicity, and the Gail Risk Assessment (Table 1). Participants were at moderate breast cancer risk for their age given a mean (SD) Gail 5-year risk estimate of 1.50% (0.67%).

Recent (within 18 months) outcome information was available on 15931 women (95.9% of randomized participants). Survival status was known for 16067 participants (96.7%), including 485 (2.9%) known to be deceased. At the time of this study, the mean follow-up was 5.6 years with a maximum of 8.6 years. As previously described,[8] at the time of our interim study, 42% of estrogen plus progestin and 38% of placebo participants stopped their study medications for at least some period. Drop-ins, based on women who self-reported discontinuation of study medication and subsequently received any menopausal hor-

Figure 1. Breast Cancer by Category and Treatment Group (Estrogen Plus Progestin vs Placebo)



Hazard ratios (HRs) are from unweighted Cox proportional hazards regression models, stratified by age and dietary modification randomization group. Z statistics and *P* values are from weighted Cox proportional hazards regression models, stratified by age and dietary modification randomization group. CI indicates confidence interval.

mones through other sources, were 6.2% in the estrogen plus progestin group and 10.7% in the placebo group.

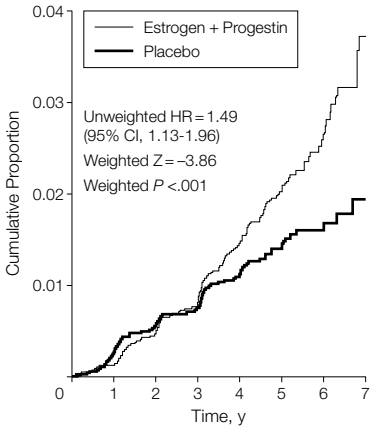
In intent-to-treat analyses, estrogen plus progestin increased total (245 vs 185 cases; HR, 1.24; weighted $P<.001$) and invasive (199 vs 150 cases; HR, 1.24; weighted $P=.003$) breast cancers compared with placebo (*P* values from weighted Cox proportional hazards regression models, FIGURE 1). The nominal 95% CI for the unweighted HR for invasive breast cancer was 1.01 to 1.54. Accounting for the sequential monitoring gives an adjusted 95% CI of 0.97 to 1.59. There was also a suggestion of an increase for in situ breast cancers in the estrogen plus progestin group (47 vs 37 cases; HR, 1.18; weighted $P=.09$).

Sensitivity analyses examining the impact of nonadherence suggest a stronger effect on invasive breast cancer incidence when events in nonadherent women are excluded (HR, 1.49; weighted $P<.001$), including the possibility of an earlier divergence in the cumulative hazard estimates (FIGURE 2).

The number of invasive breast cancers by year and treatment group for all women and stratified by prior hormone use are shown in TABLE 2. For women with no menopausal hormone use before entering the study, invasive breast cancer rates were lower for the initial 2 years in the estrogen plus progestin group compared with placebo, and similar in the third year. In the fourth year and thereafter, invasive breast cancer rates were higher in the estrogen plus progestin group, with a significant trend for increasing breast cancer risk over time ($Z=2.31$). In women with prior menopausal hormone use, the rate of invasive breast cancer incidence was greater in the third year and beyond for women receiving estrogen plus progestin.

The relationship between variables in Table 1 and treatment were examined in the form of interactions, none of which were significant, although power was limited by small sample size within subgroups. These results, as well as subgroup specific analyses, are presented for selected covariates in TABLE 3. Overall, findings in specific risk categories underscored the consistency of the main results; women assigned to estrogen plus progestin had higher rates of invasive breast cancer in nearly all subgroups. Effects by race/ethnicity were examined and no differences were found.

Figure 2. Sensitivity Analysis of Invasive Breast Cancers in Adherent Participants by Treatment Group



Participants were censored 6 months after becoming nonadherent (defined as taking <80% of study medication or starting nonprotocol hormone therapy). Hazard ratio (HR) is from unweighted Cox proportional hazards regression model, stratified by age and dietary modification randomization group. Z statistic and *P* value are from weighted Cox proportional hazards regression model, stratified by age and dietary modification randomization group. CI indicates confidence interval.

These data suggest that women reporting prior menopausal hormone use may have had higher HRs for breast

cancer associated with estrogen plus progestin use than those who never used menopausal hormones (among never users, 141 vs 121; HR, 1.09; for women with <5 years of prior use, 37 vs 21; HR, 1.70; and women with ≥5 years of prior use, 21 vs 8; HR, 2.27), but the trend with duration of use was not statistically significant (weighted $P=.15$).

Breast Cancer Characteristics

Invasive breast cancers associated with estrogen plus progestin use were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; $P=.04$), were more likely to be node positive (25.9% vs 15.8%, respectively; $P=.03$), and were diagnosed at a significantly more advanced stage (regional/metastatic 25.4% vs 16.0%, respectively; $P=.04$) compared with placebo use (TABLE 4). There was no difference in tumor grade by treatment group. The percentages and distribution of invasive ductal, invasive lobular, mixed ductal, and lobular as well as tubular carcinomas were similar in the estrogen plus progestin group vs the placebo group.

The number of both receptor-positive and receptor-negative breast cancers were greater in the estrogen plus progestin group; the distribution of estrogen receptor-positive and progesterone-receptor cancers did not differ significantly between the estrogen plus progestin and placebo groups when considering tumors with known receptor status. There was a modest difference in receptor status ascertainment between treatment groups that could not be attributed to tumor size differences (data not shown).

For in situ breast cancers, the tumor grade did not differ between study groups ($P=.56$). The size of the in situ cancers was slightly larger in the estrogen plus progestin group (mean [SD], 1.6 cm [2.0] vs 1.1 cm[0.6], respectively), but the difference was not statistically significant ($P=.33$), and a substantial number of in situ cancers had no measurable size. At this time, few deaths have been attributed to breast cancer (4 in the estrogen plus progestin group and 4 in the placebo group).

Mammography

Mammography clearance was required before entry for all participants. Eighty-two women with mammographic abnormalities suspicious or highly suggestive of malignancy were entered after medical clearance; only 3 subsequently developed invasive breast cancers. Detailed mammogram reading results (other than cancer/no cancer) were available for 14607 women at baseline. At baseline, the percentage of women with an abnormal mammogram was closely comparable with the 2 treatment groups (TABLE 5).

After the first year, the percentage of women with abnormal mammograms (with recommendations for either short interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was substantially higher in the estrogen plus progestin group vs the placebo group (716 [9.4%] of 7656 vs 398 [5.4%] of 7310 women with abnormal mammograms, respectively; $P<.001$). The frequency of abnormal mammograms was higher in women aged 50 to 59 years in the hormone therapy group after 1 year as well (8.8% vs 5.9%, respectively; $P<.001$). In each year thereafter, the percentage of women with abnormal mammograms was significantly higher in the estrogen plus progestin group vs the placebo group. In total, 31.5% of women in the estrogen plus progestin group had at least 1 abnormal mammogram vs 21.2% of women in the placebo group ($P<.001$). Thus, even short-term estrogen plus progestin use resulted in a substantial increase in abnormal mammograms requiring medical evaluation.

Table 2. Invasive Breast Cancers (Annualized Percentage) by Treatment Group and Prior Menopausal Hormone Therapy*

	Time After Entry, y						Z for Trend
	1	2	3	4	5	≥6	
Without Prior Menopausal Hormone Use							
Estrogen plus progestin (n = 6277)	7 (0.11)	15 (0.24)	19 (0.31)	35 (0.58)	28 (0.54)	37 (0.69)	2.31
Placebo (n = 6020)	14 (0.23)	22 (0.37)	19 (0.33)	23 (0.40)	17 (0.34)	26 (0.56)	
HR (95% CI)	0.48 (0.19-1.20)	0.65 (0.34-1.25)	0.96 (0.51-1.82)	1.45 (0.85-2.45)	1.61 (0.88-2.94)	1.24 (0.75-2.05)	
With Prior Menopausal Hormone Use							
Estrogen plus progestin (n = 2225)	5 (0.23)	11 (0.50)	10 (0.46)	9 (0.42)	15 (0.82)	8 (0.39)	1.62
Placebo (n = 2079)	5 (0.24)	10 (0.49)	3 (0.15)	4 (0.20)	4 (0.23)	3 (0.17)	
HR (95% CI)	0.90 (0.26-3.15)	1.10 (0.47-2.61)	3.09 (0.84-11.27)	2.16 (0.66-7.05)	3.56 (1.18-10.73)	1.99 (0.52-7.60)	
Overall							
Estrogen plus progestin (N = 8506)	12 (0.14)	26 (0.31)	29 (0.35)	44 (0.54)	43 (0.61)	45 (0.61)	2.56
Placebo (N = 8102)	19 (0.24)	32 (0.40)	22 (0.28)	27 (0.35)	21 (0.32)	29 (0.45)	
HR (95% CI)	0.60 (0.29-1.23)	0.77 (0.46-1.30)	1.26 (0.73-2.20)	1.54 (0.95-2.49)	1.99 (1.18-3.35)	1.35 (0.85-2.16)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Data are No. (%) unless otherwise specified. Hazard ratios and 95% CIs are from unweighted Cox proportional hazards regression models, stratified by age and dietary modification randomization group.

COMMENT

This report provides randomized clinical trial evidence that postmenopausal estrogen plus progestin use significantly increases the incidence of breast cancer within a 5-year period. The breast cancers diagnosed in women in the hormone therapy group had similar histology and grade but were more likely to have advanced stage vs women in the placebo group. These results suggest that invasive breast cancers developing in women receiving estrogen plus progestin therapy may have an unfavorable prognosis. Follow-up continues in these women to determine survival outcome.

Mammographic breast density was not routinely measured, but when the mammographic results were examined over time by treatment group, a substantial and statistically significant increase in the percentage of women with abnormal mammograms requiring additional medical evaluation was observed beginning in the first year of hormone use. The absolute increase in abnormal mammograms of about 4% per year in women receiving estrogen plus progestin translates into approximately 120 000 otherwise avoidable abnormal mammograms annually for the estimated 3 million US postmenopausal women currently using this hormone regimen. Prior reports of menopausal hormone therapy influence on mammographic interpretation have been mixed, varying from no effect to substantial negative influence.[13,15] Our literature review found no prior large randomized trials with comprehensive serial mammographic assessment reporting the effects of estrogen plus progestin on the frequency of abnormal mammograms.

Estrogen plus progestin use increases mammographic breast density vs estrogen alone or placebo,[10-12] but the biological significance of such changes or their effect on mammographic interpretation is not established.[12] An ongoing ancillary study in the WHI, formally evaluating mammographic breast density on a subset of participants, may provide additional information on the

Table 3. Invasive Breast Cancers (Annualized Percentage) by Baseline Characteristics and Treatment Group

	No. (%)			
	Estrogen + Progestin	Placebo	HR (95% CI)*	*P* Value for Interaction†
No. of participants randomized	8506	8102		
Follow-up time, mean (SD), mo	67.8 (16.2)	66.8 (15.2)		
Invasive breast cancer	199 (0.41)	150 (0.33)	1.24 (1.01-1.54)	.003
Selected covariates for invasive breast cancer				
Age at screening, y				
50-59	52 (0.31)	40 (0.26)	1.20 (0.80-1.82)	.20
60-69	94 (0.44)	72 (0.36)	1.22 (0.90-1.66)	
70-79	53 (0.54)	38 (0.41)	1.34 (0.88-2.04)	
Gail Risk Assessment, % per 5 y				
<1.25	49 (0.30)	34 (0.22)	1.35 (0.87-2.09)	.33
1.25-1.74	73 (0.45)	53 (0.35)	1.27 (0.89-1.80)	
≥1.75	77 (0.49)	63 (0.43)	1.13 (0.81-1.57)	
Prior oral contraceptive use, y				
No	122 (0.45)	99 (0.39)	1.15 (0.88-1.50)	.31
<5	52 (0.46)	24 (0.24)	2.06 (1.27-3.35)	
5-10	17 (0.36)	13 (0.28)	1.38 (0.67-2.86)	
>10	8 (0.16)	14 (0.29)	0.54 (0.22-1.28)	
Prior menopausal hormone use, y				
No prior hormone use‡	141 (0.40)	121 (0.36)	1.09 (0.86-1.39)	.15
<5	37 (0.42)	21 (0.25)	1.70 (0.99-2.91)	
≥5	21 (0.54)	8 (0.24)	2.27 (1.00-5.15)	
Prior estrogen-only use, y				
No prior hormone use‡	141 (0.40)	121 (0.36)	1.09 (0.86-1.39)	.32
<5	23 (0.59)	13 (0.35)	1.77 (0.89-3.53)	
≥5	7 (0.54)	3 (0.27)	2.06 (0.53-7.99)	
Prior estrogen plus progestin use, y				
No prior hormone use‡	141 (0.40)	121 (0.36)	1.09 (0.86-1.39)	.21
<5	22 (0.36)	9 (0.16)	2.34 (1.07-5.11)	
≥5	14 (0.55)	6 (0.28)	2.04 (0.77-5.39)	
Recency of hormone use, y§				
Current	13 (0.41)	4 (0.15)	2.86 (0.91-8.97)	.65
Past, <5	17 (0.40)	8 (0.21)	2.02 (0.87-4.69)	
Past, 5-10	10 (0.53)	5 (0.29)	2.49 (0.82-7.55)	
Past, ≥10	18 (0.52)	12 (0.36)	1.43 (0.69-2.99)	
BMI				
<25	45 (0.31)	32 (0.23)	1.35 (0.86-2.13)	.12
25-30	72 (0.42)	49 (0.31)	1.40 (0.97-2.01)	
≥30	82 (0.50)	68 (0.45)	1.08 (0.78-1.49)	
Smoking				
Never	92 (0.39)	66 (0.30)	1.29 (0.94-1.77)	.23
Past	86 (0.45)	70 (0.40)	1.14 (0.83-1.56)	
Current	21 (0.43)	9 (0.19)	2.28 (1.04-4.98)	
NSAID medication use				
No	190 (0.41)	142 (0.33)	1.25 (1.01-1.56)	.75
Yes	9 (0.42)	8 (0.37)	1.10 (0.41-2.90)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.
*Hazard ratios and 95% CIs are from unweighted Cox proportional hazards regression models, stratified by age and dietary modification randomization group.
†Weighted Cox proportional hazards regression models, stratified by age and dietary modification randomization group.
‡Users of alternate preparations are excluded.
§Recency of use only applies to women who have ever taken hormones. Current users had 3 months wash out before entry.

Table 4. Characteristics of Invasive Breast Cancers by Treatment Group*

	No. (%)		
	Estrogen + Progestin (N = 199)	Placebo (N = 150)	*P* Value†
No. of participants randomized	8506	8102	
Follow-up, mean (SD), mo	67.8 (16.2)	66.8 (15.2)	
Tumor size, mean (SD), cm‡	1.7 (1.1)	1.5 (0.9)	.04
No tumor found/no primary mass	0	1 (0.7)	.50
Microscopic focus or foci, cm	8 (4.3)	9 (6.4)	
≤0.5	18 (9.7)	17 (12.1)	
>0.5-1	45 (24.2)	36 (25.5)	
>1-2	73 (39.2)	56 (39.7)	
>2-5	37 (19.9)	21 (14.9)	
>5	5 (2.7)	1 (0.7)	
Missing	13 (6.5)	9 (6.0)	.84
Lymph nodes examined			
No	19 (9.9)	13 (9.1)	.79
Yes	172 (90.1)	130 (90.9)	
Missing	8 (4.0)	7 (4.7)	.77
No. of lymph nodes examined, mean (SD)§	10.3 (7.9)	10.9 (7.8)	.52
No. of positive lymph nodes			
None	129 (74.1)	112 (84.2)	.08
1-3	36 (20.7)	15 (11.3)	
≥4	9 (5.2)	6 (4.5)	
Missing	25 (12.6)	17 (11.3)	.73
Lymph nodes positive (yes)	45 (25.9)	21 (15.8)	.03
SEER stage			
Localized	144 (74.6)	124 (82.7)	.048
Regional	47 (24.4)	21 (14.0)	
Metastatic	2 (1.0)	3 (2.0)	
Missing	6 (3.0)	2 (1.3)	.47
SEER stage regional/metastatic (yes)	49 (25.4)	24 (16.0)	.04
Histology			
Invasive ductal carcinoma	135 (67.8)	101 (67.3)	.89
Invasive lobular carcinoma	22 (11.1)	16 (10.6)	
Invasive ductal and invasive lobular	15 (7.5)	8 (5.3)	
Invasive carcinoma with ductal and lobular features	1 (0.5)	1 (0.7)	
Tubular	8 (4.0)	6 (4.0)	
Other	17 (8.5)	18 (12.0)	
Morphology, grade			
Well differentiated	41 (25.0)	26 (20.3)	.61
Moderately differentiated	71 (43.3)	61 (47.7)	
Poorly differentiated/anaplastic	52 (31.7)	41 (32.0)	
Missing	35 (17.6)	22 (14.7)	.46
Receptor status			
Estrogen-receptor assay			
Positive	158 (86.8)	112 (88.2)	.72
Negative	24 (13.2)	15 (11.8)	
Missing	17 (8.5)	23 (15.4)	.049
Progesterone-receptor assay			
Positive	135 (75.0)	86 (69.9)	.33
Negative	45 (25.0)	37 (30.0)	
Missing	19 (9.5)	27 (18.0)	.02

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
*Tumors <1 cm with no node or missing nodes were classified as local; tumors ≥1 cm with no nodes or missing nodes on pathology review were not given a stage if there was no clinical statement in the medical record regarding nodal involvement.
†From a 2-sample *t* test for continuous variables or from a χ^2 or Fisher exact test for categorized variables. The first *P* value for a given characteristic tests association with treatment group by using only known values of the characteristic. *P* value corresponding to the "missing" rows tests the association of percentage missing for the given characteristic with treatment group.
‡Mean (SD) only applies to those with a known tumor size (n = 170 for estrogen plus progestin and n = 128 for placebo).
§Mean (SD) only applies to those with a known number of lymph nodes examined, including those with zero nodes examined (n = 191 for estrogen plus progestin and n = 143 for placebo).

relationships among mammographic breast density change, mammographic interpretation, and breast cancer risk.

Given the known psychological sequelae and requirement for medical evaluations associated with any abnormal mammography report,[16,17] the substantially increased frequency of women receiving estrogen plus progestin who have abnormal mammograms represents an additional adverse effect of menopausal hormone use. This is an important consideration for women choosing even short-term estrogen plus progestin therapy, because the increase in women with abnormal mammograms was observed within the first year.

The breast cancers among women in the estrogen plus progestin group vs those in the placebo group were diagnosed initially at a slightly lower rate, subsequently at a higher rate, and were at a similar grade but a more advanced stage at the time of diagnosis. This pattern, coupled with the increased frequency of women with abnormal mammograms, suggests the hypothesis that estrogen plus progestin stimulates breast cancer growth and delays breast cancer diagnosis, perhaps mediated through differences in mammographic detection.

Although a longer time to diagnosis could explain some of the increases in tumor size observed in the hormone therapy group, direct effects of estrogen plus progestin on tumor growth cannot be excluded. The pattern of differential breast cancer diagnosis observed over time is also consistent with the delay hypothesis. This problem supports the use of weighted Cox proportional hazards regression model statistics that are not highly sensitive to events early in the follow-up period for comparisons between treatment groups.

Observational studies linking the characteristics of breast cancers associated with menopausal hormone therapy, mostly involving the use of estrogen alone, have given mixed results.[18,19] Overall, most report favorable stage[20-22] and favorable prognostic characteris-

Table 5. Mammographic Findings by Treatment Group and Time From Entry*

	Baseline		Year 1		Year 2		Year 3	
	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo
Mammography performance of women due for visit with mammography in study period, %	100	100	90.3	90.5	88.8	88.0	87.3	86.7
Mammography recommendation								
Negative	4125 (56.4)	4118 (56.5)	3766 (49.2)	4012 (54.9)	3799 (50.7)	3895 (55.0)	3712 (50.6)	3744 (53.9)
Benign finding (negative)	2807 (38.4)	2810 (38.5)	3174 (41.5)	2900 (39.7)	3045 (40.6)	2799 (39.5)	2971 (40.5)	2796 (40.3)
Abnormal (total)	384 (5.2)	363 (5.0)	716 (9.4)†	398 (5.4)	651 (8.7)†	386 (5.5)	650 (8.9)	405 (5.8)
Short interval follow-up suggested	341 (4.7)	324 (4.4)	625 (8.2)	332 (4.5)	564 (7.5)	326 (4.6)	556 (7.6)	347 (5.0)
Suspicious abnormality	43 (0.6)	38 (0.5)	85 (1.1)	59 (0.8)	82 (1.1)	55 (0.8)	86 (1.2)	52 (0.7)
Highly suggestive of malignancy	0 (0)	1 (<0.1)	6 (0.1)	7 (0.1)	5 (0.1)	5 (0.1)	8 (0.1)	6 (0.1)

	Year 4		Year 5		Year 6 and Later		Cumulative‡	
	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo	Estrogen + Progestin	Placebo
Mammography performance of women due for visit with mammography in study period, %	87.0	86.3	87.0	86.7	89.1	89.2	97.3	97.8
Mammography recommendation								
Negative	3397 (48.8)	3471 (52.6)	2358 (47.3)	2366 (51.0)	2094 (51.1)	1834 (54.6)	1359 (16.5)	1631 (20.7)
Benign finding (negative)	2901 (41.7)	2696 (40.9)	2153 (43.2)	2004 (43.2)	1634 (39.9)	1301 (38.7)	4294 (52.0)	4590 (58.1)
Abnormal (total)	661 (9.5)†	432 (6.5)	478 (9.6)†	269 (5.8)	371 (9.1)†	224 (6.7)	2601 (31.5)†	1677 (21.2)
Short interval follow-up suggested	553 (7.9)	364 (5.5)	398 (8.0)	245 (5.3)	303 (7.4)	188 (5.6)	2121 (25.7)	1395 (17.7)
Suspicious abnormality	94 (1.4)	58 (0.9)	71 (1.4)	20 (0.4)	58 (1.4)	33 (1.0)	428 (5.2)	247 (3.1)
Highly suggestive of malignancy	14 (0.2)	10 (0.2)	9 (0.2)	4 (0.1)	10 (0.2)	3 (0.1)	52 (0.6)	35 (0.4)

*Data are No. (%) unless otherwise specified. A total of 100% of estrogen plus progestin participants had mammograms at baseline; because of form changes, participants with version 1 of the mammography form are not displayed in this table.
†$P<.001$ for comparison of frequency of abnormal mammogram (short interval follow-up, suspicious abnormality, highly suggestive of malignancy) in the estrogen plus progestin compared with placebo group.
‡Most severe mammography recommendation category during the entire follow-up period.

tics[23-25] with a predominance of receptor-positive cancers.[21,26] In the WHI randomized trial, breast cancers that occurred among women taking estrogen plus progestin did not have such favorable characteristics. The demonstration of an increased number of more advanced breast cancers without favorable characteristics directly challenges the concept that hormone therapy might simply lead to earlier diagnosis of more favorable cancers. This discrepancy could be related to differential mammography use in women receiving hormones in observational studies, an issue difficult to address directly since retrospectively recalled frequency of mammography has proven relatively unreliable.[27]

Some[28-30] but not all[20] recent observational studies evaluating combined estrogen plus progestin therapy report a striking and, in some cases, almost exclusive increase in invasive lobular breast cancers with little effect on invasive ductal cancers. In the WHI trial, the number of cases in most subtypes is small, but there is no evidence of a differential effect; all major categories of invasive breast cancer were increased in the estrogen plus progestin group, with only a slight excess in the invasive lobular or mixed invasive ductal and lobular carcinoma categories.

The relatively early development of more breast cancers in the estrogen plus progestin group was unexpected because most recent reviews of observational studies suggest that breast cancer risk would be increased mainly with longer term (>5 years) menopausal hormone use.[31-33] This discrepancy could be related to estrogen plus progestin hindering mammographic identification of breast cancers as suggested by the current results. If this is correct, determination of the effect of even short-term estrogen plus progestin use relative to breast cancer risk becomes a vexing clinical problem.

A nonsignificant trend for higher HRs for breast cancer in women randomized to estrogen plus progestin was observed for women reporting prior menopausal hormone use. This observation suggests a role for cumulative exposure. However, this finding could also reflect selection biases and, for this reason, reliable interpretation is precluded. Despite the somewhat increased breast cancer risk for estrogen plus progestin vs placebo use among prior hormone users, prior hormone users were at somewhat lower risk vs never users (Table 2). It is unclear whether this is due to a successful user effect, wherein prior long-term users already demonstrated themselves to be less susceptible to breast cancer, or to other factors such as greater vasomotor symptoms reflecting lower estrogen levels.

The magnitude of the increased breast cancer risk observed with estrogen plus progestin in this clinical trial closely parallels observational study results,[4,5] but the fact that the cancers developed after a shorter than predicted interval suggests an effect on growth of established breast cancers. Evidence from other randomized trials on this question is limited. In the Heart and Estrogen Replacement Study trial, which included women with coronary heart disease, more breast cancers occurred with estrogen plus progestin therapy compared with placebo (34 vs 25 cases, respectively), but the difference was not statistically significant.[34]

The strengths of the WHI study of estrogen plus progestin include the randomized double-blind study design, the large ethnically diverse study population, comprehensive and detailed assessment of a range of breast cancer risk factors at baseline, use of placebo controls, the requirement for baseline and ongoing yearly mammography and clinical breast examination in both study groups, and the central adjudication of the breast cancer end point via pathology report review. The rates of discontinuation of study medications in both study groups are limitations. However, these discontinuation rates are comparable with those observed in other trials of menopausal hormones and are less than observed in current clinical practice.[35] Furthermore, the discontinuation of study hormones in the WHI trial is likely to dilute the estimate of effects of estrogen plus progestin, suggesting that the underlying biological effect may be greater. Finally, the early stopping based on these results provides less precision and may have introduced some anticonservative bias in the HR estimates.

Because vaginal bleeding led to a high prevalence of de facto unblinding, some potential for detection bias exists. The amount of bias, if any, is likely to be small based on several factors. First, the WHI achieved very high compliance with annual mammography, which was nearly identical between study groups throughout follow-up. Furthermore, the readings and response to mammographic findings were managed by the women's own physicians, independent of WHI and with no access to study reports, thereby minimizing the opportunity for reported bleeding to influence these findings. The potential influence of estrogen plus progestin on breast cancer diagnostic decisions and procedures, including sensitivity and specificity of mammograms and clinical breast examinations, represents a complex issue that will be the focus of future analyses.

The WHI evaluated a single drug regimen, conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d), and therefore cannot inform questions regarding risk associated with other oral or topical menopausal hormone therapies. A parallel study of the WHI evaluating conjugated equine estrogens alone compared with placebo for women with prior hysterectomy continues in a blinded fashion with data and safety monitoring board oversight (scheduled to be completed in 2005). Importantly, the data and safety monitoring board indicated on May 31, 2002, that at this time no increase in breast cancer has been observed in the trial of conjugated equine estrogens.

In summary, results from this prospective randomized trial indicate that combined estrogen plus progestin use increases the risk of incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and substantially increases the frequency of abnormal mammograms. In light of these findings, abnormal mammograms in women receiving menopausal hormone therapy deserve heightened scrutiny. The increased frequency of abnormal mammograms requiring medical evaluation and increased breast cancer risk should be added to the already known risks of short-duration menopausal hormone use. Consideration for use of estrogen plus progestin for any duration by postmenopausal women should incorporate the current findings into established[8,36,37] and emerging[38] risks and benefits of these agents.

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