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Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density
The Women's Health Initiative Randomized Trial

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THE WOMEN'S HEALTH INITIA-tive (WHI) trial of estrogen plus progestin was a randomized, controlled, double-blind trial designed to determine the effects of estrogen plus progestin compared with placebo on a number of important chronic diseases of older women.[1] After an average follow-up of 5.2 years, the trial was stopped early because of safety concerns. Hip and clinical vertebral fractures were significantly reduced by 34% and total osteoporotic fractures by 24%. However, the overall risk-benefit profile of estrogen plus progestin, summarized in a global index, was not consis-

tent with a viable intervention for primary prevention of chronic diseases in postmenopausal women.

This article provides an updated final analysis of fracture end points

Context In the Women's Health Initiative trial of estrogen-plus-progestin therapy, women assigned to active treatment had fewer fractures.

Objective To test the hypothesis that the relative risk reduction of estrogen plus progestin on fractures differs according to risk factors for fractures.

Design, Setting, and Participants Randomized controlled trial (September 1993-July 2002) in which 16608 postmenopausal women aged 50 to 79 years with an intact uterus at baseline were recruited at 40 US clinical centers and followed up for an average of 5.6 years.

Intervention Women were randomly assigned to receive conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcome Measures All confirmed osteoporotic fracture events that occurred from enrollment to discontinuation of the trial (July 7, 2002); bone mineral density (BMD), measured in a subset of women (n=1024) at baseline and years 1 and 3; and a global index, developed to summarize the balance of risks and benefits to test whether the risk-benefit profile differed across tertiles of fracture risk.

Results Seven hundred thirty-three women (8.6%) in the estrogen-plus-progestin group and 896 women (11.1%) in the placebo group experienced a fracture (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.69-0.83). The effect did not differ in women stratified by age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, BMD, or summary fracture risk score. Total hip BMD increased 3.7% after 3 years of treatment with estrogen plus progestin compared with 0.14% in the placebo group ($P<.001$). The HR for the global index was similar across tertiles of the fracture risk scale (lowest fracture risk tertile, HR, 1.20; 95% CI, 0.93-1.58; middle tertile, HR, 1.23; 95% CI, 1.04-1.46; highest tertile, HR, 1.03; 95% CI, 0.88-1.24) (P for interaction=.54).

Conclusions This study demonstrates that estrogen plus progestin increases BMD and reduces the risk of fracture in healthy postmenopausal women. The decreased risk of fracture attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture.
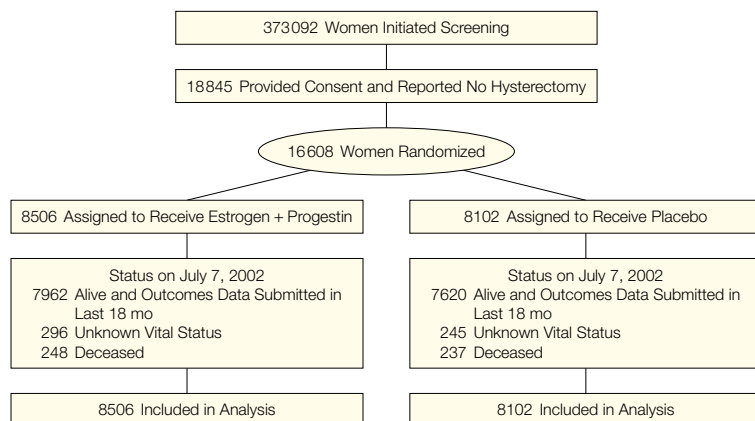
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Figure 1. Flow of Study Participants

through the termination of the trial on July 7, 2002. We also tested the hypothesis that the relative risk reduction of estrogen plus progestin on fracture differed by risk factors for fracture. We report the lumbar spine and total hip bone mineral density (BMD) outcomes for the subset of study participants undergoing this assessment. Finally, we tested the hypothesis that the risk-benefit profile of treatment with estrogen plus progestin differed across tertiles of fracture risk.

METHODS
Overview
Details of the WHI design are reported elsewhere.[1,2] In brief, 16608 postmenopausal women with an intact uterus who were aged 50 to 79 years at baseline were randomized to either conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d, in a single tablet (n=8506) or placebo (n=8102) and followed up for an average of 5.6 years (**FIGURE 1**). Trial recruitment began in September 1993 with the first randomization in December 1993. Follow-up is ongoing, but the intervention was terminated approximately 3 years earlier than planned because of an adverse effect on breast cancer and an excess risk of events as determined by the global index assessment summarizing the balance of risks and benefits.[1] The protocol and consent forms were approved by the institutional review boards of all

participating institutions and all women provided written informed consent.

Risk Factors for Osteoporosis
Information on baseline risk factors for fractures was assessed in a standardized manner by questionnaire, interview, and clinical examination. Weight was measured on a balance beam scale while wearing indoor clothing. Height was measured with a fixed stadiometer. Weight and height were used to calculate body mass index (BMI; weight in kilograms divided by the square of height in meters). Race/ethnicity categorization was based on self-declaration. Information on falls, fracture history, family history of fracture, smoking, alcohol consumption, and general health status was obtained by questionnaire. Dietary calcium intake was assessed using a modification of the Block food frequency questionnaire and expressed in milligrams per day.[3] Information on use of calcium supplements in the previous 2 weeks was obtained by an interviewer-administered medication inventory. Total calcium intake was derived from the sum of dietary and supplemental sources.

Information on medication use at baseline included use of estrogen, progestin, thiazide diuretics, and thyroid medications. Participants were asked to bring all medications, vitamins, and supplements to the clinic for verification of current use. Information on past use of hormone therapy was collected

by questionnaire. Women were excluded if they reported use of tamoxifen. Women using postmenopausal hormones at the initial screening could be enrolled after a 3-month washout period. Information was collected on use of other antiresorptive agents at baseline and follow-up years 1, 3, and 6. If a woman initiated open-label use of hormone therapy or any selective estrogen receptor modulator after randomization, she was required to discontinue study medications.

Outcomes
Reports of hip, vertebral, and other osteoporotic fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae were ascertained by a semiannual questionnaire. If a fracture was reported, radiology reports were obtained. The initial report of the WHI estrogen-plus-progestin trial was based on local adjudication.[1] In this report, hip fractures were centrally adjudicated. The agreement between local and central adjudication for hip fracture was 94%. All other fractures at clinical centers where BMD was not measured were locally adjudicated. All adjudicators were blinded to treatment assignment. Fracture outcomes included hip, wrist/lower arm, clinical vertebral, and total fractures.

In an attempt to summarize important aspects of health benefits vs risk, a global index was created that included the earliest occurrence of coronary heart disease, invasive breast cancer, stroke, pulmonary embolus, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.[1] Compared with total mortality, which may be relatively insensitive, this index summarizes differences in the incidence of the 7 listed diseases as well as other causes of mortality. The global index of these outcomes played a supportive role in trial monitoring as the summary measure of the overall balance of risks and benefits.

Bone Mineral Density
Bone mineral density of the lumbar spine (L2-L4), and total hip was measured by dual x-ray absorptiometry (QDR 2000, 2000+, or 4500W, Hologic Inc, Bed-

ford, Mass) in 3 of the 40 US clinical centers (Pittsburgh, Pa, Birmingham, Ala, and Tucson/Phoenix, Ariz). At these 3 BMD centers, women were excluded if their femoral neck BMD was more than 3 SDs below the corresponding age-specific mean (Z score ≤–3.0). Bone mineral density was measured at baseline and years 1, 3, and 6. Because few women had yet had BMD measured at year 6, our analyses are confined to measurements at baseline plus years 1 and 3. The BMD clinical centers were chosen to provide maximum racial diversity.

Standard protocols for positioning and analysis were used by technologists who were trained and certified by the University of California, San Francisco bone densitometry reading center. The ongoing quality assurance program was similar to that used in other studies.[4]

Statistical Analysis

All primary analyses used time-to-event methods and are based on the intention-to-treat principle. Outcome comparisons are presented as hazard ratios (HRs) and nominal 95% confidence intervals (nCIs) from Cox proportional hazards analyses stratified by age, prior fracture history, and randomization status in the low-fat diet and calcium/vitamin D trials of the WHI. The calcium/vitamin D trial is a randomized clinical trial testing whether calcium and vitamin D supplements decrease the risk of hip fracture. Equal proportions of women in the estrogen-plus-progestin and placebo groups participated in the calcium/vitamin D trial. Nominal 95% CIs are presented throughout except for the hip fracture outcome, which was 1 of 7 outcomes monitored by the data and safety monitoring board. To account for the multiple outcomes, we also present adjusted 95% CIs (aCIs) for hip fracture, as was specified in the trial monitoring plan.

Because a substantial number of women (42% taking estrogen plus progestin and 36% taking placebo) stopped taking their study medications at some point during the follow-up period,[1] we examined the sensitivity of the HR estimates and BMD changes to actual use of study medications. In these analyses, par-

Table 1. Baseline Characteristics by Randomization Assignment*

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value
Age at screening, y			
50-59	2839 (33.4)	2683 (33.1)	
60-69	3853 (45.3)	3657 (45.1)	.80
70-79	1814 (21.3)	1762 (21.8)	
Mean (SD)	63.2 (7.10)	63.3 (7.10)	.39
Years since menopause			
<10	2782 (36.23)	2712 (36.12)	
10-19	3047 (39.68)	2994 (39.87)	.97
≥20	1850 (24.09)	1803 (24.01)	
Race/ethnicity			
White	7140 (83.9)	6805 (84.0)	
Black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.6)	416 (5.1)	.33
American Indian	26 (0.3)	30 (0.4)	
Asian/Pacific Islander	194 (2.3)	169 (2.1)	
Unknown	125 (1.5)	107 (1.3)	
Height, mean (SD), cm	161.5 (6.60)	161.7 (6.50)	.19
Weight, mean (SD), kg	74.5 (16.40)	74.8 (16.80)	.19
Weight <57 kg (127 lb)	1078 (12.7)	993 (12.3)	.42
Body mass index†			
<25	2579 (30.5)	2479 (30.8)	
25 to <30	2992 (35.3)	2834 (35.2)	.89
≥30	2899 (34.2)	2737 (34.0)	
Mean (SD)	28.5 (5.80)	28.5 (5.90)	.66
Total calcium intake, mg/d			
<600	2002 (24.4)	1894 (24.2)	
600-1200	3329 (40.5)	3159 (40.3)	.85
>1200	2882 (35.1)	2783 (35.5)	
Baseline thiazide diuretic use	414 (4.9)	395 (4.9)	.98
Baseline thyroid medication use	875 (10.3)	876 (10.8)	.27
General health			
Fair/poor	530 (6.3)	556 (6.9)	.10
Good/very good/excellent	7927 (93.9)	7493 (93.1)	
Hormone therapy use			
Never	6277 (73.8)	6020 (74.3)	
Past	1671 (19.7)	1588 (19.6)	.47
Current use at baseline	554 (6.5)	491 (6.1)	
Hormone therapy duration of use, y			
<5	1539 (69.0)	1470 (70.6)	
5 to <10	427 (19.2)	356 (17.1)	.22
≥10	263 (11.8)	255 (12.3)	
Smoking			
Never	4178 (49.6)	3999 (50.0)	
Past	3362 (39.9)	3157 (39.5)	.85
Current	880 (10.5)	838 (10.5)	
No. of falls in past 12 mo			
0	5168 (66.2)	5172 (67.5)	
1	1643 (21.0)	1545 (20.2)	.22
≥2	1000 (12.8)	948 (12.4)	
History of fracture	2950 (38.8)	2947 (39.1)	.72
Maternal history of hip fracture after age 40 y	887 (12.4)	873 (12.5)	.84
Parental history of fracture after age 40 y	3182 (40.5)	3012 (40.3)	.80
Total hip BMD, mean (SD), g/cm²‡	0.83 (0.13)	0.84 (0.14)	.77
Total hip BMD T score, mean (SD)‡	–0.94 (0.98)	–0.91 (1.04)	.79

(continued)

Table 1. Baseline Characteristics by Randomization Assignment* (cont)

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value
Spine BMD, mean (SD), g/cm²‡	0.94 (0.16)	0.95 (0.16)	.87
Spine BMD T score, mean (SD)‡	−1.30 (1.39)	−1.26 (1.42)	.87
Summary fracture risk score			
0-2 (Low)	2393 (34.5)	2350 (34.4)	
3-5 (Moderate)	2691 (42.7)	2910 (42.6)	.93
>5 (High)	1575 (22.7)	1571 (23.0)	

Abbreviation: BMD, bone mineral density.
*Data are expressed as No. (%) unless otherwise specified. Denominators for percentages differ because of missing data.
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.
‡Analyzed in a subset of participants in the estrogen-plus-progestin (n = 546) and placebo (n = 478) groups.

ticipants' outcome data were censored 6 months after they became nonadherent (taking <80% of or stopping study drug or initiating nonstudy hormone therapy). The mean follow-up time in the sensitivity analysis was 3.7 years.

The effect modification of fracture risk with estrogen plus progestin by potential risk factors was assessed by Cox proportional hazards analyses with tests of interaction between the risk factor and treatment assignment. Women were divided into groups based on age, race/ethnicity, BMI,[5] history of fracture, past use of hormone therapy, falls in the previous 12 months, parental history of fracture, and total calcium intake. In a subgroup of women with BMD measurements (n=1024), we also examined strata defined by a T score of less than −2.5 at the lumbar spine, total hip, or femoral neck using the National Health and Nutrition Examination Survey reference database for the hip and the manufacturer's database for the spine. The race/ethnicity and BMD stratifications were limited to total fractures. We report nominal P values throughout. In this risk factor analysis, we explored more than 100 subgroups and, by chance alone, at least 5 would be expected to be statistically significant at the P=.05 level.

We developed a summary fracture risk score in the placebo group using methods developed by Black et al.[6] Their index identified 20 fracture risk factors. We did not have hip BMD measurements for all women, nor did we have information on use of arms to stand from a chair, "4 or fewer hours on feet per day," or height at age 25 years. Our summary frac-ture risk score used current height and included race/ethnicity. Variables that were significant (P<.10) in the individual age-adjusted logistic regression hip fracture models were entered into a multivariable model and included age, non-black race/ethnicity, prior fracture after age 55 years, fall in past 12 months, current smoking, BMI of 22.4 or less, and no walking for exercise. Age, prior fracture, current smoking, and BMI were all significant (P<.05) and were included in the final risk factor set. The summary fracture risk score was computed as described by Black et al.[6] Briefly, using the additive properties of the logistic function, the coefficients from the final model were multiplied by a constant, rounded to the nearest integer, multiplied by each individual's risk factor values, and then summed. The area under the receiver operating characteristic curve for the final model was 0.785 (95% CI, 0.73-0.84) for hip fracture, indicating moderate predictive strength.

Absolute differences and percentage changes in BMD of the lumbar spine and total hip from baseline to year 1 and to year 3 were calculated. We used linear regression to compare the rates of change in BMD in women randomized to estrogen plus progestin vs placebo in the entire population with BMD and in medication-adherent women. We adjusted for clinic site and race/ethnicity.

To test whether the risk-benefit profile of estrogen plus progestin differed in women according to their risk of hip fracture, we examined the HR (95% CI) of the global index across tertiles of the summary fracture risk score. All analy-ses were performed using SAS statistical software, version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline characteristics including risk factors for fracture were similar in the 8506 women randomized to estrogen plus progestin and the 8102 women in the placebo group (**TABLE 1**). The mean age of the women was 63 years; 44% were older than 65 years. Examination of risk factors for fractures revealed that 74% had no prior history of hormone use; 10% were current smokers; 39% had a personal history of fracture; 12% reported a maternal history of hip fracture; 33% reported at least 1 fall in the previous 12 months; 14% had experienced at least 1 fracture after age 55 years; and 23% were considered to be at higher risk of fracture based on our summary fracture risk score. Use of a bisphosphonate at baseline was low (approximately 1%) but increased to about 6% among women in the estrogen-plus-progestin group and to 10% among women in the placebo group by year 6. Use of raloxifene and calcitonin was low in each group (<2%) by year 6.

In the subgroup of 1024 women with BMD measurements, there was no difference in baseline BMD by treatment randomization (Table 1). Only 4% of women in the estrogen-plus-progestin group and 6% of women in the placebo group were considered to have osteoporosis at the total hip using World Health Organization criteria.[7]

We compared the characteristics of women in the BMD subsample with the remaining women. As expected, there were larger proportions of nonwhite women and women reporting never using hormones in the BMD subsample. This may have reflected the lower prevalence of hormone use among minority women.[8] Other risk factors for fracture, such as age and body weight, did not differ.

Fractures

A total of 733 women (8.6%) in the estrogen-plus-progestin group and 896 (11.1%) in the placebo group experi-

enced a fracture during the follow-up period of 5.6 years. There were 52 hip fractures in the treatment group and 73 in the placebo group. There were 189 lower arm/wrist fractures in the treatment group and 245 in the placebo group; there were 41 clinical vertebral fractures in the treatment group and 60 in the placebo group. Overall fracture rates per 10 000 person-years in the estrogen-plus-progestin and placebo groups, respectively, were: hip fracture, 11 and 16; wrist/lower arm, 44 and 62; clinical vertebral, 11 and 17; and total fractures, 152 and 199.

Estrogen plus progestin reduced the risk of hip fracture by 33% (HR, 0.67; 95% nCI, 0.47-0.96; 95% aCI, 0.41-1.10) (TABLE 2). In subgroup analyses, estrogen plus progestin decreased the risk of hip fracture by 60% among women who reported a baseline calcium intake of more than 1200 mg/d but not among women with lower calcium intake (P for interaction=.02). Estrogen plus progestin reduced the risk of hip fracture in women with a BMI of less than 25 (HR, 0.50; 95% nCI, 0.28-0.90) and with a BMI of 25 to less than 30 (HR, 0.67; 95% nCI, 0.37-1.20) but not in women with a BMI of 30 or more; however, the interaction of hormone therapy with BMI was not statistically significant (P=.41). The risk of hip fracture was reduced by estrogen plus progestin to a similar degree in women stratified by age, smoking, fall and fracture history, past use of hormone therapy, parental fracture history, years since menopause, and summary fracture risk score.

Hazard ratios for total fractures were also lower for women randomized to estrogen plus progestin in virtually all subgroups examined and did not differ from the overall HR (TABLE 3). There was no significant interaction between treatment assignment and race/ethnicity for total fractures. When participants were stratified by summary fracture risk score, the annualized incidence of total fractures in the placebo group was 1.3%, 2.0%, and 2.7% in the lowest, middle, and highest risk groups, respectively, with similar HRs for total fractures (HR, 0.82; 95% nCI, 0.66-1.02 for the lowest risk

group; HR, 0.68; 95% nCI, 0.58-0.81 for the middle risk group; and HR, 0.85; 95% nCI, 0.70-1.03 for the highest risk group) (Table 3). The HR for all nonspine fractures was 0.75 (95% nCI, 0.68-0.83).

Time Trends

The Kaplan-Meier estimates of cumulative hazards for each type of fracture indicated that the differences between treatment groups began to develop soon after randomization and implementation of the study medication (FIGURE 2). The difference in the cumulative incidence of fractures between women assigned to estrogen plus progestin and those assigned to placebo increased over time. The Kaplan-Meier curves suggest con-

Table 2. Hazard Ratio of Hip Fracture by Randomization Assignment and Stratification*

Outcomes	Estrogen + Progestin, No. (%) (N = 8506)†	Placebo, No. (%) (N = 8102)†	Hazard Ratio (95% Nominal Confidence Interval)	P Value for Interaction
Total population	52 (0.11)	73 (0.16)	0.67 (0.47-0.96)	
Age at screening, y				
50-59	1 (0.01)	5 (0.03)	0.17 (0.02-1.43)	
60-69	19 (0.09)	23 (0.11)	0.76 (0.41-1.39)	.72
70-79	32 (0.33)	45 (0.48)	0.69 (0.44-1.08)	
Years since menopause				
<10	2 (0.01)	2 (0.01)	0.95 (0.13-6.75)	
10-19	17 (0.10)	21 (0.13)	0.80 (0.42-1.53)	.54
≥20	27 (0.27)	44 (0.46)	0.58 (0.36-0.94)	
Body mass index‡				
<25	18 (0.12)	34 (0.24)	0.50 (0.28-0.90)	
25 to <30	19 (0.11)	27 (0.17)	0.67 (0.37-1.20)	.41
≥30	15 (0.09)	12 (0.08)	1.11 (0.52-2.39)	
Smoking				
Current	7 (0.14)	10 (0.21)	0.65 (0.24-1.71)	.76
Never/past	45 (0.11)	59 (0.15)	0.73 (0.49-1.07)	
No. of falls in past 12 mo				
0	30 (0.11)	41 (0.15)	0.73 (0.45-1.16)	
1	11 (0.12)	15 (0.18)	0.73 (0.33-1.60)	.17
≥2	7 (0.12)	16 (0.30)	0.39 (0.16-0.96)	
Total calcium intake at baseline, mg/d				
<600	15 (0.13)	14 (0.13)	0.94 (0.45-1.96)	
600-1200	24 (0.13)	25 (0.14)	0.91 (0.52-1.59)	.02
>1200	13 (0.08)	31 (0.20)	0.40 (0.21-0.76)	
Parental history of fracture				
No	26 (0.10)	40 (0.16)	0.63 (0.38-1.04)	.54
Yes	22 (0.12)	26 (0.15)	0.77 (0.44-1.36)	
History of hormone therapy, y				
Never	45 (0.13)	54 (0.16)	0.79 (0.53-1.18)	
<5	2 (0.02)	15 (0.18)	0.13 (0.03-0.56)	
5 to <10	3 (0.12)	3 (0.15)	0.57 (0.11-2.92)	.57
≥10	2 (0.14)	1 (0.07)	0.13 (0.03-0.56)	
History of fracture				
No	15 (0.06)	28 (0.11)	0.52 (0.28-0.98)	.34
Yes	31 (0.19)	41 (0.26)	0.77 (0.48-1.22)	
Summary fracture risk score				
0-2 (Low)	0	3 (0.02)	Not applicable	
3-5 (Moderate)	15 (0.09)	18 (0.12)	0.81 (0.41-1.61)	.35
>5 (High)	28 (0.34)	40 (0.49)	0.70 (0.43-1.13)	

*All proportional hazards models were stratified by age (50-54, 55-59, 60-69, or 70-79 years), prior hip fracture, diet modification randomization group, and calcium/vitamin D randomization group, except for models by age (not stratified by age) and models by prior fracture (not stratified by prior fracture).
†Data are expressed as number of women with fractures (annualized percentage).
‡Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Table 3. Hazard Ratio of Total Fractures by Randomization Assignment and Stratification*

Outcomes	Estrogen + Progestin, No. (%) (N = 8506)†	Placebo, No. (%) (N = 8102)†	Hazard Ratio (95% Nominal Confidence Interval)	P Value for Interaction
Total population	733 (1.52)	896 (1.99)	0.76 (0.69-0.83)	
Age at screening, y				
50-54	67 (1.05)	90 (1.53)	0.68 (0.49-0.93)	
55-59	124 (1.18)	126 (1.29)	0.91 (0.71-1.16)	
60-64	168 (1.53)	184 (1.85)	0.80 (0.65-0.98)	.47
65-69	161 (1.53)	238 (2.35)	0.68 (0.49-0.93)	
70-74	142 (2.11)	174 (2.61)	0.81 (0.65-1.01)	
75-79	71 (2.38)	84 (3.09)	0.73 (0.53-1.00)	
Years since menopause				
<10	187 (1.17)	221 (1.44)	0.80 (0.66-0.98)	
10-19	255 (1.55)	327 (2.03)	0.75 (0.64-0.89)	.95
≥20	200 (2.03)	257 (2.69)	0.74 (0.61-0.89)	
Body mass index‡				
<25	237 (1.62)	312 (2.25)	0.71 (0.60-0.84)	
25 to <30	245 (1.44)	308 (1.94)	0.75 (0.63-0.89)	.18
≥30	246 (1.51)	270 (1.79)	0.82 (0.69-0.97)	
Smoking				
Current	71 (1.45)	84 (1.80)	0.79 (0.57-1.08)	.77
Never/past	656 (1.54)	795 (2.00)	0.76 (0.69-0.84)	
Falls in past 12 mo				
0	392 (1.40)	519 (1.85)	0.74 (0.65-0.85)	
1	145 (1.59)	169 (1.99)	0.82 (0.65-1.02)	.84
≥2	115 (2.05)	139 (2.65)	0.76 (0.59-0.97)	
Total calcium intake at baseline, mg/d				
<600	171 (1.50)	204 (1.93)	0.78 (0.64-0.96)	
600-1200	293 (1.56)	359 (2.02)	0.76 (0.65-0.89)	.81
≥1200	249 (1.53)	304 (1.98)	0.76 (0.64-0.89)	
Parental history of fracture				
No	356 (1.35)	465 (1.87)	0.71 (0.62-0.82)	.28
Yes	320 (1.77)	368 (2.19)	0.80 (0.69-0.93)	
History of hormone therapy, y				
Never	555 (1.57)	678 (2.03)	0.76 (0.68-0.85)	
<5	109 (1.23)	149 (1.79)	0.70 (0.55-0.90)	.39
5 to <10	42 (1.72)	37 (1.88)	0.80 (0.51-1.26)	
≥10	27 (1.89)	32 (2.30)	0.70 (0.55-0.90)	
Race/ethnicity				
White	673 (1.66)	823 (2.16)	0.76 (0.69-0.84)	
Black	21 (0.68)	36 (1.15)	0.58 (0.34-1.00)	
Hispanic	18 (0.71)	17 (0.76)	0.79 (0.40-1.56)	.77
American Indian	1 (0.69)	2 (1.28)	Not applicable	
Asian/Pacific Islander	10 (0.97)	10 (1.12)	0.71 (0.28-1.79)	
Unknown	10 (1.50)	8 (1.43)	1.25 (0.47-3.35)	
History of fracture				
No	298 (1.18)	391 (1.57)	0.74 (0.63-0.86)	.59
Yes	330 (2.07)	417 (2.62)	0.78 (0.68-0.91)	
Baseline BMD T score >2.5 SD below young normal§				
No	44 (1.69)	43 (1.90)	0.87 (0.57-1.34)	.15
Yes	11 (1.44)	22 (3.16)	0.53 (0.25-1.10)	
Summary fracture risk score				
0-2 (Low)	149 (1.10)	175 (1.33)	0.82 (0.66-1.02)	
3-5 (Moderate)	224 (1.41)	312 (1.99)	0.68 (0.58-0.81)	.65
>5 (High)	191 (2.33)	223 (2.71)	0.85 (0.70-1.03)	

*All proportional hazards models were stratified by age (50-54, 55-59, 60-69, or 70-79 years), any prior fracture, diet modification trial randomization group, and calcium/vitamin D trial randomization group except models by age (not stratified by age) and models by prior fracture (not stratified by prior fracture).
†Data are expressed as number of women with fractures (annualized percentage).
‡Body mass index was calculated as weight in kilograms divided by the square of height in meters.
§Bone mineral density (BMD) from total hip, femoral neck, or spine (L2-L4); n = 1024.

tinuing beneficial effects of estrogen plus progestin on fracture reduction throughout the observation period.

Sensitivity Analysis

Exclusion of follow-up time for nonadherence had little effect on the HRs (hip fracture, HR, 0.63; 95% nCI, 0.38-1.06; wrist/lower arm, HR, 0.67; 95% nCI, 0.54-0.84; vertebral fracture, HR, 0.60; 95% nCI, 0.38-0.95; total fractures, HR, 0.72; 95% nCI, 0.64-0.81).

Bone Mineral Density

Estrogen plus progestin showed consistent positive effects on BMD. Total hip BMD increased a mean of 1.7% during the first year of estrogen-plus-progestin treatment and improved by 3.7% by year 3 compared with a loss of 0.44% at year 1 and a 0.14% improvement at year 3 in the placebo group (P<.001) (FIGURE 3A). Similar findings were observed at the lumbar spine (Figure 3B). After 1 year of hormone therapy, the mean percentage change in BMD was 3.3% higher at the lumbar spine and 2.1% higher at the total hip. After 3 years of treatment, the percentage difference in favor of hormone therapy was greater, with mean differences of 4.5% and 3.6% at the lumbar spine and total hip, respectively. A total of 194 (36%) women in the estrogen-plus-progestin group and 249 (32%) in the placebo group had a year 6 BMD measurement. By year 6, the percentage increase in lumbar spine BMD was 7.5% in women in the estrogen-plus-progestin group compared with 2.6% in the placebo group. Sensitivity analyses limited to adherent women revealed larger increases in BMD; the average percentage increase in BMD from baseline to year 3 was 7.6% in the lumbar spine and 4.5% in the total hip among women randomized to estrogen plus progestin compared with 1.5% and –0.3%, respectively, among women randomized to placebo.

Global Index

Among women in the lowest tertile of fracture risk based on our summary fracture risk score, the global index HR

was 1.20 (95% nCI, 0.93-1.58); in the middle tertile of risk, the HR was 1.23 (95% nCI, 1.04-1.46); and in the highest tertile of risk, the HR was 1.03 (95% nCI, 0.88-1.24). The interaction between treatment effect and summary fracture risk on the global index was not significant (P=.54). Thus, there was no evidence of a net benefit, even in women at high risk of fracture.

COMMENT

The WHI estrogen-plus-progestin trial is the first randomized clinical trial demonstrating that combination postmenopausal hormone therapy reduces the risk of fractures at the hip, vertebrae, and wrist. These findings are consistent with observational data[9,10] and several recent meta-analyses of the efficacy of hormone therapy in reducing of fractures in postmenopausal women.[11-13] Torgersen and Bell-Syer[12] reported a greater effect among women younger than 60 years with little or no benefit observed among older women. However, this conclusion was primarily based on one study in each age group.[14] In the WHI, we found no evidence that the effect differed by age or time since menopause.

Figure 2. Kaplan-Meier Estimates of Cumulative Hazards for Fracture
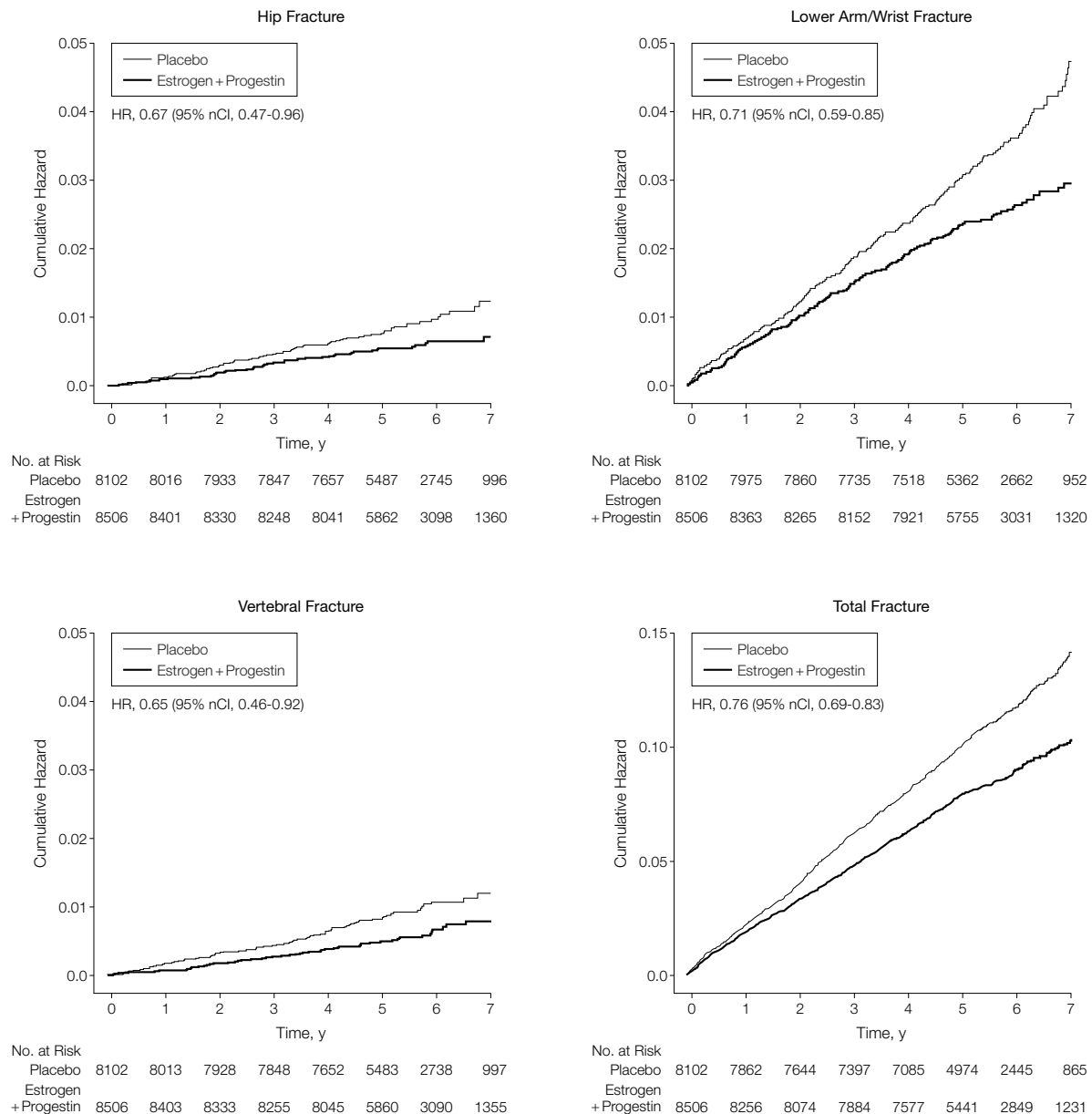
HR indicates hazard ratio; nCI, nominal confidence interval.

Figure 3. Mean Percentage Change in Total Hip and Spine BMD During 3 Years of Follow-up
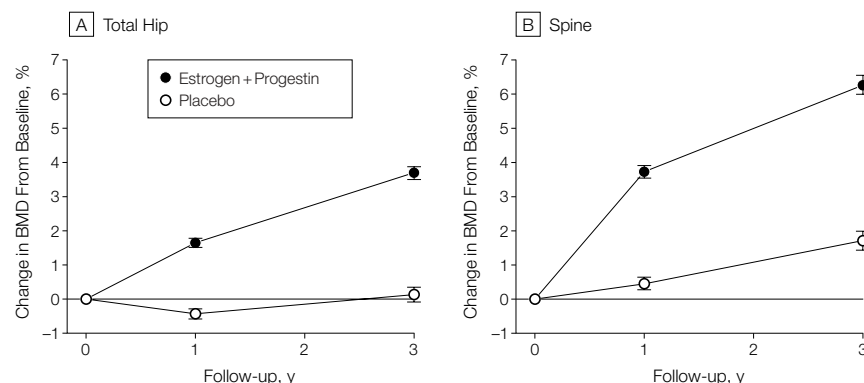
BMD indicates bone mineral density. Error bars indicate SEs.

The overall benefit vs risk of estrogen-plus-progestin therapy is a central focus of the WHI. Overall, the global index showed a nominally significant 15% increase in the estrogen-plus-progestin group, indicating more harm than benefit in women randomized to hormone therapy.[1] Since estrogen plus progestin has shown a beneficial effect on fracture incidence, there is interest in determining whether there might be a subgroup of women at high risk of fracture for whom the benefits from estrogen plus progestin would outweigh the risks. In the analyses described here, we found no evidence that the efficacy of estrogen plus progestin differed according to any risk factors for fractures, including age, BMI, smoking, history of falls, calcium intake, personal and family history of fracture, and past use of hormones. Risk factors for fracture were combined in a summary fracture risk score, and we found that estrogen plus progestin reduced fractures to a similar degree in women who were considered at low, medium, and high risk of fracture. Even among women who were considered at high risk of fracture, the HR for the global index did not indicate net benefit. These results imply that the benefit of fracture reduction does not outweigh the risks of cardiovascular disease and breast cancer, even in women at higher risk of fracture. In addition, the fracture risk score gives substantial weight to increasing age, and another analysis of WHI data found a 2-fold increase in dementia among women aged 65 years or older who were randomized to estrogen plus progestin vs those randomized to placebo.[15]

The WHI is the first randomized controlled trial to include a large group of nonwhite women. Among black women, estrogen plus progestin reduced the risk of total fractures by 42%; however, this outcome did not achieve statistical significance because of the small number of fractures in this subgroup of women. Nevertheless, there was no evidence of an interaction between treatment and race/ethnicity.

Treatment with estrogen plus progestin resulted in consistent positive effects on BMD in the lumbar spine and total hip. Similar to other antiresorptive therapies, the increase in BMD was greatest in the lumbar spine, a site that contains a large proportion of trabecular bone. The differences in BMD that we observed between the estrogen-plus-progestin group and the placebo group were consistent with results from a recent meta-analysis of hormone therapy for prevention and treatment of osteoporosis in postmenopausal women.[11]

Unlike in other randomized trials of osteoporosis treatments, women enrolled in the WHI were, for the most part, healthy. Hip fracture rates were about 50% lower than expected for a similar age-matched cohort.[16] Although BMD measurements were confined to a small sample of the enrollees, a relatively small proportion of women in the WHI had osteoporosis at the baseline assessment. Hence, the study results are likely to be applicable to healthy postmenopausal women. The bisphosphonate trials showed a reduction in risk of hip and nonspine fractures in women with osteoporosis but not in women without osteoporosis.[17-20] It may be that treatment with estrogen plus progestin reduces fractures in women without osteoporosis through a reduction in falls and improvement in muscle strength, although the evidence for this is sparse and conflicting.[21-23] Other trials that have examined fracture reduction in participants without osteoporosis are limited by the small number of participants, and the failure to observe a treatment effect may be a consequence of inadequate statistical power to detect an effect.

In the Heart and Estrogen/Progestin Replacement Study (HERS), there was no effect of estrogen-progestin therapy on clinical fractures.[24,25] Indeed, continued open-label follow-up of the women in HERS reported a *higher* rate of hip fracture among women originally randomized to estrogen plus progestin.[26] The lack of observed benefit on fractures in HERS was interpreted as being consistent with the lack of benefit observed with other agents in women without osteoporosis.[19,20] It is not apparent why the WHI and HERS findings differ because both trials enrolled women without osteoporosis. The women in HERS were, on average, slightly older and all had coronary heart disease and reported a higher prevalence of medications such as nitrates[27] and statins[28] that may influence bone. Finally, the sample size of WHI was much larger than that of HERS, which may have provided the necessary power to detect a treatment effect.

Strengths of the WHI include its randomized design, large sample size of ethnically diverse postmenopausal women across a wide age range, complete follow-up for outcomes on 93% of the women randomized, and confirmation of all fractures by medical record. There

are, however, a number of limitations. Only one estrogen-progestin formulation was tested, although it was the most commonly prescribed postmenopausal hormone therapy regimen in the United States at the time the study was designed. Furthermore, no prior trials have demonstrated differential effects by type of estrogen or for unopposed or combination therapy on BMD.[11] The WHI estrogen-only trial is ongoing, with completion anticipated in 2005. Fractures are also secondary end points of that randomized trial.

A number of screening tools have been developed to identify women with osteoporosis. For the most part, these tools have only poor to moderate specificity and have not been validated in populations other than the ones for which they were created.[29] We developed a summary fracture risk score using risk factors for hip fracture similar to the method developed by Black et al.[6] While this score correlated with the risk of fracture, the ratio of highest to lowest risk was modest (2.0). Bone mineral density and prevalent vertebral fractures are stronger predictors of future fracture,[29,30] but we did not collect these data for all women in the trial; hence, we were unable to identify a group of women with severe osteoporosis in whom the benefits of estrogen plus progestin might exceed the risks.

We tested for interactions of estrogen plus progestin with a number of risk factors for fracture; none were significant. However, differential benefit could occur in the absence of significant interactions if the baseline risk of fracture is different in the various subgroups. For example, the absolute risk of fracture was 2-fold higher in the high-risk fracture group compared with the low-risk group. Hence, even if the HRs did not differ in the 2 groups, the absolute number of fractures prevented would be greater in the high-risk group.

The WHI enrolled a large group of ethnically diverse women, but we had limited power to test for an interaction between treatment and race/ethnicity. We had a relatively high rate of discontinuation of study drug in the active treat-ment group, but sensitivity analyses limited to adherent women yielded similar results. Assessment of vertebral fractures was limited to clinically symptomatic fractures, which represent only about one third of all vertebral fractures.[31] Finally, the global index was designed to focus on potentially life-threatening events and therefore included hip fractures, which have been shown to have significant morbidity[32] and mortality,[33] but not other fractures, such as vertebral fractures. Vertebral fractures have also been associated with an increased risk of mortality[34] and disability.[35] In a separate analysis, the overall balance of risks and benefits of hormone therapy on quality of life did not show a clinically significant benefit.[36]

In conclusion, estrogen plus progestin increases BMD and reduces the risk of fracture in healthy postmenopausal women and appears to do so regardless of presence or absence of risk factors. When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit in this study, even in women considered to be at high risk of fracture. Given the overall unfavorable risk-benefit ratio and the availability of other agents for prevention and treatment of osteoporosis, treatment with estrogen plus progestin should not be recommended for prevention or for treatment of osteoporosis in women without vasomotor symptoms. Before the combination of estrogen and progestin is considered for the purpose of fracture prevention, women should be fully informed of the potential adverse effects.

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