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Calcium plus Vitamin D Supplementation and the Risk of Fractures

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ABSTRACT

BACKGROUND

The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal.

METHODS

We recruited 36,282 postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. We randomly assigned participants to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D_3 daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers.

RESULTS

Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group ($P<0.01$). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels.

CONCLUSIONS

Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones. (ClinicalTrials.gov number, NCT00000611.)

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Osteoporosis, a major cause of injury, loss of independence, and death,[1,2] contributes to more than 300,000 hip fractures in the United States annually.[3] Observational evidence[4] and data from randomized clinical trials[5,6] suggest that calcium or vitamin D supplements or both may slow bone loss[5,6] and reduce the risk of falls[7,8] in postmenopausal and elderly women. However, evidence from trials,[5,9-19] observational studies,[20,21] and meta-analyses[6,22,23] of calcium and vitamin D supplementation with respect to hip and other fractures is limited. In two recent randomized trials, calcium plus vitamin D supplements (1000 mg of calcium and 800 IU of vitamin D_3) did not reduce the risk of nonvertebral fractures among older women.[18,19] When the calcium plus vitamin D trial of the Women's Health Initiative (WHI) was designed, in the early 1990s, guidelines recommended daily intakes of 800 to 1200 mg of calcium with 400 IU of vitamin D for the prevention of osteoporosis. Many American women consumed less.

In this context, the WHI calcium with vitamin D trial was designed to test the primary hypothesis that postmenopausal women randomly assigned to calcium plus vitamin D supplementation would have a lower risk of hip fracture and, secondarily, of all fractures than women assigned to placebo.[24] Another secondary hypothesis was that women receiving calcium with vitamin D supplementation would have a lower rate of colorectal cancer than those receiving placebo; the results of that investigation are reported elsewhere in this issue of the *Journal*.[25]

METHODS

PARTICIPANTS AND STUDY DESIGN

Participants enrolled in the WHI Dietary Modification trial, WHI Hormone Therapy trials, or both were invited to join the calcium with vitamin D trial at their first or second annual follow-up visit. Detailed descriptions of the eligibility criteria and recruitment methods have been published previously.[24]

Eligible women were 50 to 79 years of age at the initial screening and had no evidence of a medical condition associated with a predicted survival of less than three years and no safety, adherence, or retention risks. Exclusion criteria included hypercalcemia, renal calculi, corticosteroid use, and calcitriol use. Personal supplemental calcium (up to 1000 mg per day) and vitamin D (up to 600 IU per day) were allowed. In 1999, after the publication of reports from the Institute of Medicine,[26,27] the upper limit of personal vitamin D intake was raised to 1000 IU. The calcium with vitamin D trial permitted the use of bisphosphonates and calcitonin. Use of estrogen (with or without a progestin) was according to randomization among women in the Hormone Therapy trials. Independent use of hormone therapy or selective estrogen-receptor modulators was permitted for women in the Dietary Modification trial.

Eligible women were randomly assigned in a double-blind fashion to receive supplements or placebo (provided by GlaxoSmithKline) in equal proportions with use of a permuted-block algorithm stratified according to clinical center and age. Active tablets, chewable or swallowable (after July 1997), contained 500 mg of elemental calcium (as calcium carbonate) and 200 IU of vitamin D_3. Participants were instructed to take two tablets per day in divided doses and with meals to maximize absorption. Cross-sectional comparison of 25-hydroxyvitamin D levels from 227 women taking active supplements and 221 women taking placebo two years after randomization revealed that the 25-hydroxyvitamin D level was 28 percent higher among the women assigned to active calcium plus vitamin D than among those assigned to placebo.

The protocol was approved by the institutional review board at each participating institution. Written informed consent was obtained from each woman at the calcium with vitamin D randomization visit. The WHI Investigators and National Institutes of Health sponsors all contributed to the design and execution of the study. All the authors contributed to drafts or revisions of the manuscript. Statistical analyses and data management were conducted at the WHI Clinical Coordinating Center, and the investigators and statistical team vouch for the completeness and veracity of the data and statistical analyses.

FOLLOW-UP AND DATA COLLECTION

The presence and severity of symptoms, safety concerns, and outcomes were ascertained at annual clinic visits and telephone or clinic visits at intervening six-month intervals.[24] Adherence to the study medication was established by weighing returned pill bottles during clinic visits. Par-

ticipants were followed for major outcomes, regardless of their adherence to the study medication, until death, loss to follow-up, or study close-out. Risk factors for fracture were assessed by questionnaire, interview, and clinical examination. The total daily calcium intake before randomization was defined as the sum of the following: the dietary calcium intake (assessed with the use of a modification of the Block food-frequency questionnaire[28]), the intake of calcium from supplements in the previous two weeks, and the intake of calcium from prescription medications (assessed through an interviewer-administered medication survey). Total vitamin D intake was similarly determined on the basis of diet and supplement use.

DISCONTINUATION OF STUDY MEDICATIONS

During the trial, intolerable gastrointestinal symptoms were managed without unblinding by reducing the number of times per day or days per week that the study medication was taken. If renal calculi or hypercalcemia developed or renal dialysis was required, calcium with vitamin D study medication was permanently discontinued, according to the protocol.

ASCERTAINMENT OF OUTCOMES

Total fractures were defined as all reported clinical fractures other than those of the ribs, sternum, skull or face, fingers, toes, and cervical vertebrae. All included fractures were verified by review of radiologic, magnetic resonance imaging, or operative reports by centrally trained and blinded physician adjudicators at each clinical center.[24] Final adjudication of hip fractures was performed centrally by blinded adjudicators; agreement between central and local adjudication was 94 percent.

A subgroup of 2431 women (1230 in the calcium with vitamin D group and 1201 in the placebo group) at 3 of the 40 clinical centers (Pittsburgh; Birmingham, Ala.; and Tucson, Ariz.) underwent dual-energy x-ray absorptiometry of the lumbar spine (L2, L3, and L4), total hip, and total body (QDR 2000, QDR 2000+, or QDR 4500W; Hologic). Bone mineral density was measured at the calcium with vitamin D randomization visit and at annual visits 3, 6, and 9 according to standard protocols.[24] Three Hologic phantoms (spine, hip, and linearity) were exchanged among these three centers and measured in array mode five times, once each day for five consecutive days, to assess cross-calibration. Spine, hip, and linearity phantoms were in close agreement (interscanner variability, <1.5 percent for the spine, 4.8 percent for the hip, and 1.7 percent for linearity).

ANALYSIS OF VITAMIN D LEVELS

Blood specimens, which were obtained after an overnight fast, were collected at the randomization visit. To determine whether the effect of calcium plus vitamin D on the risk of fracture varied according to prerandomization 25-hydroxyvitamin D levels, a nested case–control study was performed with all adjudicated cases of hip, spine, and lower arm or wrist fracture used as cases (357 case–control pairs for hip fracture and 1491 pairs for total fracture). Controls were free of fracture for the duration of the study and were individually matched to case participants according to age, latitude of the clinical center, race or ethnic group, and date of venipuncture. Levels of 25-hydroxyvitamin D were measured with the use of the DiaSorin Liaison chemiluminescent immunoassay system at DiaSorin headquarters (Stillwater, Minn.) in one continuous batch with blinded control runs at periodic intervals (coefficient of variation, 11.8 percent).

STATISTICAL ANALYSIS

All primary outcomes were analyzed on a time-to-event basis according to the intention-to-treat principle. We present both the total number of events and the annualized percentage for these fracture rates for each group. Comparisons are represented with hazard ratios and nominal 95 percent confidence intervals from Cox proportional-hazards models, stratified according to age group, prior fracture, and randomization status (randomly assigned to active hormone therapy or placebo, dietary intervention vs. dietary control, or both) in the Hormone Therapy and Dietary Modification trials.

To assess whether the effect of calcium with vitamin D on the risk of fracture varied according to baseline levels of risk factors, the same Cox proportional-hazards models were extended. In formal tests for interaction, continuous variables were used whenever possible. Fifteen participant characteristics were examined for each of four fracture outcomes. Up to three statistically significant interaction tests ($P<0.05$) would be expected on the basis of chance alone.

To examine the effect of nonadherence (to ac-

Table 1. Characteristics of the Participants in the Calcium with Vitamin D Trial at the Time of the WHI Screening, According to Randomly Assigned Group.*

Characteristic	Calcium + Vitamin D (N = 18,176)	Placebo (N = 18,106)
Age at screening		
Mean — yr	62.4±7.0	62.4±6.9
50 to 59 yr — no. (%)	6,728 (37.0)	6,694 (37.0)
60 to 69 yr — no. (%)	8,275 (45.5)	8,245 (45.5)
70 to 79 yr — no. (%)	3,173 (17.5)	3,167 (17.5)
Race or ethnic group — no. (%)†		
White	15,047 (82.8)	15,106 (83.4)
Black	1,682 (9.3)	1,635 (9.0)
Hispanic	789 (4.3)	718 (4.0)
American Indian or Native American	77 (0.4)	72 (0.4)
Asian or Pacific Islander	369 (2.0)	353 (1.9)
Unknown or not identified	212 (1.2)	222 (1.2)
Family history of fracture after 40 yr of age — no. (%)	6,835 (37.6)	6,692 (37.0)
History of fracture — no. (%)		
At any age	6,311 (34.7)	6,228 (34.4)
At age ≥55 yr	1,948 (10.7)	1,968 (10.9)
No. of falls in previous 12 mo — no. (%)		
None	11,193 (61.6)	11,200 (61.9)
1	3,421 (18.8)	3,386 (18.7)
2	1,462 (8.0)	1,426 (7.9)
≥3	732 (4.0)	701 (3.9)
Weight <58 kg — no. (%)	1,660 (9.1)	1,676 (9.3)
Body-mass index		
Mean	29.1±5.9	29.0±5.9
<25 — no. (%)	4,745 (26.1)	4,833 (26.7)
25 to <30 — no. (%)	6,472 (35.6)	6,483 (35.8)
≥30 — no. (%)	6,867 (37.8)	6,695 (37.0)
Physical activity		
Mean — MET/wk	10.7±12.7	10.6±12.4
0 to 3.00 MET/wk — no. (%)	5,517 (30.4)	5,478 (30.3)
>3.00 to <11.75 MET/wk — no. (%)	5,463 (30.1)	5,477 (30.2)
≥11.75 MET/wk — no. (%)	5,566 (30.6)	5,493 (30.3)
Calcium supplementation ≥500 mg/day — no. (%)	5,192 (28.6)	5,313 (29.3)
Total calcium intake (supplements, diet, and medications)		
Mean — mg/day	1148±654	1154±658
<800 mg/day — no. (%)	6,104 (33.6)	6,003 (33.2)
800 to <1200 mg/day — no. (%)	4,715 (25.9)	4,655 (25.7)
≥1200 mg/day — no. (%)	7,002 (38.5)	7,095 (39.2)
Total vitamin D intake (supplements and diet)		
Mean — IU/day	365±265	368±266
<200 IU/day	6,827 (37.6)	6,671 (36.8)
200 to <400 IU/day	3,379 (18.6)	3,423 (18.9)
400 to <600 IU/day	4,188 (23.0)	4,295 (23.7)
≥600 IU/day	3,427 (18.9)	3,364 (18.6)

Table 1. (Continued.)

Characteristic	Calcium + Vitamin D (N = 18,176)	Placebo (N = 18,106)
Solar irradiance of region‡		
Mean	382±60	382±60
300 to 325 Langleys	5,366 (29.5)	5,351 (29.6)
350 Langleys	3,920 (21.6)	3,880 (21.4)
375 to 380 Langleys	2,012 (11.1)	2,009 (11.1)
400 to 430 Langleys	3,018 (16.6)	3,015 (16.7)
475 to 500 Langleys	3,860 (21.2)	3,851 (21.3)
Alcohol use — no. (%)		
None	1,863 (10.2)	1,891 (10.4)
Use in the past	3,192 (17.6)	3,209 (17.7)
<1 drink/mo	2,529 (13.9)	2,520 (13.9)
<1 drink/wk	3,863 (21.3)	3,758 (20.8)
1 to <7 drinks/wk	4,683 (25.8)	4,706 (26.0)
≥7 drinks/wk	1,910 (10.5)	1,900 (10.5)
Smoking — no. (%)		
Never	9,325 (51.3)	9,428 (52.1)
Past	7,255 (39.9)	7,133 (39.4)
Current	1,405 (7.7)	1,356 (7.5)
Enrollment in Dietary Modification trial — no. (%)		
Not enrolled	5,582 (30.7)	5,490 (30.3)
Assigned to intervention	4,767 (26.2)	4,878 (26.9)
Assigned to control	7,827 (43.1)	7,738 (42.7)
Enrollment in Hormone Therapy trial — no. (%)		
Not enrolled	10,122 (55.7)	10,071 (55.6)
Assigned to active hormone therapy	4,039 (22.2)	4,078 (22.5)
Assigned to placebo	4,015 (22.1)	3,957 (21.9)
Use of hormone therapy — no. (%)§		
Never	5,814 (32.0)	5,690 (31.4)
Past	3,004 (16.5)	2,932 (16.2)
Current	9,358 (51.5)	9,484 (52.4)
Hip BMD at annual visit 1 — total no.¶	1,230	1,201
Mean	0.87±0.14	0.86±0.14
Hip T score at annual visit 1 — total no.¶	1,230	1,201
Mean	–0.65±1.03	–0.77±1.05
T score above –1.0	757 (61.5)	694 (57.8)
T score below –1.0 and above –2.5	436 (35.4)	459 (38.2)
T score below –2.5	37 (3.0)	48 (4.0)

* Plus–minus values are means ±SD. Because of rounding or missing data, not all percentages total 100. MET denotes metabolic equivalent, and BMD bone mineral density.
† Race or ethnic group was self-reported.
‡ The Langley is a unit of solar radiance and relates to the amount that reaches a given area of the earth's surface. The information is from national weather data on total solar irradiance in the United States and is adapted from Garland and Garland.[30]
§ Values reflect hormone-therapy use during year 1 of the clinical trial, including exposure in the Hormone Therapy trials.
¶ The data are from the subgroup of women in whom bone mineral density was measured. The T score represents the bone mineral density of an individual subject as compared with the mean (±SD) score in a young, healthy population.

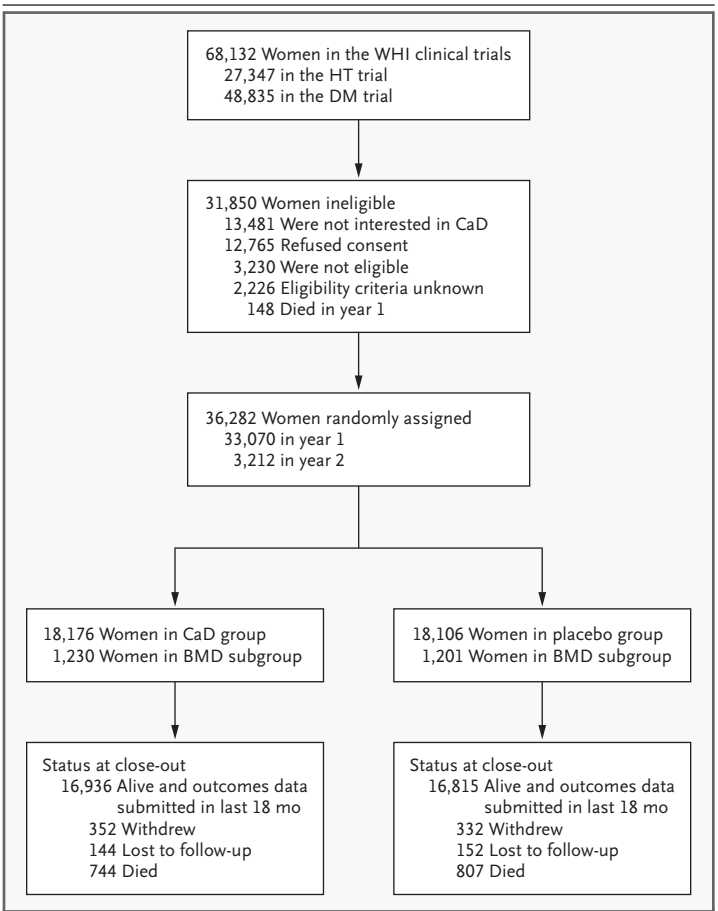

Figure 1. Profile of the Calcium with Vitamin D Trial of the Women's Health Initiative (WHI).

HT denotes hormone therapy, DM dietary modification, CaD calcium with vitamin D, and BMD bone mineral density.

tive supplements or placebo), sensitivity analyses were conducted in which participants were allowed to contribute follow-up time until six months after the first visit at which nonadherence, defined as use of less than 80 percent of the study medication, was detected. Full-adherence hazard ratios were also estimated with inverse probability of censoring weighted estimators with adjustment for 10 covariates associated with adherence.[29]

Changes in bone mineral density during follow-up were calculated as mean percent differences (and standard errors) from bone mineral density at the time of enrollment in the calcium plus vitamin D trial. Linear regression was used to compare rates of change in bone mineral density between the groups, after adjustment for clinical center and race or ethnic group.

The calcium with vitamin D trial was designed to have 85 percent power to detect an intervention effect of 18 percent for hip fracture, assuming a sample size of 35,000 women and an annual hip-fracture rate in the placebo group of 33.6 per 10,000 persons per year. The power to detect an intervention effect of similar magnitude for total fracture was greater than 99 percent.

RESULTS

BASELINE CHARACTERISTICS

Between 1995 and 2000, 36,282 women were randomly assigned in the calcium with vitamin D trial: 18,176 were assigned to active supplementation, and 18,106 to placebo. Demographic characteristics, health behavior, and medical history were well balanced between the groups at baseline (Table 1). The women had a mean age of 62 years and a mean body-mass index (the weight in kilograms divided by the square of the height in meters) of 29. Sixteen percent were not white. The average calcium intake was approximately 1150 mg per day. More than half the women (52 percent) were taking hormone therapy (10,725 reported personal use of hormones, and 8117 had been randomly assigned to receive active-hormone study medication). The rate of use of other osteoporosis medications was 1 percent (1 used a selective estrogen-receptor modulator, 366 bisphosphonate, and 33 calcitonin).

RETENTION AND ADHERENCE

At the termination of the trial, on March 31, 2005, 1551 participants (4.3 percent) had died and 2.7 percent had withdrawn or had been lost to follow-up (Fig. 1). The rate of adherence (defined as use of 80 percent or more of the assigned study medication) ranged from 60 to 63 percent during the first three years of follow-up, with an additional 13 to 21 percent of the participants taking at least half of their study pills. At the end of the trial, 76 percent were still taking the study medication, and 59 percent were taking 80 percent or more of it.

BONE MINERAL DENSITY

Women receiving calcium with vitamin D supplements had greater preservation of total-hip bone mineral density at annual visits 3, 6, and 9 than women assigned to placebo (Fig. 2). The mean differences between the treatment groups, all in favor of calcium with vitamin D, were 0.59 per-

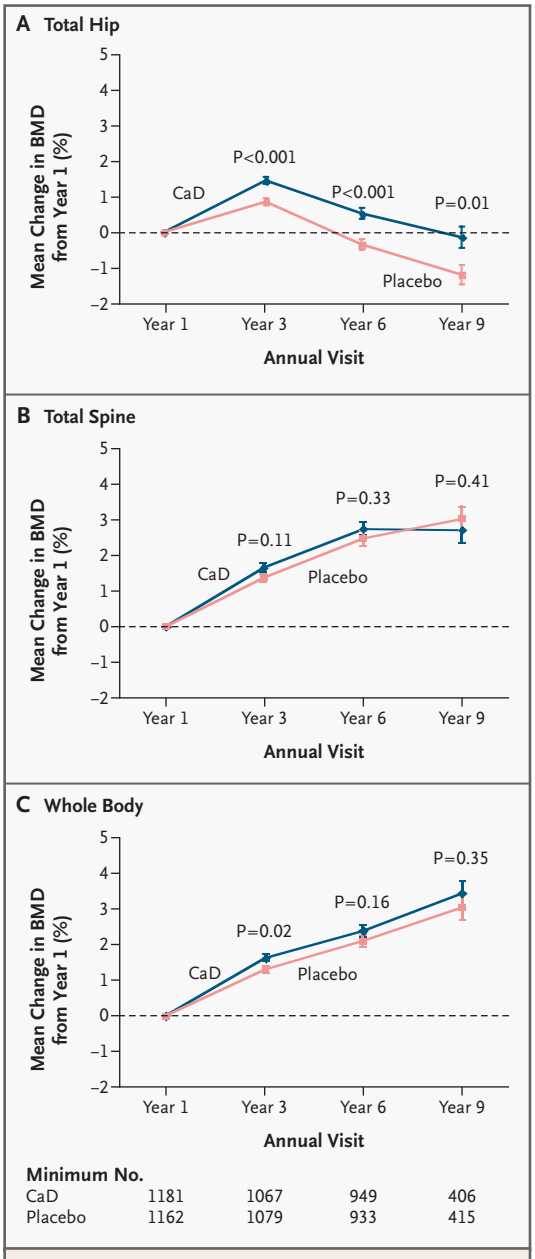

Figure 2. Hip, Spine, and Total-Body Bone Mineral Density (BMD).

P values for the comparison between the group assigned to calcium with vitamin D supplementation and the placebo group were <0.001, <0.001, and 0.01 at years 3, 6, and 9, respectively, for total-hip values and 0.02 at year 3 for whole-body values, according to linear models adjusted for clinical center and race or ethnic group. The numbers of participants shown below the graphs are the minimum sample sizes for comparison between the visit year and year 1.

cent at annual visit 3, 0.86 percent at annual visit 6, and 1.06 percent at annual visit 9. Nonsignificant differences favoring the calcium with vitamin D group were observed in spine and whole-body bone mineral density.

HIP AND OTHER FRACTURES

During a mean of 7.0 years of follow-up, there were 2102 fractures (including 175 hip fractures) among women assigned to calcium with vitamin D and 2158 fractures (including 199 hip fractures) among women assigned to placebo (Table 2). Annualized fracture rates per 10,000 person-years in the calcium with vitamin D and placebo groups, respectively, were as follows: hip fracture, 14 and 16; fracture of the lower arm or wrist, 44 and 44; clinical vertebral fracture, 14 and 15; and total fractures, 164 and 170.

Table 2. Effect of Calcium with Vitamin D Supplementation on Clinical Outcomes, According to Randomly Assigned Group.*

Analysis	Calcium + Vitamin D	Placebo	Hazard Ratio (95% CI)†
Intention-to-treat analysis			
Follow-up time — yr	7.0±1.4	7.0±1.4	
Rate of fracture — no. of cases (annualized %)			
Hip	175 (0.14)	199 (0.16)	0.88 (0.72–1.08)
Clinical vertebral	181 (0.14)	197 (0.15)	0.90 (0.74–1.10)
Lower arm or wrist	565 (0.44)	557 (0.44)	1.01 (0.90–1.14)
Total	2102 (1.64)	2158 (1.70)	0.96 (0.91–1.02)
Analysis excluding follow-up time for participants 6 mo after nonadherence detected			
Follow-up time — yr	3.8±2.9	3.9±2.9	
Rate of fracture — no. of cases (annualized %)			
Hip	68 (0.10)	99 (0.14)	0.71 (0.52–0.97)
Clinical vertebral	91 (0.13)	104 (0.15)	0.89 (0.67–1.19)
Lower arm or wrist	312 (0.45)	308 (0.43)	1.05 (0.90–1.23)
Total	1119 (1.63)	1222 (1.72)	0.94 (0.87–1.02)

* Plus–minus values are means ±SD. CI denotes confidence interval.
† The hazard ratios are for the group assigned to calcium with vitamin D as compared with the placebo group. Hazard ratios, 95 percent confidence intervals, and P values were calculated in Cox proportional-hazards analyses stratified according to age; randomization assignment in the Hormone Therapy and Dietary Modification trials; and presence or absence of prior fracture.

Table 3. Effect of Calcium with Vitamin D Supplementation on Hip Fractures, According to Baseline Characteristics.*

Outcome	Calcium + Vitamin D	Placebo	Hazard Ratio (95% CI)†	P Value for Interaction‡
	no. of cases (annualized %)			
Overall	175 (0.14)	199 (0.16)	0.88 (0.72–1.08)	
Age group at screening — yr				0.05
50 to 59	29 (0.06)	13 (0.03)	2.17 (1.13–4.18)	
60 to 69	53 (0.09)	71 (0.13)	0.74 (0.52–1.06)	
70 to 79	93 (0.44)	115 (0.54)	0.82 (0.62–1.08)	
Race or ethnic group§				0.87
White	167 (0.16)	189 (0.18)	0.89 (0.72–1.09)	
Black	3 (0.03)	4 (0.04)	0.73 (0.16–3.32)	
Hispanic	0 (0.00)	3 (0.06)		
American Indian	1 (0.19)	1 (0.20)		
Asian or Pacific Islander	4 (0.16)	1 (0.04)	2.98 (0.33–27.01)	
Unknown or not identified	0 (0.00)	1 (0.07)		
Weight				0.44
<58 kg	23 (0.20)	21 (0.18)	1.18 (0.65–2.14)	
≥58 kg	152 (0.13)	178 (0.15)	0.86 (0.69–1.06)	
Body-mass index				0.36
<25	69 (0.20)	66 (0.19)	1.05 (0.75–1.47)	
25 to <29	63 (0.14)	74 (0.16)	0.87 (0.62–1.22)	
≥30	43 (0.09)	59 (0.13)	0.73 (0.49–1.09)	
Smoking				0.97
Never or past	159 (0.14)	178 (0.15)	0.90 (0.72–1.11)	
Current	14 (0.14)	16 (0.17)	0.85 (0.41–1.74)	
Region by solar irradiance¶				0.73
300 to 325 Langleys	46 (0.12)	53 (0.14)	0.86 (0.58–1.28)	
350 Langleys	37 (0.14)	49 (0.18)	0.74 (0.48–1.14)	
375 to 380 Langleys	25 (0.18)	17 (0.12)	1.64 (0.88–3.08)	
400 to 430 Langleys	25 (0.12)	37 (0.17)	0.67 (0.40–1.11)	
475 to 500 Langleys	42 (0.16)	43 (0.16)	0.97 (0.63–1.49)	
No. of falls in past 12 mo				0.05
0	87 (0.11)	117 (0.15)	0.74 (0.56–0.98)	
1	39 (0.16)	41 (0.17)	0.96 (0.62–1.49)	
2	22 (0.22)	19 (0.19)	1.16 (0.63–2.16)	
≥3	16 (0.32)	6 (0.12)	2.51 (0.97–6.48)	

Women assigned to calcium with vitamin D supplements had a nonsignificant, 12 percent lower risk of hip fracture than women assigned to placebo (hazard ratio, 0.88; 95 percent confidence interval, 0.72 to 1.08). There were no significant reductions in clinical vertebral fracture, fracture of the lower arm or wrist, or total fractures (Table 2).

SECONDARY AND SUBGROUP ANALYSES

Among women who were adherent (i.e., those who took at least 80 percent of their study medication), calcium with vitamin D supplementation resulted in a 29 percent reduction in hip fracture (hazard ratio, 0.71; 95 percent confidence interval, 0.52 to 0.97); there were 167 cases of hip fracture among these women (Table 2). The hazard ratio

Table 3. (Continued.)

Outcome	Calcium + Vitamin D	Placebo	Hazard Ratio (95% CI)†	P Value for Interaction‡
	no. of cases (annualized %)			
Physical activity				0.57
0 to 3.00 MET	53 (0.14)	63 (0.17)	0.84 (0.58–1.21)	
>3.00 to <11.75 MET	49 (0.13)	63 (0.17)	0.81 (0.56–1.18)	
≥11.75 MET	59 (0.15)	56 (0.15)	1.04 (0.72–1.50)	
Prior fracture				0.71
No	77 (0.11)	83 (0.12)	0.92 (0.68–1.26)	
Yes	81 (0.19)	98 (0.23)	0.84 (0.63–1.13)	
Total calcium intake: supplements, diet, and medications				0.29
<800 mg/day	58 (0.13)	71 (0.17)	0.80 (0.57–1.14)	
800 to <1200 mg/day	41 (0.12)	53 (0.16)	0.76 (0.51–1.15)	
≥1200 mg/day	73 (0.15)	68 (0.14)	1.12 (0.80–1.55)	
Total vitamin D intake: supplements and diet				0.82
<200 IU/day	65 (0.13)	65 (0.14)	0.95 (0.67–1.35)	
200 to <400 IU/day	32 (0.13)	42 (0.17)	0.79 (0.50–1.26)	
400 to <600 IU/day	34 (0.12)	46 (0.15)	0.77 (0.49–1.20)	
≥600 IU/day	41 (0.17)	39 (0.17)	1.00 (0.65–1.55)	
Hormone therapy				0.23
Never	73 (0.18)	86 (0.22)	0.83 (0.61–1.14)	
Past	46 (0.22)	38 (0.18)	1.20 (0.78–1.85)	
Current	56 (0.08)	75 (0.11)	0.75 (0.53–1.06)	
Assignment in Hormone Therapy trial				0.07
Placebo	67 (0.24)	61 (0.22)	1.15 (0.81–1.63)	
Active hormone therapy	28 (0.10)	49 (0.17)	0.58 (0.37–0.93)	

* Plus–minus values are means ±SD. CI denotes confidence interval, and MET metabolic equivalent.
† The hazard ratios are for the group assigned to calcium with vitamin D as compared with placebo. Hazard ratios, 95 percent confidence intervals, and P values were calculated in Cox proportional-hazards analyses stratified according to age; randomization assignment in the Hormone Therapy and Dietary Modification trials; and presence or absence of prior fracture.
‡ P values were obtained from an interaction term between treatment assignment and potential risk factor of interest in a Cox proportional-hazards analysis stratified according to age; status of enrollment in the Hormone Therapy and Dietary Modification trials, and prior fracture.
§ Race or ethnic group was self-reported.
¶ The Langley is a unit of solar radiance and relates to the amount that reaches a given area of the earth's surface. The information is from national weather data on total solar irradiance in the United States and is adapted from Garland and Garland.[30] Values reflect hormone-therapy use during year 1 of the clinical trial, including exposure in the Hormone Therapy trial.

based on the inverse-probability weighting method was nearly identical. For all other fracture outcomes, the hazard ratios were similar to those obtained in the intention-to-treat analyses.

The hazard ratio for hip fracture among women 60 years of age or older was 0.79 (95 percent confidence interval, 0.64 to 0.98), with an indication of increased risk among women 50 to 59 years of age (P for interaction=0.05) (Table 3). There was a lower hazard ratio among women with no falls than among women with at least one fall (P for interaction=0.05). No other significant interactions were observed for any fracture outcome.

There was no evidence that either baseline

levels of total calcium or total vitamin D intake modified the association between calcium with vitamin D supplementation and fracture (Table 3). Dietary calcium intake remained stable during follow-up, whereas the intake of calcium from supplements increased by approximately 100 mg daily in both treatment groups. In both treatment groups, participants with initially low levels of total calcium intake (<400 mg daily) had larger increases (200 mg daily) in supplemental calcium intake than did other participants. The effects of calcium with vitamin D intervention on the risk of hip fracture tended to be greater among participants not using personal calcium supplements during follow-up: the hazard ratio was 0.70 (95 percent confidence interval, 0.51 to 0.98) among nonusers, 0.87 (95 percent confidence interval, 0.61 to 1.24) among those taking less than 500 mg per day, and 1.22 (95 percent confidence interval, 0.83 to 1.79) among those taking 500 mg or more per day (P for interaction = 0.11).

Use of osteoporosis medications increased during follow-up, with 3890 of the women (10.7 percent) taking alendronate, 654 (1.8 percent) taking risedronate, 1094 (3.0 percent) taking raloxifene, and 451 (1.2 percent) taking calcitonin. Censoring data from these participants after their first recorded use of these medications yielded hazard ratios of 0.87 (95 percent confidence interval, 0.69 to 1.09) for hip fracture and 0.93 (95 percent confidence interval, 0.74 to 1.18) for clinical vertebral fracture.

SERUM VITAMIN D LEVELS

In the nested case–control assessment of 25-hydroxyvitamin D, the mean (±SD) baseline 25-hydroxyvitamin D level was 46.0±22.6 nmol per liter among the participants who had hip fracture and 48.4±23.5 nmol per liter among their controls (P = 0.17). No statistically significant interactions were found between calcium with vitamin D supplementation and baseline 25-hydroxyvitamin D level with respect to either hip or total fractures (Table 4).

INTERACTION BETWEEN CALCIUM WITH VITAMIN D AND HORMONE THERAPY

Of the women in the WHI calcium with vitamin D trial, 16,089 were concomitantly enrolled in the WHI Hormone Therapy trial, in which estrogen was found to have strong effects on hip and other fractures.[31,32] The hazard ratios for hip fracture with calcium with vitamin D supplementation were 0.58 (95 percent confidence interval, 0.37 to 0.93) among women assigned to active hormone therapy and 1.15 (95 percent confidence interval, 0.81 to 1.63) among those assigned to placebo (P for interaction = 0.07). When the analyses included both exposure in the randomized Hormone Therapy trial and personal use, the trend toward an interaction between calcium with vitamin D supplementation and hormone therapy with respect to hip fracture was no longer present.

SAFETY AND TOLERABILITY

As of March 31, 2005, there were 744 deaths in the calcium with vitamin D group and 807 deaths in the placebo group (hazard ratio, 0.91; 95 percent confidence interval, 0.83 to 1.01). No statistically significant risks or benefits were seen with regard to any major disease outcomes, including cardiovascular diseases and cancer. Kidney stones were reported by 449 women in the calcium with vitamin D group, as compared with 381 women in the placebo group (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34), and appeared to be unrelated to high baseline calcium intake. There were no significant differences in gastrointestinal symptoms: 8.9 percent of the participants in the placebo group and 10.3 percent of those in the calcium with vitamin D group reported moderate-to-severe constipation, and 19.5 percent and 20.4 percent, respectively, reported bloating or gas.

DISCUSSION

The WHI calcium with vitamin D study was a large-scale, randomized, double-blind, placebo-controlled trial designed to test whether calcium and vitamin D supplementation reduced the risk of hip fracture in a large population of healthy postmenopausal women. The trial demonstrated that calcium with vitamin D supplementation diminishes bone loss at the hip, but the observed 12 percent reduction in the incidence of hip fracture (the primary outcome) was not statistically significant. There were no significant reductions in the incidence of clinical vertebral fractures, fractures of the lower arm or wrist, or total fractures. The main adverse effect noted was a small but significant increase in the proportion of women with renal calculi.

There are several plausible alternative expla-

Table 4. Odds Ratios for Hip Fracture and Total Fractures According to Quartiles of Serum 25-Hydroxyvitamin D Level and Study Group, as Determined in a Nested Case–Control Study.*

Fracture Category and 25-Hydroxyvitamin D Level†	Main-Effect Odds Ratio (95% CI)‡	Calcium + Vitamin D	Placebo	Intervention Odds Ratio (95% CI)§	P Value for Interaction¶
		no. of case participants/ no. of controls			
Hip fracture					0.64
≥60.2 nmol/liter	1.00	32/49	42/40	0.61 (0.32–1.15)	
43.7–60.1 nmol/liter	1.51 (0.96–2.37)	44/40	52/39	0.86 (0.48–1.53)	
32.2–43.6 nmol/liter	1.17 (0.73–1.89)	43/48	48/49	0.92 (0.53–1.62)	
<32.2 nmol/liter	1.32 (0.82–2.13)	47/44	49/48	1.06 (0.60–1.86)	
Total fractures					0.15
≥60.2 nmol/liter	1.00	178/185	177/201	1.09 (0.81–1.47)	
43.7–60.1 nmol/liter	1.12 (0.91–1.38)	170/179	205/191	0.89 (0.66–1.18)	
32.2–43.6 nmol/liter	1.18 (0.94–1.47)	179/183	204/181	0.87 (0.66–1.16)	
<32.2 nmol/liter	1.14 (0.91–1.44)	196/167	182/204	1.32 (0.99–1.76)	

* CI denotes confidence interval.
† 25-Hydroxyvitamin D levels were measured by Bruce Hollis, Ph.D., with use of the DiaSorin Liaison chemiluminescent immunoassay system at DiaSorin headquarters (Stillwater, Minn.) in one continuous batch with blinded control runs at periodic intervals (coefficient of variation, 11.8 percent). To convert the values for 25-hydroxyvitamin D from nanomoles per liter to nanograms per milliliter, multiply by 0.401.
‡ The odds ratios were obtained from a logistic-regression model, conditioned on case–control pairs, and estimated the main effect of serum 25-hydroxyvitamin D on the risk of fracture. P=0.51 for trend with regard to hip fracture. P=0.23 for trend with regard to total fractures.
§ The odds ratios were obtained from a logistic-regression model, conditioned on case–control pairs, and estimated the effect of calcium with vitamin D intervention on the risk of fracture according to 25-hydroxyvitamin D level.
¶ P values for interaction were computed by maximum likelihood from a conditional logistic model including the main effects of randomized study group and 25-hydroxyvitamin D as a continuous covariate and their interaction.

nations for the results seen in the intention-to-treat analyses. It is conceivable that calcium with vitamin D, at the doses studied in the WHI, has no significant effect on fracture reduction. The observed lack of efficacy in reducing clinical vertebral fractures is discordant with the results of meta-analyses of clinical trials that suggest a trend toward a small reduction in vertebral fractures with calcium alone[6] and a significant, 37 percent reduction in vertebral fractures with vitamin D supplementation.[22] The lack of a reduction in the risk of hip or total fractures would be consistent with the findings of recent studies that showed no evidence of reduction in nonvertebral fractures in healthy, older women living in the community.[15,18,19]

The effect of calcium with vitamin D supplementation on fracture reduction might require higher doses of vitamin D than were used in the WHI. This dose–response concept[33] is supported by studies indicating that supplementation with 400 IU of vitamin D has a small effect or no effect on the risk of fracture,[16,17] whereas the majority of studies supporting a benefit from calcium with vitamin D supplements evaluated vitamin D at doses that were the equivalent of 600 IU or higher.[8,10,13,14,33]

It is also plausible that there was a benefit only among the women who adhered to the study treatment. Although 76 percent of the women in this trial were still taking study pills at the end of the trial, only 59 percent were taking the intended dose. In sensitivity analyses, there was a decrease in the risk of hip fracture among adherent participants, yielding an absolute benefit of four fewer hip fractures per 10,000 women, or a significant, 29 percent relative decrease — a finding consistent with the results of other trials that showed that efficacy in fracture reduction is enhanced among women adherent to calcium with vitamin D supplementation[11] or is present only in this group.

This trial cannot separate the independent effects of calcium and vitamin D. The study popu-

lation was not selected to be deficient in calcium and vitamin D, since the participants were allowed to take multivitamins as well as calcium and vitamin D up to specified levels during the trial. The average daily total calcium intake at randomization was estimated to be 1100 to 1200 mg; only 7.2 percent of the participants had an intake of less than 400 mg.

The effect of calcium with vitamin D supplements may also differ according to baseline vitamin D levels. Chapuy et al. reported that calcium with vitamin D (1000 mg of calcium and 800 IU of vitamin D per day) significantly reduced the risk of hip and nonvertebral fractures among elderly women who were believed to be vitamin D–deficient (on the basis of low vitamin D levels in a subgroup analysis at baseline).[10] Studies involving persons who were potentially less deficient in vitamin D have failed to confirm this benefit.[18] We found no significant interactions between baseline serum 25-hydroxyvitamin D levels and a calcium with vitamin D treatment effect.

Finally, it is also plausible that calcium with vitamin D supplementation has a real but small effect in reducing the risk of hip fracture among postmenopausal women, but the WHI calcium with vitamin D trial was not sufficiently powered to detect such a small effect, even with 36,282 women enrolled. The trial design assumed an 18 percent reduction in the risk of hip fracture and projected a hip-fracture rate (approximately 34 per 10,000 persons per year) that was more than twice that observed (16 per 10,000). The lower-than-projected hip-fracture rate reduced the power of the study to approximately 48 percent. This may be attributable to the higher-than-anticipated body-mass index, the recruitment of fewer women over the age of 70 years than was projected, or a fracture rate already suppressed by high personal calcium intake or hormone-therapy use. Some support is provided by subgroup analyses suggesting that among women over the age of 60 years who had a higher absolute risk of hip fracture, calcium with vitamin D supplementation significantly reduced the risk of hip fractures.

The trend toward a reduction in the incidence of hip fracture, with no benefit at other skeletal sites, could be consistent with the pathophysiology of hip fracture relative to other osteoporotic fractures. Up to 60 percent of patients with hip fractures have one or more biomarkers consistent with a negative calcium balance, such as secondary hyperparathyroidism, low 25-hydroxyvitamin D levels, or low urine calcium excretion.[34] These perturbations in calcium metabolism associated with hip fracture might be amenable to treatments that would improve the calcium balance.

The trial yielded conflicting data regarding hip fracture and the interaction between hormone use and calcium with vitamin D supplementation. Though not statistically significant, the observed interaction between active calcium with vitamin D and hormone therapy may reflect a synergistic role of enhanced calcium balance with hormone therapy. This possibility is consistent with the previously reported additive effects of calcium with vitamin D and hormone therapy on bone mineral density.[35,36] However, when hormone-therapy use outside the trial was included, there was no interaction, and a 17 percent reduction in the incidence of hip fracture with calcium with vitamin D was observed among participants who had never used hormone therapy (hazard ratio, 0.83; 95 percent confidence interval, 0.61 to 1.14).

Participants in the WHI trial were healthy, postmenopausal women living in the community who were generally free of disability. The average calcium intake at baseline exceeded 1000 mg per day, close to the current national recommendations.[37] Nevertheless, we found significantly higher hip bone density but a nonsignificant reduction (12 percent) in the rate of hip fracture among those assigned to calcium with vitamin D. In secondary analyses, the intervention effect appeared greater among women who adhered to the regimen, women over 60 years of age, and women not taking personal calcium supplements. Using the intention-to-treat results from this study, we estimate that for healthy postmenopausal women over the age of 50 years, the number needed to treat to prevent one hip fracture per year is 5045. This number would be reduced to 1914 among women over the age of 60 years, who are at higher absolute risk for hip fracture. Although the statistically null primary effect argues against recommending universal calcium with vitamin D supplementation for already calcium-replete women, the findings provide evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women.

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Dr. Jackson reports having received consulting fees from Procter & Gamble Pharmaceuticals and lecture fees from the Alliance for Better Bone Health; she also reports that she currently receives grant support from Novartis. Dr. LaCroix reports having received consulting fees from Pfizer, Procter & Gamble, and the Alliance for Better Bone Health and having received a lecture fee from Schering-Plough. Dr. Robbins reports that he has worked on grants with industry support but that he has received no salary support. Dr. Lewis reports that she currently has grant support from Pfizer and Novartis. Dr. Brunner reports that he is principal investigator for a study funded by the National Cancer Institute of Canada and Pfizer through March 31, 2007. Dr. Cauley reports having received consulting fees from Novartis for serving on the HORIZON Study steering committee and grant support from Lilly, Pfizer, and Novartis. Dr. Hays reports having received lecture fees for conferences sponsored by Procter & Gamble Pharmaceuticals. Dr. Howard reports having received lecture fees from Schering-Plough and having served as a consultant for Merck, the Egg Nutrition Council, and General Mills. Dr O'Sullivan reports that she currently receives grant support from Pfizer. Dr. Assaf reports having been an employee of Pfizer since December 2002 and owning Pfizer stock and stock options. No other potential conflict of interest relevant to this article was reported.

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APPENDIX 1

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APPENDIX 2

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