Calcium plus Vitamin D Supplementation and the Risk of Fractures

Rebecca D. Jackson, M.D., Andrea Z. LaCroix, Ph.D., Margery Gass, M.D., Robert B. Wallace, M.D.,
John Robbins, M.D., Cora E. Lewis, M.D., Tamsen Bassford, M.D., Shirley A.A. Beresford, Ph.D., Henry R. Black, M.D.,
Patricia Blanchette, M.D., Denise E. Bonds, M.D., Robert L. Brunner, Ph.D., Robert G. Brzyski, M.D.,
Bette Caan, Dr.P.H., Jane A. Cauley, Dr.P.H., Rowan T. Chlebowski, M.D., Steven R. Cummings, M.D.,
Iris Granek, M.D., Jennifer Hays, Ph.D., Gerardo Heiss, M.D., Susan L. Hendrix, D.O., Barbara V. Howard, Ph.D.,
Judith Hsia, M.D., F. Allan Hubbell, M.D., Karen C. Johnson, M.D., Howard Judd, M.D., Jane Morley Kotchen, M.D.,
Lewis H. Kuller, M.D., Robert D. Langer, M.D., Norman L. Lasser, M.D., Marian C. Limacher, M.D., Shari Ludlam, M.P.H.,
JoAnn E. Manson, M.D., Karen L. Margolis, M.D., Joan McGowan, Ph.D., Judith K. Ockene, Ph.D.,
Mary Jo O'Sullivan, M.D., Lawrence Phillips, M.D., Ross L. Prentice, Ph.D., Gloria E. Sarto, M.D.,
Marcia L. Stefanick, Ph.D., Linda Van Horn, Ph.D., Jean Wactawski-Wende, Ph.D., Evelyn Whitlock, M.D.,
Garnet L. Anderson, Ph.D., Annlouise R. Assaf, Ph.D., and David Barad, M.D.,
for the Women's Health Initiative Investigators*

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.)

OSTEOPOROSIS, A MAJOR CAUSE OF IN-jury, 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 non-vertebral 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.)

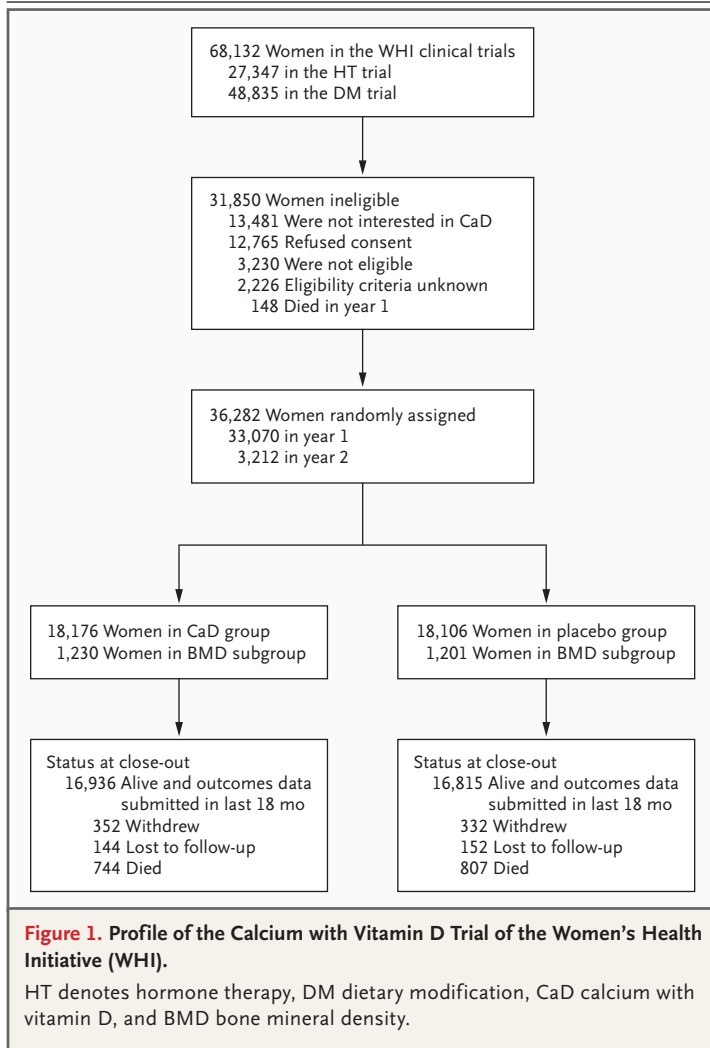| Characteristic	Calcium + Vitamin D (N = 18,176)	Placebo (N = 18,106)
Solar irradiance of region‡		
Mean	382±60	382±60
300 to 325 Langleys	5,366 (29.5)	5,351 (29.6)
350 Langleys	3,920 (21.6)	3,880 (21.4)
375 to 380 Langleys	2,012 (11.1)	2,009 (11.1)
400 to 430 Langleys	3,018 (16.6)	3,015 (16.7)
475 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.

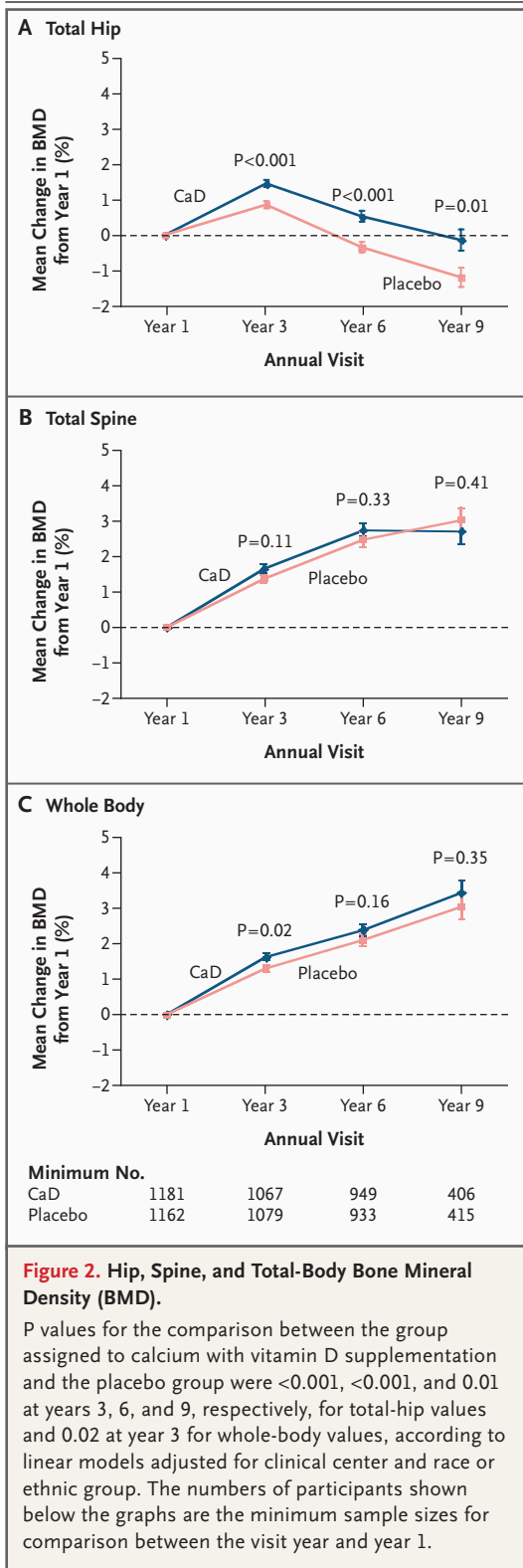## RESULTS

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

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.

APPENDIX 1

The WHI investigators are as follows: *Program Office* (National Heart, Lung, and Blood Institute, Bethesda, Md.): B. Alving, J. Rossouw, L. Pottern, S. Ludlam, J. McGowan, N. Geller, and L. Ford. *Clinical Coordinating Centers:* Fred Hutchinson Cancer Research Center, Seattle — R. Prentice, G. Anderson, A. LaCroix, R. Patterson, A. McTiernan, B. Cochrane, J. Hunt, L. Tinker, C. Kooperberg, M. McIntosh, C.Y. Wang, C. Chen, D. Bowen, A. Kristal, J. Stanford, N. Urban, N. Weiss, and E. White; Wake Forest University School of Medicine, Winston-Salem, N.C. — S. Shumaker, R. Prineas, and M. Naughton; Medical Research Laboratories, Highland Heights, Ky. — E. Stein, P. Laskarzewski; San Francisco Coordinating Center, San Francisco — S.R. Cummings, M. Nevitt, and L. Palermo; University of Minnesota, Minneapolis — L. Harnack; Fisher BioServices, Rockville, Md. — F. Cammarata and S. Lindenfelser; University of Washington, Seattle — B. Psaty and S. Heckbert. *Clinical Centers:* Albert Einstein College of Medicine, Bronx, N.Y. — S. Wassertheil-Smoller, W. Frishman, J. Wylie-Rosett, D. Barad, and R. Freeman; Baylor College of Medicine, Houston — J. Hays, R. Young, J. Anderson, S. Lithgow, and P. Bray; Brigham and Women's Hospital, Harvard Medical School, Boston — J.E. Manson, J.M. Gaziano, C. Chae, K. Rexrode, and C. Solomon; Brown University, Providence, R.I. — A.R. Assaf, C. Wheeler, C. Eaton, and M. Cyr; Emory University, Atlanta — L. Phillips, M. Pedersen, O. Strickland, M. Huber, and V. Porter; Fred Hutchinson Cancer Research Center, Seattle — S.A.A. Beresford, V.M. Taylor, N.F. Woods, M. Henderson, and R. Andersen; George Washington University, Washington, D.C. — J. Hsia, N. Gaba, and J. Ascensao; Harbor–UCLA Research and Education Institute, Torrance, Calif. — R. Chlebowski, R. Detrano, A. Nelson, and M. Geller; Kaiser Permanente Center for Health Research, Portland, Oreg. — E. Whitlock, P. Elmer, V. Stevens, and N. Karanja; Kaiser Permanente Division of Research, Oakland, Calif. — B. Caan, S. Sidney, G. Bailey, and J. Hirata; Medical College of Wisconsin, Milwaukee — J.M. Kotchen, V. Barnabei, T.A. Kotchen, M.C. Gilligan, and J. Neuner; MedStar Research Institute and Howard University, Washington, D.C. — B.V. Howard, L. Adams-Campbell, L. Lessin, M. Rainford, and G. Uwaifo; Northwestern University, Chicago and Evanston, Ill. — L. Van Horn, P. Greenland, J. Khandekar, K. Liu, and C. Rosenberg; Rush University Medical Center, Chicago — H. Black, L. Powell, E. Mason, and M. Gulati; Stanford Prevention Research Center, Stanford, Calif. — M.L. Stefanick, M.A. Hlatky, B. Chen, R.S. Stafford, and S. Mackey; State University of New York at Stony Brook, Stony Brook — D. Lane, I. Granek, W. Lawson, G. San Roman, and C. Messina; Ohio State University, Columbus — R. Jackson, R. Harris, E. Paskett, W.J. Mysiw, and M. Blumenfeld; University of Alabama at Birmingham, Birmingham — C.E. Lewis, A. Oberman, J.M. Shikany, M. Safford, and M. Fouad; University of Arizona, Tucson and Phoenix — T. Bassford, C. Thomson, M. Ko, A.M. Lopez, and C. Ritenbaugh; University at Buffalo, Buffalo, N.Y. — J. Wactawski-Wende, M. Trevisan, E. Smit, S. Graham, and J. Chang; University of California at Davis, Sacramento — J. Robbins and S. Yasmeen; University of California at Irvine, Irvine — F.A. Hubbell, G. Frank, N. Wong, N. Greep, and B. Monk; University of California at Los Angeles, Los Angeles — H. Judd, D. Heber, and R. Elashoff; University of California at San Diego, La Jolla and Chula Vista — R.D. Langer, M.H. Criqui, G.T. Talavera, C.F. Garland, and M.A. Allison; University of Cincinnati, Cincinnati — M. Gass and S. Wernke; University of Florida, Gainesville and Jacksonville — M. Limacher, M. Perri, A. Kaunitz, R.S. Williams, and Y. Brinson; University of Hawaii, Honolulu — J.D. Curb, H. Petrovitch, B. Rodriguez, K. Masaki, and S. Sharma; University of Iowa, Iowa City and Davenport — R. Wallace, J. Torner, S. Johnson, L. Snetselaar, and J. Robinson; University of Massachusetts, Fallon Clinic, Worcester — J. Ockene, M. Rosal, I. Ockene, R. Yood, and P. Aronson; University of Medicine and Dentistry of New Jersey, Newark — N. Lasser, B. Singh, V. Lasser, J. Kostis, and P. McGovern; University of Miami, Miami — M.J. O'Sullivan, L. Parker, T. DeSantis, D. Fernandez, and P. Caralis; University of Minnesota, Minneapolis — K.L. Margolis, R.H. Grimm, M.F. Perron, C. Bjerk, and S. Kempainen; University of Nevada, Reno — R. Brunner, W. Graettinger, V. Oujevolk, and M. Bloch; University of North Carolina, Chapel Hill — G. Heiss, P. Haines, D. Ontjes, C. Sueta, and E. Wells; University of Pittsburgh, Pittsburgh — L. Kuller, J. Cauley, and N.C. Milas; University of Tennessee Health Science Center, Memphis — K.C. Johnson, S. Satterfield, R.W. Ke, S. Connelly, and F. Tylavsky; University of Texas Health Science Center, San Antonio — R. Brzyski, R. Schenken, J. Trabal, M. Rodriguez-Sifuentes, and C. Mouton; University of Wisconsin, Madison — G.E. Sarto, D. Laube, P. McBride, J. Mares-Perlman, and B. Loevinger; Wake Forest University School of Medicine, Winston-Salem, N.C. — D. Bonds, G. Burke, R. Crouse, M. Vitolins, and S. Washburn; Wayne State University School of Medicine and Hutzel Hospital, Detroit — S. Hendrix, M. Simon, and G. McNeeley. *Former Principal Investigators and Project Officers:* Baylor College of Medicine — J. Foreyt; Emory University — D. Hall, S. McNagny, and N. Watts; George Washington University — Valery Miller; Kaiser, Oakland — R. Hiatt; Kaiser, Portland — B. Valanis; National Cancer Institute — C. Clifford (deceased); University of Arizona — T. Moon; University of California, Irvine — F. Meyskens, Jr.; University of Cincinnati — J. Liu; University of Miami — Marianna Baum; University of Nevada — S. Daugherty (deceased); University of North Carolina, Chapel Hill — D. Sheps, B. Hulka; University of Tennessee, Memphis — W. Applegate; University of Wisconsin — C. Allen (deceased). *Data and Safety Monitoring Board:* J. Wittes (chair), E. Braunwald, M. Chesney, H. Cohen, E. Barrett-Connor, D. DeMets, L. Dunn, J. Dwyer, R.P. Heaney, D. Marson, V. Vogel, L. Walters, K. Yaffe, and S. Yusuf.

APPENDIX 2

From the Ohio State University, Columbus (R.D.J.); the Fred Hutchinson Cancer Research Center, Seattle (A.Z.L., R.L.P., G.L.A.); the University of Cincinnati, Cincinnati (M.G.); the University of Iowa, Iowa City and Davenport (R.B.W.); the University of California at Davis, Sacramento (J.R.); the University of Alabama at Birmingham, Birmingham (C.E.L.); the University of Arizona, Tucson and Phoenix (T.B.); the University of Washington, Seattle (S.A.A.B.); Rush Medical Center, Chicago (H.R.B.); the University of Hawaii, Honolulu (P.B.); Wake Forest University School of Medicine, Winston-Salem, N.C. (D.E.B.); the University of Nevada, Reno (R.L.B.); the University of Texas Health Science Center, San Antonio (R.G.B.); Kaiser Permanente Division of Research, Oakland, Calif. (B.C.); the University of Pittsburgh, Pittsburgh (J.A.C., L.H.K.); the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, Calif. (R.T.C.); San Francisco Coordinating Center, San Francisco (S.R.C.); State University of New York at Stony Brook, Stony Brook (I.G.); Baylor College of Medicine, Houston (J.H.); the University of North Carolina, Chapel Hill (G.H.); Wayne State University School of Medicine and Hutzel Hospital, Detroit (S.L.H.); MedStar Research Institute and Howard University, Washington, D.C. (B.V.H.); George Washington University Medical Center, Washington, D.C. (J.H.); the University of California at Irvine, Irvine (F.A.H.); the University of Tennessee Health Science Center, Memphis (K.C.J.); the University of California at Los Angeles, Los Angeles (H.J.); Medical College of Wisconsin, Milwaukee (J.M.K.); the University of California at San Diego, La Jolla and Chula Vista (R.D.L.); the University of Medicine and Dentistry of New Jersey, Newark (N.L.L.); the University of Florida, Gainesville and Jacksonville (M.C.L.); the National Lung, Heart, and Blood Institute, Bethesda, Md. (S.L.); Brigham and Women's Hospital and Harvard Medical School, Boston (J.E.M.); the University of Minnesota, Minneapolis (K.L.M.); the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Md. (J.M.); the University of Massachusetts, Fallon Clinic, Worcester (J.K.O.); the University of Miami, Miami (M.J.O.); Emory University, Atlanta (L.P.); the University of Wisconsin, Madison (G.E.S.); Stanford Prevention Research Center, Stanford, Calif. (M.L.S.); Northwestern University, Chicago and Evanston, Ill. (L.V.H.); the University of Buffalo, Buffalo, N.Y. (J.W.-W.); Kaiser Permanente Center for Health Research, Portland, Oreg. (E.W.); Brown University, Providence, R.I. (A.R.A.); and the Albert Einstein College of Medicine, Bronx, N.Y. (D.B.).

REFERENCES

1. Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. J Bone Miner Res 1997;12:1761-8.

2. Melton LJ III. How many women have osteoporosis now? J Bone Miner Res 1995; 10:175-7.

3. Healthcare Cost and Utilization Project. HCUP Nationwide Inpatient Sample (NIS), 2003. (Accessed January 26, 2006, at http://www.hcup-us.ahrq.gov/nisoverview. jsp.)

4. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 1994;4:245-52.

5. Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. Calcif Tissue Int 1990;47:194-201.

6. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23:552-9.

7. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004;291: 1999-2006.

8. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005; 293:2257-64.

9. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670-6.

10. Chapuy MC, Arlot ME, Duboeuf F, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.

11. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ 1994; 308:1081-2.

12. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 1996;11:1961-6.

13. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326:469-72.

14. Chapuy MC, Pamphile P, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002;13:257-64.

15. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res 2004;19:370-8.

16. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res 2002;17:709-15.

17. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124: 400-6.

18. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621-8.

19. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 2005;330:1003.

20. Cumming RG, Nevitt MC. Calcium for the prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 1997;12:1321-9.

21. Kanis JA. The use of calcium in the management of osteoporosis. Bone 1999; 24:279-90.

22. Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII. Meta-analyses of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:560-9.

23. Gillespie WJ, Avenell A, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2001;1:CD000227.

24. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. Ann Epidemiol 2003;13:Suppl:S98-S106.

25. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006;354:684-96.

26. Food and Nutrition Board, Institute of

Medicine. Dietary reference intakes: for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press, 1997:38-144.

27. Yates AA, Schlicker SA, Suitor CW. Dietary Reference Intakes: the new basis for recommendations for calcium and related nutrients, B vitamins, and choline. J Am Diet Assoc 1998;98:699-706.

28. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178-87.

29. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 2000; 56:779-81.

30. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980;9:227-31.

31. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on the risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729-38.

32. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701-12.

33. Vieth R. Why the optimal requirement for vitamin D_3 is probably higher than what is officially recommended for adults. J Steroid Biochem Mol Biol 2004;89:575-9.

34. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 1999;281:1505-11.

35. Ettinger B, Genant HK, Cann CE. Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. Ann Intern Med 1987;106:40-5.

36. Sirola J, Kroger H, Sandini L, et al. Interaction of nutritional calcium and HRT in prevention of postmenopausal bone loss: a prospective study. Calcif Tissue Int 2003;72:659-65.

37. Department of Health and Human Services. Bone health and osteoporosis: a report of the Surgeon General. Rockville, Md.: Office of the Surgeon General, 2004.

Copyright © 2006 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE *JOURNAL*'S CUMULATIVE INDEX

At the *Journal*'s site on the World Wide Web (**www.nejm.org**),
you can search an index of all articles published since January 1975
(abstracts 1975–1992, full text 1993–present). You can search by author,
key word, title, type of article, and date. The results will include the citations
for the articles plus links to the full text of articles published since 1993.
For nonsubscribers, time-limited access to single articles and 24-hour site
access can also be ordered for a fee through the Internet (**www.nejm.org**).

CORRECTION

Calcium plus Vitamin D Supplementation and the Risk of Fractures

Calcium plus Vitamin D Supplementation and the Risk of Fractures
. On page 669, line 3 under Methods should have read, ``1000 mg
of elemental calcium as calcium carbonate,´´ rather than ``1000 mg of
calcium carbonate,´´ as printed. The article has been corrected on the
Journal's Web site at www.nejm.org.

CORRECTION

Calcium plus Vitamin D and the Risk of Fractures

To the Editor: The increased incidence of nephrolithiasis among patients taking supplemental calcium carbonate that was reported by Jackson et al. (Feb. 16 issue)[1] might have been avoided if calcium citrate had been given. It has been shown that urinary calcium oxalate crystals that form in the presence of hypercalciuria and hyperoxaluria develop into clinically important stones only after aggregation into larger particles. This aggregation is inhibited by citrate at physiologic concentrations.[2,3]

The data in Table 3 in the report suggest that calcium and vitamin D reduced the incidence of hip fracture more in older patients than in younger patients, which is not unexpected, given the pathophysiological differences between perimenopausal bone loss and senile bone loss.[4] Measurement of parathyroid hormone levels to assess the adequacy of vitamin D intake might have helped in the interpretation of these findings.[5,6] The dose of supplementary vitamin D used in this study, assuming it was the sole or major source of vitamin D, may have been too low to have had a more dramatic effect in either age group.

Susan Terris, M.D., Ph.D.
25 Coleman Ave.
Red Bank, NJ 07701

References

1. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-683. [Erratum, N Engl J Med 2006;354:1102.]

2. Glauser A, Hochreiter W, Jaeger P, Hess B. Determinants of urinary excretion of Tamm-Horsfall protein in non-selected kidney stone formers and healthy subjects. Nephrol Dial Transplant 2000;15:1580-1587.

3. Hess B, Jordi S, Zipperle L, Ettinger E, Giovanoli R. Citrate determines calcium oxalate crystallization kinetics and crystal morphology – studies in the presence of Tamm-Horsfall protein of a healthy subject and a severely recurrent calcium stone former. Nephrol Dial Transplant 2000;15:366-374.

4. Riggs BL. Overview of osteoporosis. West J Med 1991;154:63-77.

5. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. Am J Clin Nutr 1998;67:342-348.

6. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215-3224.

To the Editor: Although Jackson and coworkers conclude that calcium and vitamin D supplementation did not significantly reduce fracture rates among women 50 to 79 years of age, their observations can be interpreted to provide support for a different conclusion. Since it has been well established that bone mineral density (BMD) decreases progressively in postmenopausal women who are not treated for bone loss, one is struck by the authors' finding that the mean BMD for the total spine and the whole body in the control subjects increased steadily over the nine years of the study, and that the BMD for the total hip remained essentially unchanged, as shown in Figure 2 of the article by Jackson et al. This phenomenon was almost surely influenced by the large proportion of control subjects who were already taking calcium or vitamin D at ``therapeutic´´ doses. One would expect improved BMD to be associated with fewer fractures; the investigators did, in fact, find fracture rates for both control subjects and treated subjects to be less than half the rate historically anticipated. It is also not surprising that the administration of additional calcium and vitamin D to treated subjects further reduced hip fractures only to a limited degree, particularly since the optimal intakes of both are unknown.

Gerson T. Lesser, M.D.
Mount Sinai School of Medicine
New York, NY 10029
glesser@jhha.org

To the Editor: The results of the Women's Health Initiative (WHI) trial of calcium with vitamin D reveal that calcium and vitamin D supplementation (1000 mg of calcium carbonate with 400 IU of vitamin D) did not lower fracture rates but did increase the risk of kidney stones in calcium-replete postmenopausal women (mean intake, 1150 mg per day) whose intake of vitamin D was insufficient (serum 25-hydroxyvitamin D, 48 nmol per liter). How should these results influence clinical practice? They should have no effect on the evidence-based recommendation that postmenopausal women, who typically consume 600 mg of elemental calcium per day, should increase their calcium intake to 1200 mg per day.[1] Similarly, the results should not deter physicians from recommending 800 IU of vitamin D per day — the amount the average postmenopausal woman needs to raise her serum 25-hydroxyvitamin D level to that needed to lower the risk of fracture ($\geq$75 nmol per liter).[2] Finally, the increased risk of kidney stones among the women in the study who were consuming a mean of 2150 mg per day of calcium (usual mean intake plus supplement), as compared with those consuming 1150 mg per day, should not be assumed to apply to women who increase their intake to 1200 mg per day. It is important that the WHI trial not be used to sanction the inadequate intake of calcium and vitamin D that is so widespread among postmenopausal women today.

Bess Dawson-Hughes, M.D.
Tufts University
Boston, MA 02111
bess.dawson-hughes@tufts.edu

References

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes: for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press, 1997.

2. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713-716.

The authors reply: Dr. Terris notes that use of supplemental calcium citrate, instead of calcium carbonate, may lessen the risk of kidney stones observed in the WHI calcium with vitamin D trial, and we agree. However, calcium carbonate, perhaps because of its greater affordability, is still the most common form of calcium supplementation used in the United States. The present study did not have the power to examine changes in parathyroid hormone levels among women with hip fracture and controls, because stored specimens were available after randomization for a subsample of the trial population that consisted of only 6 percent of the subjects.

Dr. Lesser attributes the low rate of hip fracture in the placebo group to the already high levels of calcium intake at baseline. As we report, there are other powerful fracture-lowering factors that probably also contributed, including high levels of hormone use and body-mass index and the enrollment of fewer women over 70 years of age than expected. Nonetheless, we believe that the trial results provide several indications that calcium intake does reduce the risk of hip fracture. Calcium and vitamin D supplementation reduced the risk of hip fracture by 29 percent among women with an adherence of 80 percent or more, 21 percent among those 60 years of age or older at enrollment, and 30 percent among those not taking other calcium supplements during the trial (all 95 percent confidence intervals for the corresponding hazard ratios exclude 1). In fact, we believe that these data support current recommendations for adequate calcium intake.

Two other clarifications are important to make in the interpretation of the trial results. First, the increased risk of kidney stones was not associated with high baseline calcium intake. Our preliminary analyses indicated no interaction with baseline calcium intake and, in fact, a somewhat greater risk among women with a lower total calcium intake at baseline. The factors contributing to an increase in the risk of kidney stones are under investigation. Second, some have disregarded the greater effects of the calcium-plus-vitamin-D intervention in older women as being uninterpretable, claiming that the randomization was no longer intact in subgroups defined according to age. In fact, the randomization of women in all the WHI trials was stratified according to age in order to ensure that measured and unmeasured characteristics would be balanced within the age groups. There are other caveats associated with subgroup analysis (e.g., multiple comparisons and lack of power), but in the WHI trials, age-specific analyses are protected from confounding by the randomized design.

Rebecca D. Jackson, M.D.
Ohio State University
Columbus, OH 43210
jackson.20@osu.edu

Andrea Z. LaCroix, Ph.D.
Fred Hutchinson Cancer Research Center
Seattle, WA 98109

for the Women's Health Initiative Investigators