

Calcium Plus Vitamin D Supplementation and Mortality in Postmenopausal Women: The Women's Health Initiative Calcium–Vitamin D Randomized Controlled Trial

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Background. Calcium and vitamin D (CaD) supplementation trials including the Women's Health Initiative (WHI) trial of CaD have shown nonsignificant reductions in total mortality. This report examines intervention effects on total and cause-specific mortality by age and adherence.

Methods. The WHI CaD trial was a randomized, double-blind, placebo-controlled trial that enrolled 36,282 postmenopausal women aged 51–82 years from 40 U.S. clinical centers. Women were assigned to 1,000 mg of elemental calcium carbonate and 400 IU of vitamin D₃ daily or placebo with average follow-up of 7.0 years.

Results. The hazard ratio (HR) for total mortality was 0.91 (95% confidence interval [CI], 0.83–1.01) with 744 deaths in women randomized to CaD versus 807 deaths in the placebo group. HRs were in the direction of reduced risk but nonsignificant for stroke and cancer mortality, but near unity for coronary heart disease and other causes of death. HRs for total mortality were 0.89 in the 29,942 women younger than 70 years (95% CI, 0.79–1.01) and 0.95 in the 6,340 women aged 70 and older (95% CI, 0.80–1.12; *p* value for age interaction = .10). No statistically significant interactions were observed for any baseline characteristics. Treatment effects did not vary significantly by season.

Conclusions. In the WHI CaD trial, supplementation did not have a statistically significant effect on mortality rates but the findings support the possibility that these supplements may reduce mortality rates in postmenopausal women. These data can neither support nor refute recommendations for higher dose vitamin D supplementation to reduce cancer or total mortality.

Key Words: Calcium—Vitamin D—Mortality—Cause-specific mortality—Women's Health Initiative.

DESPITE predictions that some types of micronutrient supplementation might prevent cancer and cardiovascular disease (CVD) and reduce mortality, the results of large intervention trials of chemoprevention have been largely disappointing to date. Several randomized controlled trials have shown nonsignificant reductions in total mortality among women assigned to vitamin D₃, calcium carbonate alone, or the combination of calcium plus vitamin D (1–4). Among the 36,282 women who participated in the Women's Health Initiative (WHI) calcium plus vitamin D (CaD) supplementation trial, the intention-to-treat hazard ratio (HR) for total mortality

was 0.91 (95% confidence interval [CI], 0.83–1.01) (1). A recent meta-analysis, in which WHI women contributed nearly two thirds of the data, reported a significant reduction in mortality among nine trials (4) based only on previously published data.

We report here the first thorough evaluation of the possible effects of CaD supplementation on total and cause-specific mortality in the WHI CaD trial. This report also assesses the impact of adherence to CaD supplementation on treatment effect estimates and determines whether HRs for total mortality differed according to levels of selected baseline characteristics, including age.

METHODS

Design Overview

The WHI CaD trial is a randomized, double-blind, placebo-controlled trial designed to determine whether supplementation with calcium (1,000 mg/d) plus vitamin D (400 IU/d) would prevent hip fracture (the primary outcome), other fractures, or colorectal cancer (designated secondary outcome). These findings have been previously published (1,5).

Setting and Participants

Between 1993 and 1998, postmenopausal women aged 50–79 years were enrolled in the WHI randomized clinical trials designed to assess the risks and benefits of hormone therapy (HT) and dietary modification (DM) (6). One year later, participants in either the HT or the DM trial were invited to enroll in the CaD trial. Exclusion criteria for the CaD trial included a predicted survival of less than 3 years; a history of renal calculi or hypercalcemia; or current use of oral corticosteroids or calcitriol, or daily use of 600 IU or more of supplemental vitamin D (7). Personal use of calcium supplements up to 1,000 mg/d or vitamin D up to 600 IU/d was permitted. The protocol and consent forms were approved by the institutional review board at each participating institution. All women provided written informed consent.

Randomization and Intervention

Details regarding execution of the trial have been described previously (1,6). Briefly, using a permuted-block algorithm stratified by clinical center and age, 18,176 women were randomly assigned to receive one tablet of 500 mg of elemental calcium as calcium carbonate combined with 200 IU of vitamin D₃ (GlaxoSmithKline, Pittsburgh, PA) twice daily, totaling 1,000 mg of elemental calcium and 400 IU of vitamin D. A total of 18,106 women were randomized to receive an identical-appearing placebo tablet twice daily. Blinding of the study was achieved by bottle labeling.

Outcomes and Follow-Up

Participants were contacted semiannually thereafter to ascertain self-reported medical history updates. When they could not be contacted, information on vital status was sought from previously identified proxy informants, National Death Index searches, and obituary notices. Regardless of adherence, participants were followed up until they died, were lost to follow-up, requested no further contact, or until the study ended. Ninety-seven percent of participants were followed to study completion. Causes of death were determined based on available medical records, autopsy reports, and the death certificate in a blinded fashion by local and central physician adjudicators. For 352 deaths (22.7%), the death certificate was the only available source of information for determining cause of death. Ninety-six percent of reported deaths were

centrally adjudicated, 2.5% were locally adjudicated, and 1.5% could not be adjudicated.

Study pills were discontinued if women reported kidney stones, hypercalcemia, dialysis, or the use of calcitriol or daily supplements of more than 1,000 IU of vitamin D during semiannual contacts. During the study, adherence was assessed by weighing returned pill bottles.

An independent data and safety monitoring board reviewed the trial data semiannually. Closeout visits occurred as planned between October 1, 2004, and March 31, 2005, with final outcomes assessed before the treatment assignment was revealed. WHI investigators and National Institutes of Health sponsors all contributed to the study design and execution.

Nested Case-Control Study of Vitamin D Levels

Baseline serum measurements of 25-hydroxyvitamin D were available for 323 women who died and 1,962 living controls in the CaD trial from previous nested case-control studies (1,5). Levels of 25-hydroxyvitamin D were measured using the DiaSorin Liaison chemiluminescent immunoassay system at Diasorin headquarters (Stillwater, MN) as previously described (1,5).

Statistical Analysis

Primary analyses used time-to-event methods, according to the intention-to-treat principle. Mortality rates were compared in the two groups with the use of HRs (with 95 percent CIs) and stratified logrank tests from Cox proportional hazards models (8), stratified according to baseline age and treatment assignment in the HT and DM trials.

In addition, HRs were calculated by categories of causes of death (cardiovascular, cancer, other, and for CVD, coronary heart disease (CHD), and cerebrovascular cause of death separately). Because mortality rates rise markedly with age, treatment effects were examined separately for women younger and older than 70 years, the cut point prespecified in the protocol for defining older women. Analyses according to adherence to study medication were also conducted, with participants censored 6 months after first detection of becoming less than 80% adherent. Inverse probability weighting methods were used to estimate full-adherence HRs adjusting for covariates found to be associated with nonadherence (1,9).

Potential differential effects across categories of important risk factors for mortality were also tested individually with the use of a likelihood ratio test for interaction between the risk factor and the treatment assignment after including both as main effects. Twenty-three subgroup comparisons were tested; thus, about one test would be expected to be statistically significant at the .05 level by chance alone. All reported *p* values are two sided and were not adjusted for multiplicity.

Odds ratios for CaD supplementation were estimated using logistic regression across tertiles of serum 25-hydroxyvitamin D. The model stratified by randomization assignment in

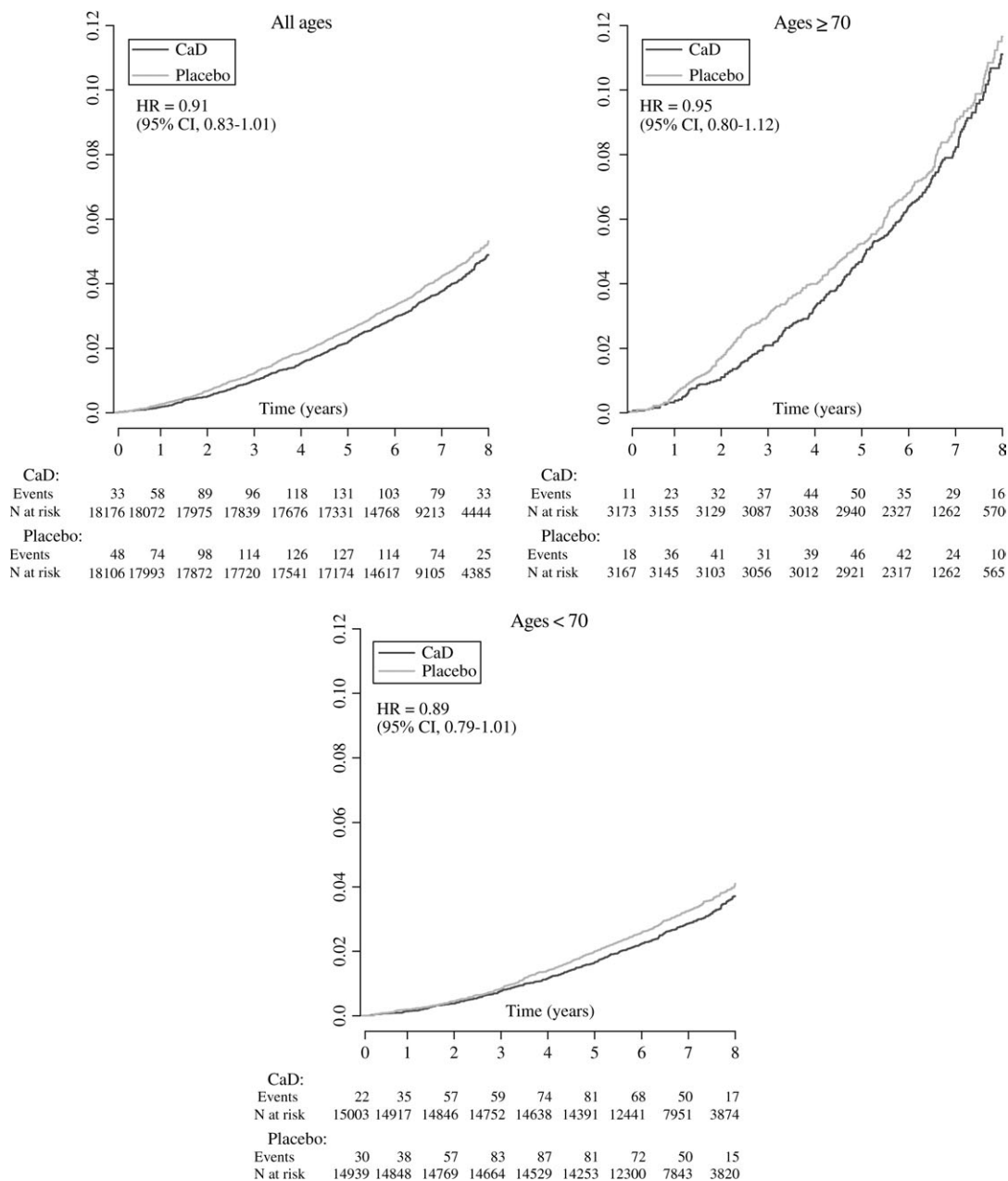


Figure 1. Cumulative mortality Kaplan–Meier curves by age group.
Note: CaD = calcium and vitamin D; CI = confidence interval; HR = hazard ratio.

another WHI trial and age group, and adjusted for age, ethnicity, and latitude of clinical center. An interaction *p* value was calculated for treatment by continuous serum level.

RESULTS

Baseline characteristics were well balanced between the treatment groups (Table 1). Twenty-nine percent of study participants were taking at least 500 mg/d of supplemental calcium on their own. Low calcium intakes (<800 mg/d) were noted in approximately one third of study participants. The mean (*SD*) duration of follow-up was 7.0 (1.4) years.

At time of closeout, 1,551 deaths had occurred, 744 in the CaD intervention group and 807 in the placebo group. The final HR for total mortality was 0.91 (95% CI, 0.83–1.01) (Table 2). CaD HRs were in the direction of reduced risk but nonsignificant for stroke and cancer mortality, whereas HRs were close to unity for CHD and other causes of death.

Intention-to-treat HRs by age at baseline (<70 vs ≥70 years) suggested lower HRs among younger women for total, stroke, and other causes of death. The HRs for total mortality were 0.89 in women younger than 70 (95% CI, 0.79–1.01) compared with 0.95 in women of ages 70 and

Table 1. Characteristics of WHI CaD Participants at WHI Screening by Randomization Arm

	CaD (N=18,176)		Placebo (N=18,106)		p Value
	N	Mean (SD) or %	N	Mean (SD) or %	
Age at screening, y					
Mean (SD)	18,176	62.4 (7.0)	18,106	62.4 (6.9)	.97
50–54	2,594	14.3	2,563	14.2	
55–59	4,134	22.7	4,131	22.8	
60–69	8,275	45.5	8,245	45.5	
70–79	3,173	17.5	3,167	17.5	
Race/ethnicity					.45
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/Native American	77	0.4	72	0.4	
Asian/Pacific Islander	369	2.0	353	1.9	
Unknown	212	1.2	222	1.2	
Education at screening					.98
High school or less	4,286	23.6	4,289	23.7	
Some school after high school	5,301	29.2	5,248	29.0	
College graduate	1,862	10.2	1,856	10.3	
Graduate school	4,693	25.8	4,687	25.9	
Hormone use at annual visit 1					.23
Never used	5,814	32.0	5,690	31.4	
Past user	3,004	16.5	2,932	16.2	
Current user	9,358	51.5	9,484	52.4	
Daily supplemental calcium use					.48
Mean (SD)	18,176	322.6 (479.2)	18,106	326.2 (482.4)	
None, mg	8,009	44.1	7,871	43.5	
<500	4,975	27.4	4,922	27.2	
>500	5,192	28.6	5,313	29.3	
Daily total calcium (supplements + diet), mg					.40
Mean (SD)	17,821	1,148.4 (654.2)	17,753	1,154.3 (658.0)	
<800	6,104	33.6	6,003	33.2	
800 to <1,200	4,715	25.9	4,655	25.7	
≥1,200	7,002	38.5	7,095	39.2	
Daily vitamin D (supplements + diet), IU					.36
Mean (SD)	17,821	365.3 (265.5)	17,753	367.9 (266.0)	
<200	6,827	37.6	6,671	36.8	
200 to <400	3,379	18.6	3,423	18.9	
400 to <600	4,188	23.0	4,295	23.7	
≥600	3,427	18.9	3,364	18.6	
History of hypertension					.88
Never hypertensive	6,944	38.2	6,925	38.2	
Untreated hypertensive	6,686	36.8	6,692	37.0	
Treated hypertensive	4,546	25.0	4,489	24.8	
Systolic blood pressure	18,176	127.4 (17.1)	18,106	127.5 (17.2)	.48
Diastolic blood pressure	18,175	75.9 (9.1)	18,101	75.9 (9.0)	.56
Smoking					.50
Never smoked	9,428	52.1	9,325	51.3	
Past smoker	7,133	39.4	7,255	39.9	
Current smoker	1,356	7.5	1,405	7.7	
Alcohol use					.88
Nondrinker	1,863	10.2	1,891	10.4	
Past drinker	3,192	17.6	3,209	17.7	
<1 drink per mo	2,529	13.9	2,520	13.9	
<1 drink per wk	3,863	21.3	3,758	20.8	
1 to <7 drinks per wk	4,683	25.8	4,706	26.0	
≥7 drinks per wk	1,910	10.5	1,900	10.5	
Physical activity					.60
Mean (SD) METs/wk	16,546	10.7 (12.7)	16,448	10.6 (12.4)	
0–3.00	5,517	30.4	5,478	30.3	
>3.00 to <11.75	5,463	30.1	5,477	30.2	
≥11.75	5,566	30.6	5,493	30.3	

Table 1. (Continued)

	CaD (N=18,176)		Placebo (N=18,106)		p Value
	N	Mean (SD) or %	N	Mean (SD) or %	
Body mass index, kg/m ²					
Mean (SD)	18,084	29.1 (5.9)	18,011	29.0 (5.9)	.24
<25	4,745	26.1	4,833	26.7	
25–29.9	6,472	35.6	6,483	35.8	
≥30	6,867	37.8	6,695	37.0	
No. of CVD risk factors					.23
None	5,544	30.5	5,579	30.8	
1–2	12,337	67.9	12,195	67.4	
>3	295	1.6	332	1.8	
History of CVD	1,173	6.5	1,221	6.7	.27
History of treated diabetes	885	4.9	875	4.8	.87
DM trial arm					.30
Placebo	7,827	43.1	7,738	42.7	
Intervention	4,767	26.2	4,878	26.9	
Not randomized	5,582	30.7	5,490	30.3	
HT trial arm					.74
Placebo	4,015	22.1	3,957	21.9	
Active	4,039	22.2	4,078	22.5	
Not randomized	10,122	55.7	10,071	55.6	
No. of chronic conditions at screening	18,176	1.2 (0.9)	18,106	1.2 (0.9)	.93
Depressive symptoms score	18,135	2.30 (2.55)	18,057	2.33 (2.59)	.18
Physical function score	18,127	81.5 (20.1)	18,061	81.4 (20.3)	.50

Note: CaD = calcium and vitamin D; CVD = cardiovascular disease; DM = dietary modification; HT = hormone therapy; MET = metabolic equivalent; WHI = Women's Health Initiative.

older (95% CI, 0.80–1.12; *p* value for age interaction = .10). HRs for cancer death were similar across age categories.

At trial closure, 76% of women enrolled were still taking study medications and 59% were taking at least 80% of study pills. When participants were censored 6 months after first detection of adherence less than 80%, HRs were 0.87 for total mortality (95% CI, 0.73–1.04), 0.85 for cancer mortality (95% CI, 0.66–1.09), and 0.57 (95% CI, 0.30–1.09) for stroke mortality. HRs suggested greater benefit for adherent women younger than 70 years, as compared with older adherent women (data not shown). Tests for age interaction were statistically significant for total mortality (*p* = .02) but not for the cause-specific categories. Estimated full-adherence HRs based on the inverse probability weighting method were similar to those for adherent women and all CIs included 1.0.

Intention-to-treat HRs did not vary significantly for any of the 23 baseline risk factors examined for mortality. In addition to the subgroups shown in Table 3, no significant differences were observed by subgroups of education, alcohol intake, history of diabetes, depressive symptoms, physical function score, and disability in activities of daily living, or randomization in the dietary modification trial. In models adjusting for season as a time-dependent variable, risk of mortality was increased during winter months, with a HR of 1.14 (95% CI, 0.99–1.32). Treatment effects did not vary significantly by season at time of death (*p* value for interaction = .20), although HRs were observed to be reduced in winter (HR = 0.81; 95% CI, 0.66–0.98), summer (HR = 0.87; 95% CI, 0.71–1.06), and

autumn (HR = 0.93; 95% CI, 0.77–1.13), but not in spring (HR = 1.10; 95% CI, 0.89–1.36).

In the nested case-control study, CaD intervention effects did not vary significantly by baseline levels of serum 25-hydroxyvitamin D (*p* = .66), although the odds ratio was in the direction of benefit for women in the lowest tertile (Table 4). Compared with women in the highest tertile of serum 25-hydroxyvitamin D, there was a significantly increased risk for death for women in the middle and low tertiles. The odds ratio for serum 25-hydroxyvitamin D level analyzed as a continuous variable was 0.80 (95% CI, 0.67–0.95) for a difference of 29.9 nmol/L (the interquartile range).

DISCUSSION

In this large randomized trial of women aged 50–79, CaD supplementation for an average of 7 years was associated with a nonsignificant reduction in the risk of death (9% with 95% CI, 17% reduction to a 1% increase in risk). The evidence was most consistent for a decrease in cancer mortality.

Among the 23 interactions tested, none was statistically significant. Age, as the strongest predictor of mortality in the general population, was of particular interest. Among the women younger than 70 years, CaD supplementation appeared to reduce risks of total, CVD, and cancer death. In older women, only cancer mortality appeared to be reduced. The interaction between CaD supplementation and age was not statistically significant for total mortality overall but was so among adherent women (*p* = .02).

Because the majority of statistical tests reported herein are not significant at the .05 level, a viable explanation for

Table 2. Effect of Calcium With Vitamin D Supplementation on Total, CVD, Cancer, and Other Mortality, According to Randomly Assigned Group

	CaD	Placebo	HR (95% CI)
	Cases (annualized %)	Cases (annualized %)	
Follow-up time, y (mean \pm SD)	7.0 \pm 1.4	7.0 \pm 1.4	
Total mortality	744 (0.58)	807 (0.63)	0.91 (0.83–1.01)
CVD death	226 (0.18)	244 (0.19)	0.92 (0.77–1.10)
CHD death	130 (0.10)	128 (0.10)	1.01 (0.79–1.29)
Cerebrovascular death	54 (0.04)	60 (0.05)	0.89 (0.62–1.29)
Cancer death	344 (0.27)	382 (0.30)	0.89 (0.77–1.03)
Other/unknown death	174 (0.14)	181 (0.14)	0.95 (0.77–1.17)
Participants younger than 70 years			
Follow-up time, y (mean \pm SD)	7.1 \pm 1.4	7.1 \pm 1.4	
Total mortality	466 (0.44)	517 (0.49)	0.89 (0.79–1.01)
CVD death	115 (0.11)	135 (0.13)	0.85 (0.66–1.08)
CHD death	70 (0.07)	70 (0.07)	0.99 (0.71–1.38)
Cerebrovascular death	21 (0.02)	33 (0.03)	0.62 (0.36–1.08)
Cancer death	245 (0.23)	268 (0.25)	0.91 (0.76–1.08)
Other/unknown death	106 (0.10)	114 (0.11)	0.92 (0.70–1.20)
Participants 70 or older			
Follow-up time, y (mean \pm SD)	6.7 \pm 1.4	6.7 \pm 1.5	
Total mortality	278 (1.30)	290 (1.37)	0.95 (0.80–1.12)
CVD death	111 (0.52)	109 (0.51)	1.01 (0.78–1.32)
CHD death	60 (0.28)	58 (0.27)	1.02 (0.71–1.47)
Cerebrovascular death	33 (0.15)	27 (0.13)	1.20 (0.72–2.01)
Cancer death	99 (0.46)	114 (0.54)	0.86 (0.65–1.12)
Other/unknown death	68 (0.32)	67 (0.32)	1.01 (0.72–1.42)

Note: CaD = calcium and vitamin D; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

these results is chance alone. Among the younger women, there was a difference favoring intervention for reduced mortality within the first year, which is difficult to attribute to intervention. A trial designed to confirm this association would require more than 90,000 women aged 50 and older followed for 5 or more years to detect a statistically significant reduction in mortality rates of 9%–10%.

Nonetheless, previous randomized controlled trials, most of which enrolled only older women, have also shown non-significant reductions in total mortality. A recent meta-analysis of nine trials testing vitamin D supplementation reported an overall HR of 0.93 (95% CI, 0.87–0.99); however, this point estimate largely reflects the contribution of WHI women who contributed a majority of the person-time. Six of the remaining eight smaller trials showed nonsignificant reductions in total mortality (4). Cause-specific mortality was examined in only one previous trial and showed nonsignificant reductions in cardiovascular, total cancer, and colorectal cancer mortality with very wide CIs (3).

If the results did not occur by chance, multiple pathways could be involved including any elements of the supplements tested: calcium, vitamin D₃, or carbonate, or all. Calcium supplementation has been shown in small experimental studies to lower blood pressure (10) and reduce cholesterol levels (11–13). Observational epidemiological studies have shown an association of calcium intake with reduced stroke incidence and mortality (14–16) and inconsistent associations with reduced risk of coronary disease (16,17). Lower bone density has been associated with increased mortality

risks (18,19). In the WHI CaD trial, the intervention group had statistically significant but small reductions in low-density lipoprotein, weight, and waist circumference, whereas blood pressure change was slightly increased compared with placebo (20). Although the intervention improved hip-bone density by about 1%, it produced no significant differences in CHD or stroke incidence.

Vitamin D insufficiency has now been linked to a broad spectrum of human diseases from cancer to cardiovascular to autoimmune conditions (21). A recent ecological study showed consistently elevated death rates from cancer sites among U.S. women with less solar ultraviolet-B exposure (22). Vitamin D receptors are present in many cell types and 1,25-dihydroxyvitamin D has been shown to favor cell differentiation over proliferation and to inhibit potential for metastasis and invasiveness (23). Serum vitamin D levels were inversely associated with colon cancer risk in the Nurses' Health Study (24), in the WHI CaD trial (6), and with colon cancer mortality in National Health and Nutrition Examination Survey (25). Supplementation with 1,100 IU of vitamin D₃ reduced the risk of cancer in a recent small trial of healthy postmenopausal women (26). Two recent prospective studies link levels of serum 25-hydroxyvitamin D below 44.4 nmol/L (27) or 25.2 nmol/L (28) to increased risk of total mortality.

The emerging optimism over vitamin D supplementation for the prevention of cancer (29) is occurring in the absence of confirmation from large prevention trials that can determine the benefits and any currently unknown risks. Proponents argue that the necessary levels of vitamin D supplementation

Table 3. HRs Relating CaD to Risk of Total Mortality Stratified by Selected Baseline Characteristics

	CaD (N=18,176)		Placebo (N=18,106)		HR (CI)*	p Value for Interaction†
	No. of Deaths	%	No. of Deaths	%		
Ethnicity						.30
White	607	0.57	679	0.64	0.89 (0.80–0.99)	
Black	79	0.68	89	0.78	0.91 (0.67–1.23)	
Hispanic	23	0.42	11	0.22	2.28 (1.07–4.87)	
American Indian	5	0.93	4	0.79	0.84 (0.16–4.48)	
Asian/Pacific Islander	18	0.73	12	0.51	1.60 (0.75–3.43)	
Other/Unknown	12	0.83	12	0.81	0.90 (0.45–1.80)	
HT use at annual visit 1						.14
Never used	280	0.69	275	0.69	1.00 (0.84–1.18)	
Past user	118	0.56	155	0.75	0.74 (0.58–0.94)	
Current user	346	0.52	377	0.57	0.93 (0.80–1.07)	
Calcium supplementation, mg						.64
None	366	0.64	369	0.66	0.97 (0.84–1.12)	
<500	199	0.57	226	0.66	0.86 (0.71–1.04)	
≥500	179	0.50	212	0.58	0.87 (0.71–1.06)	
Baseline total calcium (supplements)						.20
<800	282	0.65	313	0.74	0.88 (0.75–1.04)	
800 to <1,200	186	0.56	204	0.63	0.88 (0.72–1.08)	
≥1,200	259	0.53	269	0.54	0.98 (0.83–1.17)	
Baseline total vitamin D (supplements)						.59
<200	275	0.56	303	0.64	0.88 (0.74–1.03)	
200 to <400	144	0.60	150	0.62	0.98 (0.78–1.23)	
400 to <600	170	0.58	189	0.63	0.92 (0.75–1.14)	
≥600	138	0.58	144	0.62	0.93 (0.73–1.17)	
Latitude of clinical center						.70
Southern: <35° north	232	0.60	255	0.67	0.89 (0.74–1.06)	
Middle: 35°–40° north	209	0.60	238	0.69	0.86 (0.71–1.03)	
Northern: >40° north	303	0.55	314	0.57	0.96 (0.82–1.13)	
Blood pressure						.39
Treated	237	0.77	278	0.92	0.84 (0.70–1.00)	
≥140/90	305	0.64	307	0.65	0.98 (0.84–1.15)	
Normal	202	0.40	222	0.45	0.90 (0.75–1.09)	
Smoking						.20
Never smoked	326	0.49	322	0.48	1.01 (0.86–1.17)	
Past smoker	300	0.59	355	0.71	0.83 (0.71–0.97)	
Current smoker	108	1.11	120	1.28	0.87 (0.67–1.13)	
Physical activity (METs/wk)						.06
≤3.00	237	0.63	278	0.75	0.85 (0.71–1.01)	
>3.00 to <11.75	218	0.58	249	0.66	0.88 (0.73–1.06)	
≥11.75	188	0.49	179	0.47	1.03 (0.84–1.26)	
No. of CVD risk factors						.59
None	130	0.32	153	0.38	0.85 (0.67–1.08)	
1–2	596	0.69	616	0.73	0.95 (0.85–1.07)	
≥3	18	0.89	38	1.70	0.49 (0.27–0.87)	
Body mass index, kg/m ²						.49
<25	197	0.58	216	0.63	0.93 (0.76–1.12)	
25 to <30	232	0.51	261	0.57	0.89 (0.74–1.06)	
≥30	315	0.66	328	0.70	0.93 (0.80–1.09)	
History of CVD						.90
No	645	0.54	694	0.58	0.92 (0.82–1.02)	
Yes	99	1.25	113	1.38	0.91 (0.70–1.20)	
Number of chronic conditions‡						.67
None	95	0.32	107	0.36	0.86 (0.65–1.14)	
1	300	0.52	298	0.52	1.00 (0.86–1.18)	
2	244	0.72	283	0.84	0.86 (0.72–1.02)	
3 or more	105	1.49	119	1.73	0.87 (0.66–1.13)	
Self-reported health status						.13
Excellent	84	0.39	79	0.36	1.14 (0.83–1.55)	
Very good	296	0.52	305	0.54	0.93 (0.79–1.09)	
Good	273	0.67	304	0.75	0.89 (0.76–1.05)	
Fair	79	0.99	106	1.28	0.79 (0.59–1.06)	
Poor	12	2.31	13	3.07	0.51 (0.18–1.43)	

Notes: CaD = calcium and vitamin D; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; HT = hormone therapy; MET = metabolic equivalent.

*HRs and 95% CIs are derived from Cox proportional hazards models stratified by age and randomization in the WHI dietary modification or HT trial, or both.

†p values are for the interaction between the subgroup variable and treatment assignment.

‡Number of chronic conditions includes self-report of coronary heart disease, congestive heart failure, treated diabetes, hypertension (treated or untreated), hip fracture, emphysema, cancer, or arthritis. HT at annual visit 1 includes randomized treatment assignment in the WHI HT trial and personal use of HT.

Table 4. ORs* for Total Mortality According to Tertile of Serum 25-Hydroxyvitamin D Level and CaD Study Group, as Determined in a Nested Case-Control Study

	Main Effect OR [†] (95% CI)	CaD, Cases/Controls	Placebo, Cases/Controls	OR (95% CI)	p Value for Interaction
Tertile of serum 25-hydroxy vitamin D, nmol/L					.65
≥52.5	1.00	53/404	50/425	1.04 (0.69–1.59)	
35.4–52.4	1.42 (1.06–1.91)	57/301	59/296	0.96 (0.64–1.45)	
<35.4	1.46 (1.07–1.99)	47/270	57/266	0.79 (0.51–1.23)	

Notes: CaD = calcium and vitamin D; CI = confidence interval; OR = odds ratios.

*ORs were derived from logistic regression models stratified by age group and randomization assignment in the hormone therapy or dietary modification trial, or both, and further adjusted for age, ethnicity (white, black, Hispanic, other), latitude of clinical center, and season of blood draw.

[†]Serum 25-hydroxyvitamin D main effects models are also adjusted for CaD treatment assignment.

to exert anticancer effects might be 1,500–2,000 IU/d based on selective findings from observational studies (30,31). The optimum dose of vitamin D for reducing cancer or mortality is unknown and, if it exists, can only be determined from future large randomized trials.

The trends toward reductions in risks of both cardiovascular and cancer mortality in this trial, if real, suggest mechanisms that may have broad physiological effects. Vitamin D supplementation has been shown experimentally to increase levels of the anti-inflammatory cytokine interleukin-10, while preventing increases in tumor necrosis factor alpha (32). Calcium and vitamin D supplementation both lower parathyroid hormone levels (PTH), and PTH levels have been associated with an increased risk of mortality in a vitamin D-deficient cohort of the very old age (33). Chronic metabolic acidosis increases with age and declining kidney function even when plasma measures of acid-base balance are normal. Administration of bicarbonate has been shown to reverse acidosis (34,35). Beneficial effects of CaD supplementation on cytokine profiles, PTH, or acidosis might be expected to produce greater benefits in older women, whereas the opposite trend was observed in this trial. However, it is also possible that mortality could be delayed by improvements in these parameters and eventually benefits diminish with disease progression in later life.

Strengths of this trial include its large size, diversity, long duration, excellent retention, and reasonably good adherence for an average of 7 years of follow-up. This study is limited by lack of statistical power for detecting intervention effects on mortality, as it was not designed for this purpose. We did not collect postintervention serum specimens for exploring potential intermediate effects of the intervention that might have influenced mortality. We cannot distinguish between effects of calcium, vitamin D, or carbonate because the intervention combined these ingredients. We do not know whether higher supplement doses of vitamin D would have produced different results.

In conclusion, the WHI CaD trial supports the hypothesis that CaD supplementation provides a modest reduction in rates of total and categories of cause-specific mortality, but the results are too imprecise to be definitive. Moreover, these data can neither support nor refute recommendations for higher dose vitamin D supplementation to reduce cancer or total

mortality. This hypothesis merits further consideration by testing alternative underlying mechanisms and possibly by testing higher dose supplements in even larger randomized trials.

SUPPLEMENTARY MATERIAL

Supplementary material can be found at: <http://biomed.gerontologyjournals.org/>.

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