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Calcium Plus Vitamin D Supplementation and Health Outcomes Five Years After Active Intervention Ended: The Women's Health Initiative

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Abstract

Background: Clinical outcomes of the Women's Health Initiative (WHI) calcium plus vitamin D supplementation trial have been reported during 7.0 years of active intervention. We now report outcomes 4.9 years after the intervention stopped and cumulative findings.
Methods: Postmenopausal women ($N = 36,282$) were randomized; postintervention follow-up continued among 29,862 (86%) of surviving participants. Primary outcomes were hip fracture and colorectal cancer. Breast cancer, all cancers, cardiovascular disease (CVD), and total mortality were predetermined major study outcomes.
Results: Hip fracture incidence was comparable in the supplement and the placebo groups, postintervention hazard ratio (HR) = 0.95, 95% confidence interval (95% CI: 0.78, 1.15) and overall HR = 0.91 (95% CI: 0.79, 1.05). Overall, colorectal cancer incidence did not differ between randomization groups, HR = 0.95 (95% CI: 0.80, 1.13). Throughout, there also was no difference in invasive breast cancer, CVD, and all-cause mortality between groups. In subgroup analyses, the invasive breast cancer effect varied by baseline vitamin D intake ($p = 0.03$ for interaction). Women with vitamin D intakes >600 IU/d, had an increased risk of invasive breast cancer, HR = 1.28 (95% CI; 1.03, 1.60). Over the entire study period, in *post hoc* analyses, the incidence of vertebral fractures, HR = 0.87 (95% CI: 0.76, 0.98) and *in situ* breast cancers, HR = 0.82 (95% CI: 0.68, 0.99) were lower among women randomized to supplementation.
Conclusion: After an average of 11 years, calcium and vitamin D supplementation did not decrease hip fracture or colorectal cancer incidence. Exploratory analyses found lower vertebral fracture and *in situ* breast cancer incidence in the supplement users. There was no effect on CVD or all-cause mortality.

Introduction

The Women's Health Initiative (WHI) calcium plus vitamin D trial assessed whether 1000 mg of elemental calcium as calcium carbonate[1] with 400 IU of vitamin D_3 reduced the risk of hip fracture and colorectal cancer in 36,282 postmenopausal women.[2,3] During an intervention that averaged 7.0 years, hip fractures rates were similar between supplement use and placebo; among women adherent to study medication, there was a 29% decrease in hip fracture for supplement users compared to the placebo group.[2] No significant differences were seen for colorectal cancer,[3] *in situ* or invasive breast cancer,[4] cardiovascular disease (CVD),[5] overall cancer incidence,[6] or all-cause mortality.[7]

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Previous trial reports included only outcomes during the intervention phase. Herein, we report postintervention outcomes through an additional 4.9 years (mean) follow-up for a total follow-up of 11.1 years. These preplanned analyses assessed the long-term effects of calcium plus vitamin D supplementation on health outcomes using intent to treat analysis. We also examined whether effects changed postintervention or differed by subgroups defined by adherence, age, total baseline vitamin D intake, and use of calcium supplements at trial entry.

Methods

Intervention phase

The trial details have been reported.[1–3] Briefly, postmenopausal women enrolled in the WHI dietary modification trial, hormone therapy trials, or both were invited to join the calcium plus vitamin supplementation D trial. Eligible women were 50 to 79 years old with anticipated 3-year survival. Personal supplemental calcium (up to 1000 mg/d) and vitamin D (up to 600 IU/d and subsequently raised to 1000 IU) were allowed.[8,9] The study protocol was approved by institutional review boards at the participating institutions and all participants provided written informed consent.

A total of 36,282 participants were randomly assigned to daily calcium (1000 mg of calcium carbonate) plus vitamin D (400 IU D_3) or matching placebo tablets (provided by GlaxoSmithKline). "Baseline" in this report refers to the baseline at the intervention phase. When the intervention phase ended as scheduled on March 30, 2005, vital status was known for 93% of women, of whom 4.6% were deceased. At that time, 76% were still taking study supplementation and 59% took 80% or more of it with little difference between groups.[3] Women were told of their treatment assignment at study closeout. The postintervention phase began on the closeout date. The current report reflects findings through September 30, 2010. After intervention ended, subsequent follow-up required reconsent which was obtained for 86% of surviving participants with no differences in participation in the follow-up by randomized group. We collected information on calcium and vitamin D supplementation at the end of the extension period.

Clinical outcomes

Outcomes were ascertained semi-annually during the intervention and annually, postintervention. If a woman reported an event, we obtained permission from her to obtain her medical records. Medical records from each event were obtained to centrally adjudicate outcomes. Primary outcomes of the trial included hip fracture and colorectal cancer. Invasive breast cancer, all cancers, coronary heart disease (CHD) including myocardial infarction (MI), stroke, total CVD, and total mortality were prespecified as secondary outcomes. A global index of outcomes was created as a summary measure of the overall risks and benefits and included hip fracture, invasive breast and colorectal cancers and death. Vertebral fractures and *in situ* breast cancer were exploratory *post hoc* analyses. Nonhip fractures were adjudicated during the intervention phase and based on self-report thereafter. In WHI, 76% of self-reported fractures were confirmed by radiographic report.[10]

Other measurements

Demographic characteristics and medical history were collected using standardized questionnaires. Calcium intake before randomization was defined as the dietary calcium intake (assessed with a modified Block food-frequency questionnaire),[11] the intake of calcium from supplements in the previous 2 weeks, and the intake of calcium from prescription medications (assessed though an interviewer-administered medication survey). Total vitamin D intake was similarly determined. Mammogram reports were obtained, reviewed, and coded for radiologist recommendation.

Statistical analyses

Baseline characteristics for women who reconsented were compared with women who did not reconsent and by randomization group using chi-square tests of association. Annualized rates of clinical events were estimated for the intervention phase, the postintervention phase, and overall by dividing the number of events by the corresponding person-time in each phase.

The primary analyses included all randomized participants using time to event methods based on the intention to treat principle.[12] Hazard ratios (HRs) were estimated using Cox proportional hazards models[13] stratified by age, prior disease (if appropriate), and randomization status in the WHI dietary modification[14] and the hormone therapy trials.[15,16] Models were constructed for each clinical outcome in which women contributed follow-up time until the end of the interval, the date of their first relevant clinical event, or the date of death or withdrawal from the study (whichever came first). Formal tests of differences between the HRs in the intervention and postintervention phase were calculated by inclusion of a binary term for trial phase as a time dependent variable as described.[12] All statistical tests were two-sided.

Nominal *p*-values are reported without adjustment for multiple outcomes or sequential looks. Age, total baseline calcium and vitamin D intake, baseline calcium supplement use (yes/no), and hormone trial stratified analyses were tested for 14 outcomes. At the 0.05 level of significance, approximately four interaction *p*-values could be statistically significant based on chance alone. To determine whether reconsent influenced risk estimates, inverse-probability weighting analyses were conducted.[17] Adherence sensitivity analyses were conducted by censoring follow-up 6 months after nonadherence (ingestion of $<80\%$ of study pills). For these analyses, participants who provided additional consent or were adherent were included in analyses that used the inverse of the participant's estimated reconsent or adherence probability as a weighting factor.

Based on differential supplement influence on invasive and *in situ* breast cancer, analyses examining mammogram diagnostic performance were conducted separately for invasive and *in situ* breast cancer. The sensitivity, specificity, and positive and negative predictive values for serial mammograms were evaluated as previously described.[18] All statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc., Cary, NC) and S-Plus software version 8.0 (TIBCO software, Inc, Sommerville, MA).

Results

Participant movement through the study is outlined in Appendix Figure A1. The results include findings from all

36,282 randomized participants through the intervention phase and additional findings from the 29,862 women who reconsented. The latter were younger, more likely to be white, slightly less likely to have a history of stroke or MI or to be obese, reported higher education and higher use of calcium and/or vitamin D supplementation compared to women who did not re-consent (Appendix Table A1). There was no significant difference in the percentage of women who joined the extension study by randomized group. Of importance, the baseline characteristics of participants in the postintervention phase were similar by randomization assignment (Table 1).

Comparison of intervention and postintervention findings

Incident clinical events by randomization assignment and corresponding HRs for the intervention, postintervention, and overall follow-up periods are summarized in Figures 1 and 2. Postintervention hip fractures were similar in the two randomized groups, HR = 0.95 (95% CI: 0.78, 1.15). Vertebral fractures were 17% lower, HR = 0.83 (95% CI: 0.71, 0.98) in the supplement group compared to placebo. Over the entire period, calcium and vitamin D supplementation significantly reduced clinical vertebral fractures but did not influence hip or other fractures.

The HR for colorectal cancer postintervention was HR = 0.80 (95% CI: 0.61, 1.07), but the HR was close to unity overall indicating no overall difference by randomized group. Over the entire follow-up, the HR for invasive breast cancer was close to unity. Postintervention, there was some suggestion that invasive breast cancer incidence was increased in the supplement group HR = 1.17 (95% CI: 0.99, 1.38), but results were not significant ($p = 0.07$ comparing HR in the intervention and postintervention periods. In contrast, postintervention, *in situ* breast cancer incidence was significantly decreased in the supplement (0.08%) compared to the placebo group (0.12%; HR = 0.63 [95% CI: 0.45, 0.88], $p = 0.07$ for difference between phases). Overall, the risk of *in situ* breast cancer was 18% lower in the supplement group (HR = 0.82; 95% CI: 0.68, 0.99).

CVD event rates in a comparison of supplement and placebo groups were similar in the intervention and postintervention phases and close to unity overall. The suggestion of lower total mortality in the supplement group during the intervention was not maintained postintervention (HR = 1.01; 95% CI: 0.92, 1.10). Overall, cancer deaths (data not shown) and deaths from all causes were similar in the two randomization groups.

Mammography use did not differ in the two randomized groups, and there was no consistent pattern of mammogram performance differences in sensitivity, specificity, or accuracy by randomized group for either invasive or *in situ* breast cancer (data not shown). The accuracy of the mammograms was >98% in both randomized groups.

Analyses stratified by age

Overall, the effect of supplementation on hip fracture did not differ by age (Table 2). Vertebral fracture risk was about 20% lower in the supplement group at least for women age >60. The risk of *in situ* breast cancer was consistently lower in women randomized to calcium plus vitamin D irrespective of age. For other outcomes there was little difference in the HR across age groups.

Analyses stratified by vitamin D intake at baseline

In the combined trial phases, the incidence of hip fracture, vertebral fracture, all fractures, and colorectal cancer in women randomized to calcium plus vitamin D or placebo did not differ by total baseline vitamin D intake (Table 3). Results for invasive breast cancer showed a significant interaction between total vitamin D intake and calcium plus vitamin D, suggesting heterogeneity in the effects of calcium and vitamin D supplementation on invasive breast cancer by total vitamin D intake. A higher incidence in invasive breast cancer was observed in women with higher baseline vitamin D intakes (>600 IU/day; HR = 1.28; 95% CI: 1.03, 1.60; $p = 0.03$ for interaction). A similar but less pronounced pattern was seen for total cancer ($p = 0.07$ for interaction), but not for *in situ* breast cancer. There was no significant effect of supplementation on CHD, stroke, total mortality, or the global index by baseline vitamin D intake.

Analyses stratified by calcium supplement use (with or without vitamin D)

There was little evidence of a differential effect of randomization assignment on most clinical outcomes when use of nonprotocol baseline calcium supplementation at baseline was considered (Table 4). However, women in the supplement group had approximately 9% lower relative risk of developing any cancer if they were not using calcium supplement at baseline ($p = 0.04$ for interaction).

Sensitivity analyses

Among women who were adherent (took >80% of study pills), calcium plus vitamin D was associated with 29% lower hip fracture risk during the intervention phase. Overall, there was a 23% statistically significant reduction in hip fracture among adherent women (HR = 0.77; 95% CI: 0.60, 0.99). Results for vertebral fracture were consistent with this observation but CI includes 1.0 (HR = 0.81; 95% CI: 0.65, 1.02). Overall, there was little effect of calcium plus vitamin D supplementation among adherent women on colorectal or invasive breast cancer. The risk of *in situ* breast cancer was lower in adherent supplement group participants, but this association was not significant (HR = 0.72; 95% CI: 0.51, 1.01). CVD and cancer mortality were similar in the two randomization groups in analyses limited to adherent women. However, all-cause mortality was lower in adherent women randomized to calcium plus vitamin D compared to placebo (HR = 0.91; 95% CI: 0.82, 1.00), respectively. The summary index of overall benefits and risks suggested a greater benefit for supplementation among adherent women (HR = 0.87; 95% CI, 0.80, 0.95).

Discussion

Over the entire intervention and postintervention period, there was no effect of calcium plus vitamin D supplementation on hip fractures or colorectal cancer, the primary outcomes of the trial. However, over the combined phases, women who were adherent to the supplement during the intervention had a significant 23% reduction in hip fracture risk and experienced greater benefits than risks. This observation is consistent with previous analyses of the calcium vitamin D trial, which demonstrated reduced hip fracture

Table 1. Descriptive Characteristics of Women's Health Initiative Calcium Plus Vitamin D Trial Extension Study Participants at Baseline by Randomization Assignment

	CaD (N = *15,025*)		*Placebo* (N = *14,837*)		
	N	%	N	%	p-*value*
Age group at screening, years					0.80
50–59	5729	38.1	5602	37.8	
60–69	6924	46.1	6883	46.4	
70–79	2372	15.8	2352	15.9	
Race/ethnicity					0.37
White	12,694	84.5	12,648	85.2	
Black	1278	8.5	1222	8.2	
Hispanic	546	3.6	480	3.2	
American Indian	55	0.4	51	0.3	
Asian/Pacific Islander	295	2.0	274	1.8	
Unknown	157	1.0	162	1.1	
Education					0.53
None to some high school	677	4.5	632	4.3	
High school diploma or equivalent	2715	18.2	2723	18.5	
School after high school	5901	39.5	5755	39.0	
College degree or higher	5640	37.8	5636	38.2	
Gail 5-year risk of breast cancer					0.84
<1.25	5176	34.4	5065	34.1	
1.25–1.74	4993	33.2	4965	33.5	
≥1.75	4856	32.3	4807	32.4	
Medical history					
Kidney stones	133	1.0	136	1.0	0.78
Stroke	111	0.7	128	0.9	0.23
Myocardial infarction	237	1.6	212	1.4	0.29
Fracture	5242	38.4	5120	38.1	0.56
Prior hormone use[a]					0.48
None	4688	31.2	4589	30.9	
Past	2456	16.3	2346	15.8	
Current estrogen-alone	3768	25.1	3764	25.4	
Current estrogen + progestin	4113	27.4	4138	27.9	
Body mass index, kg/m^2					0.21
<25	3992	26.7	4038	27.4	
25–<30	5411	36.2	5385	36.5	
≥30	5545	37.1	5335	36.1	
Physical activity, metabolic equivalents (MET), h/wk					0.78
None	2548	18.6	2491	18.4	
0.5–4.125	2848	20.7	2797	20.7	
>4.125–9.5	2763	20.1	2709	20.0	
>9.5–17.75	2823	20.6	2734	20.2	
≥17.75	2746	20.0	2788	20.6	
Alcohol intake					0.97
Nondrinker	1502	10.1	1486	10.1	
Past drinker	2467	16.5	2486	16.9	
<1 drink per month	2086	14.0	2055	13.9	
<1 drink per week	3218	21.6	3143	21.3	
1–<7 drinks per week	4016	26.9	3981	27.0	
≥7 drinks per week	1625	10.9	1587	10.8	
Smoking					0.14
Never	7774	52.2	7841	53.4	
Past	6045	40.6	5826	39.7	
Current	1060	7.1	1019	6.9	
Total vitamin D (supplements + diet), IU/d[b]					0.12
<200	5538	37.5	5348	36.7	
200–<400	2765	18.7	2830	19.4	
400–<600	3498	23.7	3567	24.4	
≥600	2955	20.0	2845	19.5	

(*continued*)

Table 1. (Continued)

	CaD (N = 15,025)		Placebo (N = 14,837)		
	N	%	N	%	p-*value*
Vitamin D supplement use[b]	7238	48.2	7188	48.4	0.64
Geographic region at randomization by latitude					0.98
Southern, < 35°N	4187	27.9	4123	27.8	
Middle, 35–40°N	4266	28.4	4227	28.5	
Northern, ≥ 40°N	6572	43.7	6487	43.7	
Total calcium intake (supplements + diet + medications), mg/d[b]					0.51
< 800	4852	32.9	4728	32.4	
800– < 1200	3904	26.5	3834	26.3	
≥ 1200	6000	40.7	6028	41.3	
Calcium and/or vitamin D supplement use[b]	8678	57.8	8662	58.4	0.27
Hormone therapy trial participant	6496	43.2	6420	43.3	0.95
Diet modification trial participant	10,543	70.2	10,467	70.5	0.48

[a]Values incorporate hormone therapy use during year 1 of the clinical trial, including exposure to the hormone therapy trials.
[b]Vitamin D and calcium variables incorporate intake reported at baseline of the Calcium/D trial.

incidence with longer term use.[19] Clinical vertebral fracture risk, a *post hoc* outcome was lower postintervention and during the cumulative follow-up period among women randomized to supplements: There would be four fewer vertebral fractures in 10,000 women taking supplements for 1 year. No overall influence of calcium plus vitamin D on invasive breast cancer was seen. Other major health risks and benefits of calcium plus vitamin D including CVD and death appeared balanced. Exploratory analysis revealed, a lower risk of *in situ* breast cancer postintervention among those randomized to supplements and was significant over the entire period: Absolute risk reduction *in situ* breast cancers would be two fewer women with *in situ* breast cancer in 10,000 women in 1 year.

While speculation has arisen regarding calcium supplementation and increased CVD risk,[20,21] our current analyses after a total of 11 years provides no evidence of an effect on CHD events including CHD death, clinical MI, and stroke. This was true in both women who took a calcium supplement at study entry and those who were not taking a calcium supplement. A lower total mortality was suggested during the main trial with calcium plus vitamin D, but this was not maintained in the postintervention and overall there was no effect of calcium plus vitamin D on total mortality. In addition, the null effect of calcium plus vitamin D on colorectal cancer was consistent throughout the trial, the extension, and overall and in subgroups defined by age, total vitamin D intake, and use of calcium supplements at study baseline.

Cumulatively, calcium and vitamin D supplementation did not reduce invasive breast cancer, and thus the main findings do not support a causal association between supplement use and reduced breast cancer. However, in the postintervention period, a possible increased risk of invasive cancer was suggested. In addition, in subgroup analysis, the effect of calcium plus vitamin D differed by intake of total vitamin D. Overall, we found a significantly increased invasive breast cancer incidence in women with the highest baseline vitamin D intake randomized to the supplement group. This finding over the combined intervention and extension period is consistent with earlier analysis of the intervention.[4] In general, epidemiologic studies on the association between vitamin D and calcium supplementation and breast cancer are mixed but most studies either supported an inverse association or a null association.[22,23] The significant interaction between calcium plus vitamin D and higher total intake of vitamin D needs replication in future studies.

While a statistically significant overall reduction *in situ* breast cancer with no effect on invasive breast cancer incidence overall is puzzling, an influence of calcium plus vitamin D on breast cancer is biologically plausible. Vitamin D influences mammary gland development and function[24,25] and some observational studies have associated lower 25-hydroxyvitamin D levels with lower invasive breast cancer risk. However, a recent meta-analysis of cohort studies found only a weak association.[26]

If women randomized to calcium plus vitamin D were less likely to obtain a routine mammogram then an ascertainment bias might explain the lower risk of *in situ* breast cancer in the supplement group. However, there was no difference in mammography use by randomized group. If vitamin D or calcium interfered with *in situ* breast cancer detection by mammography (by which diagnosis is commonly based on detection of calcifications) but not invasive breast cancer detection (by which diagnosis is commonly based on detection of a mass), a lower *in situ* breast cancer incidence could reflect diagnostic delay. However, mammogram performance was not compromised by supplement group randomization. Findings are mixed regarding the association of vitamin D use with mammographic breast density.[26,27] A previous WHI report showed that calcium and vitamin D supplementation did not affect mammographic density.[28]

While some interventions, including neoadjuvant chemotherapy[29,30] and raloxifene,[31] have greater influence on invasive compared with *in situ* breast cancer, we could find no prior intervention that lowers *in situ* breast cancer incidence but doesn't influence invasive breast cancers. The annualized rates of invasive breast cancer were about 4 times higher than the rate of *in situ* cancer, and *in situ* cancers have better survival rates.[32] Thus, the public health implication of this

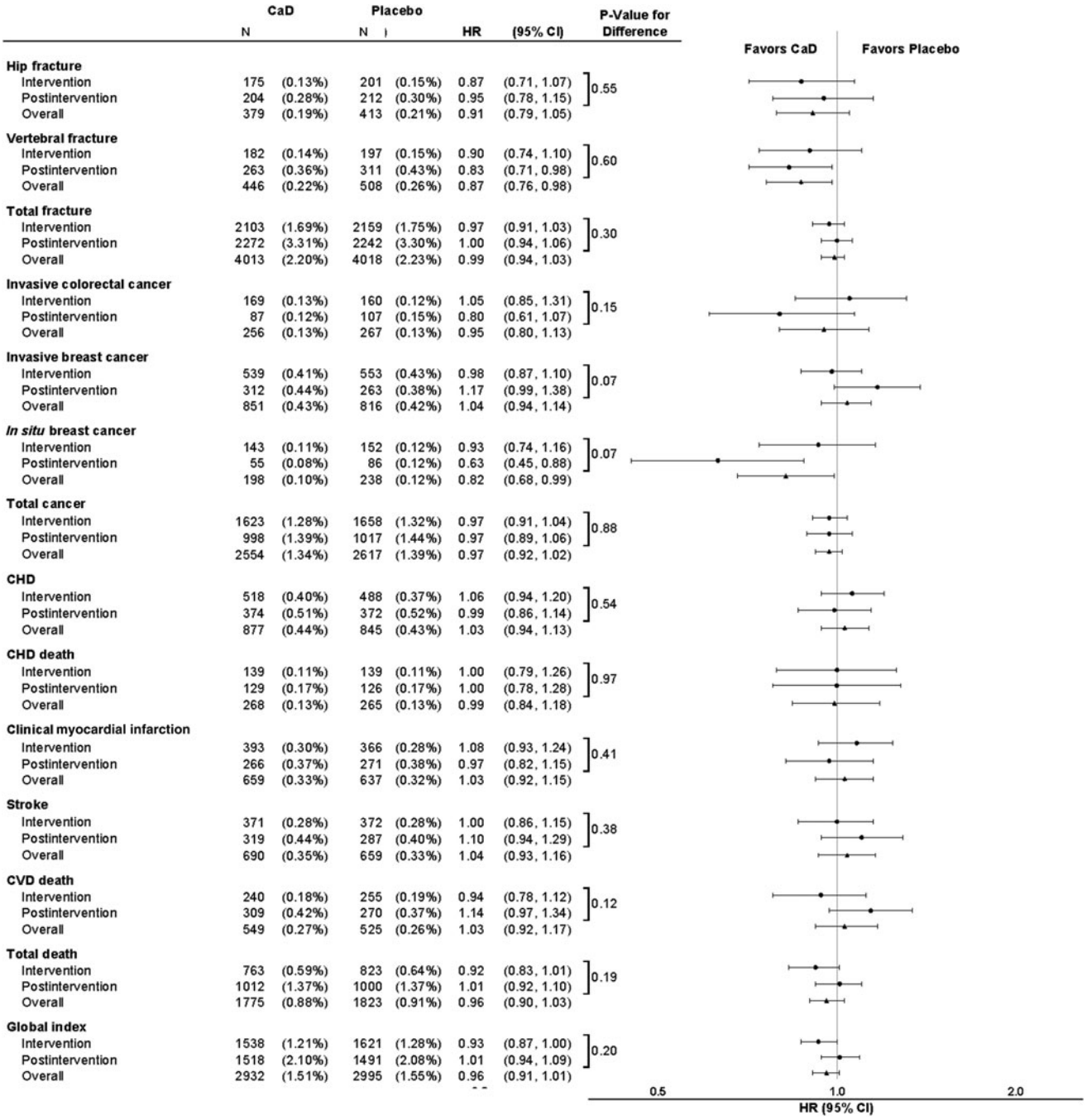

FIG. 1. Incident clinical events by randomization assignment and corresponding hazard ratios (HRs) for the intervention, postintervention, and overall follow-up period. The HR and 95% confidence interval (CI) for intervention period events are derived from a proportional hazards model stratified on age, prevalent condition (where appropriate), and randomization arm in the hormone therapy (HT) and diet modification (DM) trials, where time to event equals 0 on date of randomization. The HR and CI for postintervention period events are derived from a Cox proportional hazards model stratified on age, prevalent condition (where appropriate), and randomization arm in the HT and DM trials, where time to event equals 0 on calcium and vitamin D (CaD) trial close-out date. The HR and CI for the overall combined period events are derived from a proportional hazards model stratified by prevalent condition (where appropriate), age, HT and DM randomization arm, and trial phase (time-dependent), where time to event equals 0 on date of randomization. *P*-values for the difference between the intervention and postintervention periods are derived from a Cox proportional hazards models stratified by prevalent condition (where appropriate), age, HT and DM randomization arm, and trial phase (time-dependent), where time to event equals 0 on date of randomization. The *p*-value tests whether the HR for the intervention period equals the HR for the postintervention period. All nonhip fractures use adjudicated data during the clinical trial and self-reported data thereafter.

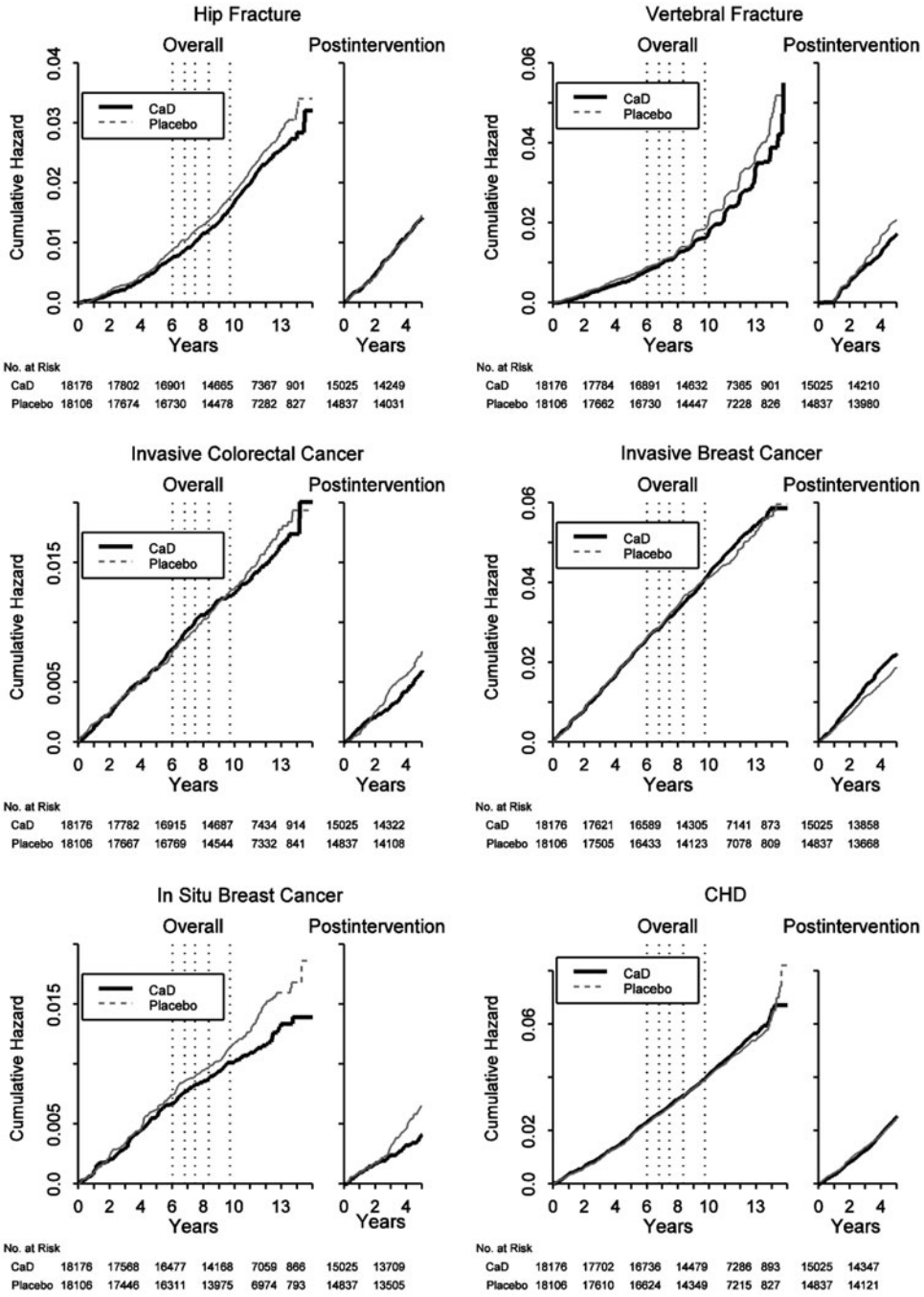

FIG. 2. Risks and benefits by randomization assignment to calcium plus vitamin D supplementation or placebo before or after termination of the intervention. Kaplan Meier cumulative hazards for clinical outcomes, by time in the trial and time after termination of the intervention. Dotted vertical lines represent quintiles of duration of the intervention in the study population (elapsed time from randomization until the main study close-out). Overall curves include events from randomization to September 30, 2010. Postintervention curves include events from CaD study close-out to September 30, 2010. CHD, coronary heart disease.

finding is uncertain. Additionally, in the current study, supplementation had no influence on benign proliferative breast disease.[33] As a result, the lower *in situ* breast cancer incidence in the supplement group could represent a chance finding. However, emergence of lower *in situ* breast cancer incidence only occurred after a long period of supplement exposure and postexposure follow-up suggests a duration effect with perhaps an influence on subsequent invasive breast cancer to emerge after still longer follow-up. Cohorts with long-term supplement exposure information could address such a hypothesis.

In the postintervention period, a significant 17% reduction in clinical vertebral fractures emerged with no difference in the effect of calcium plus vitamin D supplementation on vertebral fractures between the intervention and postintervention period. Overall, calcium plus vitamin D reduced clinical vertebral fractures. Although these results are from a *post hoc* analysis, these results are important because vertebral fractures are the most common osteoporotic fracture, occurring in an estimated 30%–50% of individuals age 50 and older.[34] Vertebral fractures are major risk factors for future fractures including hip fractures.[35,36] They also are associated with significant morbidity and mortality.[37–39] Thus, our results suggest that calcium plus vitamin D supplementation could reduce the burden of vertebral fractures over the long term, although more research is needed before this conclusion can be applied to clinical practice. Failure to see an effect on hip fractures may reflect low statistical power because we

Table 2. Cumulative Annualized Incidence Rates for Clinical Outcomes in the Women's Health Initiative Calcium and Vitamin D Supplementation Trial According to 10-Year Age Groups at Enrollment

	Overall combined phases						
	CaD		*Placebo*				
	N	%	N	%	*HR**	*(95% CI)*[a]	*Interaction* p-*value*[a]
Hip fracture							0.18
50–59	55	0.07	36	0.05	1.47	(0.97, 2.24)	
60–69	141	0.16	175	0.19	0.80	(0.64, 1.00)	
70–79	183	0.57	202	0.64	0.90	(0.73, 1.10)	
Vertebral fracture[b]							0.33
50–59	97	0.12	85	0.11	1.12	(0.84, 1.50)	
60–69	210	0.23	249	0.28	0.83	(0.69, 1.00)	
70–79	139	0.43	174	0.55	0.79	(0.63, 0.99)	
Total fracture[b]							0.34
50–59	1284	1.79	1239	1.75	1.02	(0.94, 1.10)	
60–69	1841	2.24	1825	2.24	1.00	(0.93, 1.06)	
70–79	888	3.12	954	3.42	0.92	(0.84, 1.01)	
Invasive colorectal cancer							0.87
50–59	58	0.07	59	0.08	0.97	(0.68, 1.40)	
60–69	122	0.13	136	0.15	0.88	(0.69, 1.13)	
70–79	76	0.23	72	0.22	1.06	(0.77, 1.46)	
Invasive breast cancer							0.57
50–59	308	0.40	286	0.38	1.06	(0.90, 1.25)	
60–69	397	0.45	388	0.44	1.02	(0.89, 1.18)	
70–79	146	0.46	142	0.45	1.03	(0.81, 1.29)	
In situ breast cancer							0.82
50–59	74	0.10	89	0.12	0.82	(0.60, 1.12)	
60–69	93	0.11	110	0.13	0.85	(0.64, 1.12)	
70–79	31	0.10	39	0.12	0.75	(0.46, 1.20)	
Total cancer							0.13
50–59	816	1.10	781	1.07	1.03	(0.93, 1.13)	
60–69	1233	1.44	1268	1.49	0.97	(0.89, 1.05)	
70–79	505	1.65	568	1.88	0.88	(0.78, 0.99)	
Coronary heart disease							0.28
50–59	155	0.20	149	0.19	1.01	(0.81, 1.27)	
60–69	409	0.46	413	0.46	0.99	(0.86, 1.13)	
70–79	313	0.99	283	0.90	1.10	(0.94, 1.30)	
Stroke							0.98
50–59	117	0.15	106	0.14	1.08	(0.83, 1.41)	
60–69	318	0.35	307	0.34	1.03	(0.88, 1.21)	
70–79	255	0.80	246	0.78	1.02	(0.86, 1.22)	
Total death							0.71
50–59	302	0.39	307	0.40	0.97	(0.82, 1.13)	
60–69	822	0.90	831	0.92	0.99	(0.90, 1.09)	
70–79	651	1.99	685	2.12	0.93	(0.84, 1.04)	
Global index							0.48
50–59	667	0.88	644	0.86	0.94	(0.84, 1.05)	
60–69	1343	1.53	1385	1.59	0.97	(0.90, 1.05)	
70–79	922	2.98	966	3.16	0.95	(0.87, 1.04)	

[a]From a proportional hazards model stratified by prevalent condition (where appropriate), age, hormone therapy and diet modification randomization arm, and trial phase (time-dependent). Time to event equals 0 on date of randomization.
[b]All nonhip fractures use adjudicated data during the clinical trial and self-reported data thereafter.

under-enrolled women age 70–79 in the trial, which thus influenced the observed number of hip fractures. Failure to see an effect on all fractures may reflect the heterogeneous etiology of different fracture sites.

Study strengths include the randomized double blind study design, large sample size, long follow-up, and high percentage of women who agreed to the extended follow-up. The women who reconsented to the extension differed by select characteristics, but of importance, there were no differences in characteristics by randomized group. Limitations include less than optimal adherence and the inability to separate the effects of calcium and vitamin D. Some have

Table 3. Cumulative Annualized Incidence Rates for Clinical Outcomes in the Women's Health Initiative Calcium and Vitamin D Supplementation Trial According to Baseline Total Vitamin D Intake, IU/Day

	Overall combined phases						
	CaD		*Placebo*				
	N	%	N	%	*HR*[a]	*(95% CI)*[a]	p-*value*[a]
Hip fracture							0.97
<200	138	0.18	140	0.19	0.93	(0.74, 1.18)	
200–<400	68	0.18	75	0.20	0.95	(0.68, 1.33)	
400–<600	80	0.17	112	0.24	0.74	(0.55, 0.98)	
≥600	87	0.23	77	0.21	1.07	(0.79, 1.46)	
Vertebral fracture[b]							0.70
<200	143	0.19	156	0.21	0.88	(0.70, 1.11)	
200–<400	79	0.21	93	0.25	0.85	(0.63, 1.15)	
400–<600	100	0.22	127	0.27	0.78	(0.60, 1.01)	
≥600	116	0.31	127	0.35	0.84	(0.65, 1.08)	
Total fracture[b]							0.95
<200	1456	2.11	1391	2.09	1.01	(0.93, 1.08)	
200–<400	708	2.07	771	2.25	0.93	(0.84, 1.03)	
400–<600	966	2.32	967	2.26	1.03	(0.94, 1.13)	
≥600	814	2.38	816	2.46	0.98	(0.89, 1.08)	
Invasive colorectal cancer							0.72
<200	91	0.12	95	0.13	0.95	(0.71, 1.27)	
200–<400	46	0.12	60	0.16	0.79	(0.54, 1.17)	
400–<600	70	0.15	60	0.13	1.21	(0.85, 1.71)	
≥600	43	0.11	48	0.13	0.84	(0.56, 1.28)	
Invasive breast cancer							0.03
<200	276	0.37	300	0.42	0.89	(0.76, 1.05)	
200–<400	178	0.49	168	0.45	1.10	(0.89, 1.36)	
400–<600	203	0.45	196	0.42	1.04	(0.85, 1.27)	
≥600	181	0.49	139	0.38	1.28	(1.03, 1.60)	
In situ breast cancer							0.31
<200	73	0.10	81	0.11	0.87	(0.64, 1.20)	
200–<400	37	0.10	45	0.12	0.83	(0.54, 1.28)	
400–<600	44	0.10	66	0.14	0.66	(0.45, 0.97)	
≥600	39	0.11	40	0.11	0.91	(0.58, 1.42)	
Total cancer							0.07
<200	888	1.23	942	1.36	0.91	(0.83, 0.99)	
200–<400	503	1.42	542	1.52	0.94	(0.83, 1.06)	
400–<600	588	1.34	611	1.36	0.98	(0.88, 1.10)	
≥600	529	1.49	472	1.34	1.11	(0.98, 1.26)	
Coronary heart disease							0.16
<200	339	0.45	338	0.47	0.96	(0.82, 1.11)	
200–<400	142	0.38	166	0.44	0.86	(0.69, 1.08)	
400–<600	213	0.46	184	0.39	1.19	(0.98, 1.46)	
≥600	159	0.42	136	0.37	1.13	(0.90, 1.43)	
Stroke							0.68
<200	242	0.32	227	0.31	1.03	(0.86, 1.24)	
200–<400	128	0.34	127	0.34	1.08	(0.84, 1.38)	
400–<600	174	0.38	153	0.32	1.18	(0.95, 1.47)	
≥600	130	0.34	132	0.36	0.97	(0.76, 1.24)	
Total death							0.19
<200	632	0.83	655	0.89	0.93	(0.83, 1.03)	
200–<400	312	0.83	352	0.92	0.91	(0.78, 1.06)	
400–<600	410	0.88	429	0.90	0.98	(0.85, 1.12)	
≥600	376	0.99	341	0.92	1.07	(0.92, 1.24)	
Global index							0.13
<200	1025	1.39	1073	1.51	0.92	(0.84, 1.00)	
200–<400	533	1.47	597	1.63	0.90	(0.80, 1.01)	
400–<600	691	1.54	709	1.55	1.01	(0.91, 1.13)	
≥600	617	1.69	550	1.53	1.04	(0.93, 1.17)	

[a]From a proportional hazards model stratified by prevalent condition (where appropriate), age, hormone therapy and diet modification randomization arm, and trial phase (time-dependent). Time to event equals 0 on date of randomization.
[b]All nonhip fractures use adjudicated data during the clinical trial and self-reported data thereafter.

Table 4. Cumulative Analyzed Incidence Rates for Clinical Outcomes in the Women's Health Initiative Calcium and Vitamin D Supplementation Trial: Stratified by Personal Use of Calcium Supplements (With or Without Vitamin D) at Calcium and Vitamin D Randomization

	Overall combined phases						
	CaD		*Placebo*				
	N	%	N	%	*HR**	*(95% CI)*[a]	p-*value*[a]
Hip fracture							0.28
No	153	0.16	180	0.20	0.84	(0.67, 1.04)	
Yes	226	0.21	233	0.22	0.96	(0.80, 1.16)	
Vertebral fracture[b]							0.76
No	172	0.18	192	0.21	0.89	(0.72, 1.09)	
Yes	274	0.25	316	0.29	0.84	(0.71, 0.99)	
Total fracture[b]							0.71
No	1765	2.08	1733	2.09	1.00	(0.93, 1.06)	
Yes	2248	2.31	2285	2.35	0.98	(0.92, 1.04)	
Invasive colorectal cancer							0.18
No	111	0.12	131	0.14	0.85	(0.66, 1.10)	
Yes	145	0.13	136	0.13	1.05	(0.83, 1.32)	
Invasive breast cancer							0.16
No	359	0.39	366	0.41	0.96	(0.83, 1.11)	
Yes	492	0.47	450	0.42	1.10	(0.97, 1.25)	
In situ breast cancer							0.17
No	76	0.08	106	0.12	0.69	(0.52, 0.93)	
Yes	122	0.12	132	0.13	0.91	(0.71, 1.16)	
Total cancer							0.04
No	1126	1.27	1204	1.40	0.91	(0.84, 0.99)	
Yes	1428	1.40	1413	1.38	1.02	(0.94, 1.09)	
Coronary heart disease							0.34
No	453	0.49	415	0.46	1.08	(0.95, 1.23)	
Yes	424	0.40	430	0.40	0.99	(0.86, 1.13)	
Coronary heart disease death[c]							0.55
No	130	0.14	136	0.15	0.95	(0.75, 1.22)	
Yes	138	0.13	129	0.12	1.03	(0.81, 1.32)	
Clinical myocardial infarction							0.17
No	347	0.38	309	0.34	1.11	(0.95, 1.29)	
Yes	312	0.29	328	0.31	0.96	(0.82, 1.12)	
Stroke							0.30
No	340	0.37	305	0.34	1.11	(0.95, 1.30)	
Yes	350	0.33	354	0.33	0.99	(0.85, 1.15)	
Cardiovascular disease death							0.60
No	262	0.28	257	0.28	1.00	(0.84, 1.19)	
Yes	287	0.26	268	0.25	1.06	(0.90, 1.25)	
Total death							0.38
No	852	0.91	845	0.92	0.99	(0.90, 1.09)	
Yes	923	0.85	978	0.90	0.94	(0.86, 1.02)	
Global index							0.55
No	1325	1.46	1379	1.56	0.94	(0.87, 1.02)	
Yes	1607	1.54	1616	1.54	0.97	(0.91, 1.04)	

[a]From a proportional hazards model stratified by prevalent condition (where appropriate), age, hormone therapy and diet modification randomization arm, and trial phase (time-dependent). Time to event equals 0 on date of randomization.
[b]All nonhip fractures use adjudicated data during the clinical trial and self-reported data thereafter.
[c]Coronary heart disease death includes definite and possible coronary heart disease death.

considered the vitamin D_3 dose of 400 IU daily to be a study limitation. However, the dose followed the Institute of Medicine (IOM) recommendations available during the trial.[8] These IOM recommendations were recently increased for vitamin D to 600 IU daily for those <70 years old and 800 IU daily for those 71 years.[40] Since about half of the current study participants were taking nonprotocol vitamin D, the mean vitamin D intake in the supplement groups was 773 IU daily (mean), meeting current recommendations. For the time period of the extension, we have no information on dietary

intake of calcium and vitamin D. However, 44% of those in the intervention and 42% of those in the placebo reported taking calcium and vitamin D supplements at the end of the extension. Only hip fractures were adjudicated during the extension and the validity of self-reported clinical vertebral fractures was low.[10] Finally, during the intervention phase a 17% higher risk of kidney stones was found among women in the supplement group.[2] Postintervention, these data were not collected.

In summary, after an average of 11 years, calcium and vitamin D supplementation did not decrease hip fracture or colorectal cancer, coprimary outcomes. Throughout, there was no difference in invasive breast cancer, CVD, or all-cause mortality between groups. Exploratory analyses found lower vertebral fracture and *in situ* breast cancers in supplement users, although absolute risk reduction was small. The incidence of invasive breast cancer differed across baseline intake of vitamin D with a significantly higher incidence for those with higher intakes. Overall, a decreased risk of hip fracture was observed only among women adherent during the intervention. Future research should explore the relationships with vertebral fractures and *in situ* and invasive breast cancers including potential mechanistic studies.

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Author Disclosure Statement

No competing financial interest exists.

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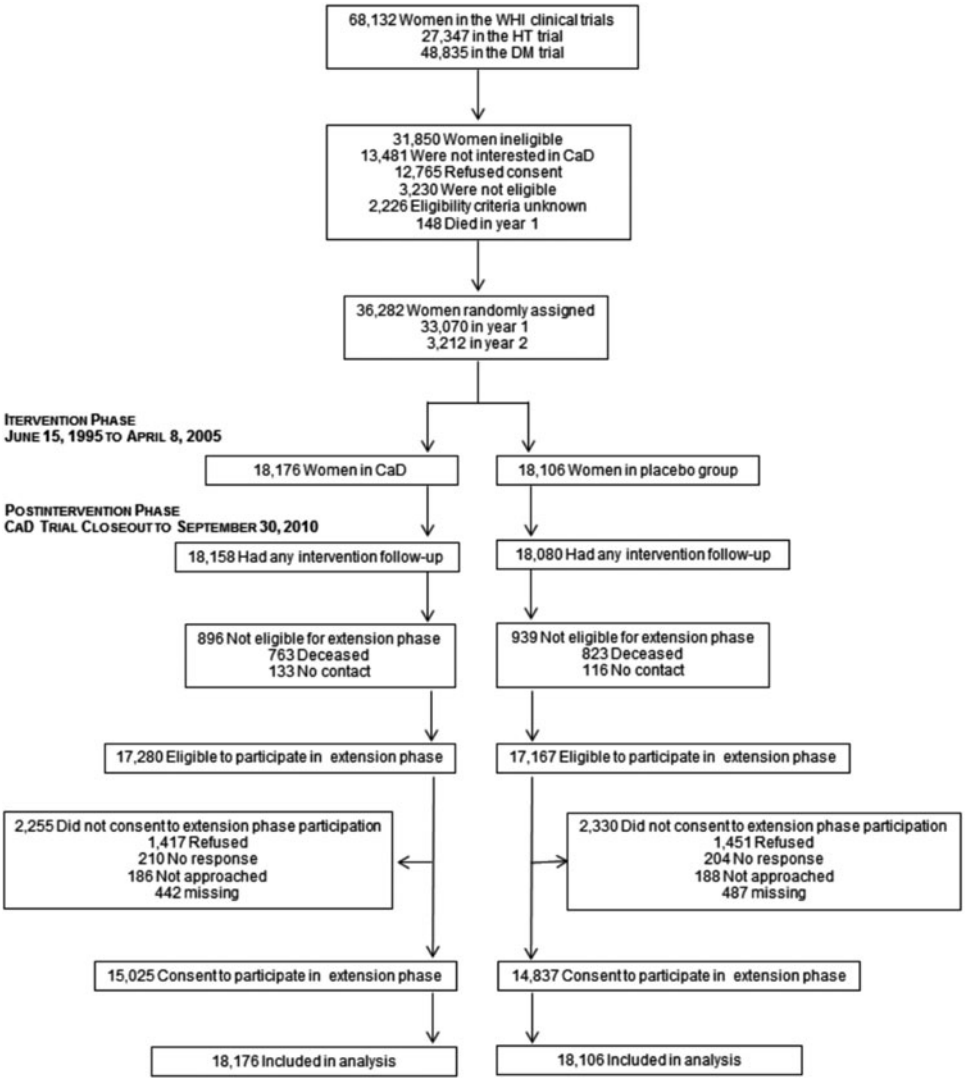
(*Appendix follows* →)

Appendix



APPENDIX FIGURE A1. Women's Health Initiative calcium and vitamin D (CaD) trial through extended follow-up.

Appendix Table A1. Baseline Characteristics of Calcium and Vitamin D Trial Participants by Extension Study Participation Status

	Nonextension participant (N = *6420*)		*Extension participant* (N = *29,862*)		
	N	%	N	%	p-*value*
Age group at screening, years					< 0.0001
50–59	2091	32.6	11,331	37.9	
60–69	2712	42.2	13,807	46.2	
70–79	1617	25.2	4724	15.8	
Race/ethnicity					< 0.0001
White	4813	75.0	25,342	84.9	
Black	815	12.7	2500	8.4	
Hispanic	476	7.4	1026	3.4	
American Indian	43	0.7	106	0.4	
Asian/Pacific Islander	152	2.4	569	1.9	
Unknown	121	1.9	319	1.1	
Education					< 0.0001
None to some high school	594	9.3	1309	4.4	
High school diploma or equivalent	1235	19.4	5438	18.3	
School after high school	2717	42.6	11,656	39.3	
College degree or higher	1826	28.7	11,276	38.0	
Gail 5-year risk of breast cancer					< 0.0001
< 1.25	2417	37.6	10,241	34.3	
1.25–1.74	1912	29.8	9958	33.3	
≥ 1.75	2091	32.6	9663	32.4	
Medical history					
Kidney stones	74	1.3	269	1.0	0.04
Stroke	109	1.7	239	0.8	< 0.0001
Myocardial infarction	205	3.2	449	1.5	< 0.0001
Fracture	2177	38.3	10,362	38.2	0.99
Colorectal cancer	12	0.2	39	0.1	0.27
Breast cancer	13	0.2	44	0.1	< 0.0001
Prior hormone use[a]					< 0.0001
None	2219	34.6	9277	31.1	
Past	1141	17.8	4802	16.1	
Current estrogen-alone	1592	24.8	7532	25.2	
Current estrogen + progestin	1468	22.9	8251	27.6	
Body mass index, kg/m^2					< 0.0001
< 25	1549	24.2	8030	27.0	
25–< 30	2167	33.9	10,796	36.3	
≥ 30	2682	41.9	10,880	36.6	
Physical activity, MET h/wk					< 0.0001
None	1285	22.4	5039	18.5	
0.5–4.125	1261	21.9	5645	20.7	
> 4.125–9.5	1113	19.4	5472	20.1	
> 9.5–17.75	1028	17.9	5557	20.4	
≥ 17.75	1060	18.4	5534	20.3	
Alcohol intake					< 0.0001
Nondrinker	766	12.1	2988	10.1	
Past drinker	1448	22.8	4953	16.7	
< 1 drink per month	907	14.3	4141	14.0	
< 1 drink per week	1253	19.7	6361	21.5	
1–< 7 drinks per week	1383	21.8	7997	27.0	
≥ 7 drinks per week	596	9.4	3212	10.8	
Smoking					< 0.0001
Never	3138	49.5	15,615	52.8	
Past	2517	39.7	11,871	40.2	
Current	682	10.8	2079	7.0	
Total vitamin D (supplements + diet), IU/d[b]					< 0.0001
< 200	2612	41.9	10,886	37.1	
200–< 400	1207	19.4	5595	19.1	
400–< 600	1418	22.8	7065	24.1	
≥ 600	991	15.9	5800	19.8	

(*continued*)

Appendix Table A1. (Continued)

	Nonextension participant (N = *6420*)		*Extension participant* (N = *29,862*)		
	N	%	N	%	p-*value*
Vitamin D supplement use[b]	2741	42.7	14,426	48.3	< 0.0001
Geographic region at randomization by latitude					< 0.0001
Southern, < 35°N	2563	39.9	8310	27.8	
Middle, 35–40°N	1550	24.1	8493	28.4	
Northern, ≥ 40°N	2307	35.9	13,059	43.7	
Total calcium intake (supplements + diet + medications), mg/d[b]					< 0.0001
< 800	2527	40.6	9580	32.6	
800– < 1200	1632	26.2	7738	26.4	
≥ 1200	2069	33.2	12,028	41.0	
Calcium and/or vitamin D supplement use[b]	3275	51.0	17,340	58.1	< 0.0001
Hormone therapy trial participant	3173	49.4	12,916	43.3	< 0.0001
Diet modification trial participant	4200	65.4	21,010	70.4	< 0.0001
CaD trial randomization assignment					
Intervention	3151	49.1	15,025	50.3	
Control	3269	50.9	14,837	49.7	

[a]Values incorporate hormone therapy use during year 1 of the clinical trial, including exposure to the Hormone Therapy trials.
[b]Vitamin D and calcium variables incorporate intake reported at year 1 of the clinical trial.
MET, metabolic equivalents; CaD, calcium and vitamin D.