

# Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer

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- Background** Although some observational studies have associated higher calcium intake and especially higher vitamin D intake and 25-hydroxyvitamin D levels with lower breast cancer risk, no randomized trial has evaluated these relationships.
- Methods** Postmenopausal women (N = 36282) who were enrolled in a Women's Health Initiative clinical trial were randomly assigned to 1000 mg of elemental calcium with 400 IU of vitamin D<sub>3</sub> daily or placebo for a mean of 7.0 years to determine the effects of supplement use on incidence of hip fracture. Mammograms and breast exams were serially conducted. Invasive breast cancer was a secondary outcome. Baseline serum 25-hydroxyvitamin D levels were assessed in a nested case-control study of 1067 case patients and 1067 control subjects. A Cox proportional hazards model was used to estimate the risk of breast cancer associated with random assignment to calcium with vitamin D<sub>3</sub>. Associations between 25-hydroxyvitamin D serum levels and total vitamin D intake, body mass index (BMI), recreational physical activity, and breast cancer risks were evaluated using logistic regression models. Statistical tests were two-sided.
- Results** Invasive breast cancer incidence was similar in the two groups (528 supplement vs 546 placebo; hazard ratio = 0.96; 95% confidence interval = 0.85 to 1.09). In the nested case-control study, no effect of supplement group assignment on breast cancer risk was seen. Baseline 25-hydroxyvitamin D levels were modestly correlated with total vitamin D intake (diet and supplements) ( $r = 0.19$ ,  $P < .001$ ) and were higher among women with lower BMI and higher recreational physical activity (both  $P < .001$ ). Baseline 25-hydroxyvitamin D levels were not associated with breast cancer risk in analyses that were adjusted for BMI and physical activity ( $P_{\text{trend}} = .20$ ).
- Conclusions** Calcium and vitamin D supplementation did not reduce invasive breast cancer incidence in postmenopausal women. In addition, 25-hydroxyvitamin D levels were not associated with subsequent breast cancer risk. These findings do not support a relationship between total vitamin D intake and 25-hydroxyvitamin D levels with breast cancer risk.

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Breast cancer is the most common cancer among women in the United States and is the focus of risk reduction efforts (1). Some preclinical (2,3) and observational (4) studies have reported associations between higher calcium intake and higher vitamin D intake (5-7) and reduced breast cancer risk in postmenopausal women, but the results have not been consistent (8-11). No randomized clinical trial has addressed whether calcium and/or vitamin D intake reduce risk of breast cancer.

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## CONTEXT AND CAVEATS

### Prior knowledge

Some observational studies have reported associations of higher calcium intake and especially higher vitamin D intake and 25-hydroxyvitamin D levels with lower breast cancer risk, but these relationships have not been analyzed in randomized trials.

### Study design

Randomized double-blind placebo-controlled clinical trial of calcium and vitamin D supplementation vs placebo among postmenopausal women and a nested case-control study of associations between baseline serum 25-hydroxyvitamin D levels, breast cancer risk factors, and risk of breast cancer.

### Contribution

Incidence of invasive breast cancer was similar in the two randomized groups after a mean of 7 years. Baseline serum 25-hydroxyvitamin D levels were correlated with supplement use and were higher among women who did more recreational physical activity and had a lower body mass index (BMI), but they were not associated with breast cancer risk after adjustment for BMI and physical activity.

### Implications

Vitamin D and calcium supplementation has no detectable effect on the risk of postmenopausal invasive breast cancer.

### Limitations

Additional use of calcium and vitamin D supplements was allowed during the study. The duration of calcium and vitamin D supplementation was short compared with how long it takes to develop breast cancer.

*From the Editors*

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Against this background, the Women's Health Initiative (WHI) designed a trial to test the hypothesis that calcium plus vitamin D supplementation would reduce risk of hip fracture (as primary endpoint) and of colorectal and breast cancer (as designated secondary endpoints) among postmenopausal women. The hip fracture and colorectal cancer results have been previously reported (12,13). Here, we report the breast cancer findings.

## Subjects and Methods

### Study Design

Women who were enrolled in the WHI randomized clinical trials evaluating hormone therapy (HT) and dietary modification (DM) (14–16) were invited to join the WHI calcium and vitamin D trial at their first or second annual follow-up visit. Details of eligibility criteria and recruitment have been previously described (12,17). Postmenopausal women aged 50–79 years with life expectancy of more than 3 years, no prior breast cancer, and no other cancer within 10 years were eligible. Women with history of hypercalcemia, kidney stones, and corticosteroid or calcitriol use were excluded. Personal use of calcium and vitamin D during the study was allowed: initially up to 600 IU daily of vitamin D, which was subsequently increased to 1000 IU daily during the course of the study.

Using a permuted block algorithm, eligible women were randomly assigned in a double-blind fashion to active supplement or an

identical-appearing placebo (both provided by GlaxoSmith Kline) stratified by clinical center and age. Active tablets contained 500 mg of elemental calcium (as calcium carbonate) combined with 200 IU of vitamin D<sub>3</sub>. Women were instructed to take two tablets per day in divided doses, with meals to maximize absorption, for a total of 1000 mg of elemental calcium and 400 IU vitamin D<sub>3</sub> daily.

The protocol was approved by institutional review boards at each clinical center, and all participants provided written informed consent. Statistical analyses and data management were conducted at the WHI Clinical Coordinating Center. The trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (Identifier: NCT 00000611).

All women had both clinical breast examination and mammography and were free of breast cancer at entry in the WHI DM or HT trials 1 or 2 years previously. Mammograms were required annually for women on the HT trials and every 2 years for those on the dietary trial. Use of estrogen or estrogen plus progestin was determined by randomization for HT participants. HT was permitted for DM trial participants. Study pills were discontinued for any of the following: kidney stones, hypercalcemia, kidney dialysis, calcitriol use, or daily personal use of vitamin D supplements greater than 600 IU and later 1000 IU outside the study protocol.

### Study Monitoring and Termination

Clinical outcomes were reviewed semiannually by an independent data and safety monitoring board. Final clinical visits occurred as planned between October 1, 2004, and March 31, 2005.

### Follow-up Procedures and Ascertainment of Outcomes

One phone contact after 4 weeks assessed symptoms and encouraged adherence. Subsequent semiannual contacts assessed clinical outcomes as well as safety and adherence. Annual clinical visits included weighing returned pill bottles as an adherence measure. Breast cancers were confirmed by both local and central medical record and pathology report review by trained adjudicators who were blinded to randomized allocation, with such records available in 98.2% of cases. Tumor characteristics were coded using the Surveillance, Epidemiology, and End Results (SEER) program guidelines (18).

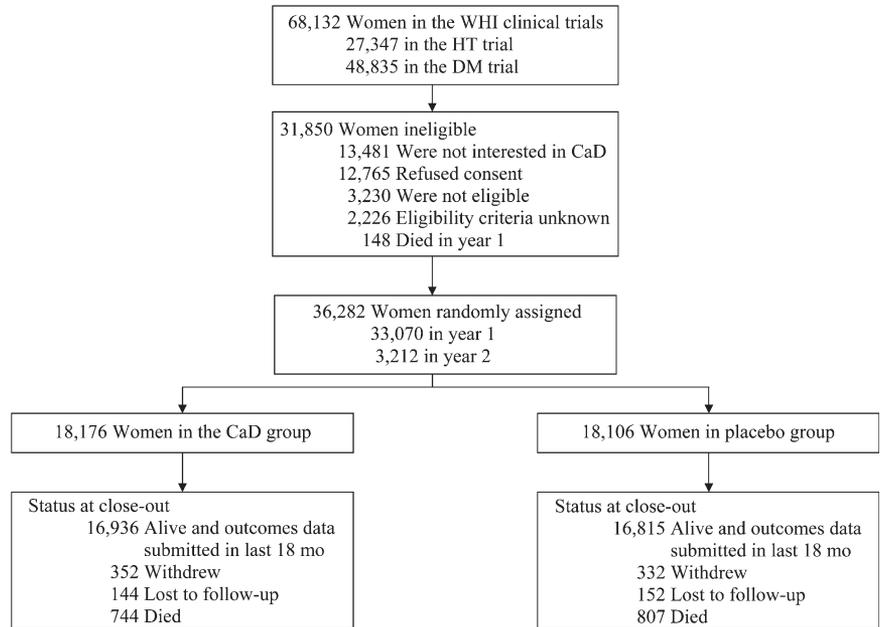
Between 1995 and 2000, of 68132 postmenopausal women enrolled in the HT or DM trials, 31850 women were ineligible for or declined participation in the calcium and vitamin D trial. Of the 36282 women randomly assigned, 25210 (69%) were in the DM trial, 16089 (44%) were in one of the HT trials, and 5017 (14%) were in both the DM and the HT trials. At the end of the study, 16936 women in the calcium and vitamin D group and 16815 in the placebo group were under active follow-up (Figure 1).

Total calcium intake included dietary intake (assessed with a modified block food frequency questionnaire) and elemental calcium from supplements. Total vitamin D intake included dietary vitamin D (intake largely from fortified dairy products and fatty fish) and vitamin D supplement use.

### Retention and Adherence

Adherence (defined as use of 80% or more of study medication) ranged from 60% to 63% during the first 3 years of follow-up, with an additional 13%–21% of participants taking at least half of their study pills. At the end of the trial, 76% were still taking study medication and 59% were taking 80% or more study pills. Over

Profile of the Calcium and Vitamin D (CaD) Component of the Women's Health Initiative



**Figure 1.** CONSORT diagram of the Women's Health Initiative randomized trial of calcium and vitamin D. Permission for reproduction was granted from The Publishing Division of the Massachusetts Medical Society (12).

the course of the study, 1551 participants (4.3%) died and 980 (2.7%) either withdrew from the trial or were lost to follow-up.

**Vitamin D Level Analyses**

Blood samples were collected at baseline after an overnight fast. The DiaSorin Liason chemiluminescent immunoassay (DiaSorin, Stillwater, MN) was used to determine 25-hydroxyvitamin D levels. Samples were assayed in batches with blinded controls with a coefficient of variation of 11.8%. The 25-hydroxyvitamin D levels were used in a nested case-control study that examined whether prerandomization levels either were associated with subsequent breast cancer risk or influenced the effect of calcium and vitamin D supplementation on breast cancer-risk. Case patients were patients with invasive breast cancer (n = 1067), and control subjects (n = 1067) were breast cancer-free and were matched to corresponding case patients on age, latitude of the clinical center, race/ethnicity, and date of blood collection.

**Statistical Analysis**

Primary results were assessed with time-to-event methods and were based on the intention-to-treat principle. Breast cancer incidence was compared in the two randomization groups using hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) estimated from Cox proportional hazards models (19) that were stratified according to age group at randomization (50–54, 55–59, 60–69, or 70–79 years), prevalent disease (yes or no), and treatment assignment in the HT (conjugated equine estrogen [CEE] therapy, CEE placebo, CEE plus medroxyprogesterone acetate [MPA] therapy, CEE plus MPA placebo, or not randomly assigned) and DM (intervention, comparison, not randomly assigned) trial. Secondary analyses of risk of breast cancer by tumor characteristics used the same Cox proportional hazards models with reported P values from Wald statistics. The proportionality assumption of the Cox models was tested by adding an

interaction term for treatment assignment by survival time. No violations of the assumption were found.

Kaplan–Meier estimates describe event rates over time. Sensitivity analyses examining the effect of nonadherence were conducted by repeating Kaplan–Meier analyses after censoring events that occurred 6 months after nonadherence (defined as consuming less than 80% of study pills). Comparisons of baseline characteristics and some breast cancer tumor characteristics were based on chi-square, Fisher's exact test, or t test. Women with missing values were excluded from analyses for that factor.

Differential effects across subgroups were evaluated using the same Cox proportional hazards models, which were extended to include the variable of interest and interaction with group assignment. When possible, continuous variables were used to test for the interaction; otherwise, the subgroup categories were used. Subgroup cut points are based on established groupings or percentiles. Twenty-two subgroups were examined, on which basis one statistically significant interaction test (P < .05) would be expected based on chance alone.

The interaction between serum 25-hydroxyvitamin D at baseline and random assignment to calcium plus vitamin D supplementation or placebo was assessed by unconditional logistic regression. Women with missing data for the adjustment variables were excluded from the models. To avoid bias, only the control group from the nested case-control study was analyzed using linear regression to examine the cross-sectional relationship between self-reported intake of vitamin D and serum 25-hydroxyvitamin D levels.

**Results**

**Participant Characteristics and Nonprotocol Supplement Use**

Demographic characteristics, health behaviors, and medical history were balanced between randomization groups (18 176 women in the

**Table 1.** Descriptive characteristics of participants at baseline by randomization assignment\*

Characteristic	CaD (N = 18 176)		Placebo (N = 18 106)	
	No.	%	No.	%
<b>Age at screening, y</b>				
50–59	6728	37.0	6694	37.0
60–69	8275	45.5	8245	45.5
70–79	3173	17.5	3167	17.5
<b>Race/ethnicity</b>				
White	15 047	82.8	15 106	83.4
Black	1682	9.3	1635	9.0
Hispanic	789	4.3	718	4.0
American Indian	77	0.4	72	0.4
Asian/Pacific Islander	369	2.0	353	2.0
Unknown	212	1.2	222	1.2
<b>Education</b>				
None—some high school	977	5.4	925	5.1
High school diploma/GED	3309	18.3	3364	18.7
School after high school	7216	40.0	7156	39.8
College degree or higher	6555	36.3	6543	36.4
<b>Gail risk, %/5 y</b>				
<1.25	6355	35.0	6303	34.8
1.25–1.74	5932	32.6	5938	32.8
≥1.75	5889	32.4	5865	32.4
<b>Age at menarche, y</b>				
≤11	3985	22.0	3983	22.1
12–13	10 011	55.3	9904	54.9
≥14	4109	22.7	4162	23.1
<b>No. of first-degree relatives with breast cancer</b>				
None	14 677	86.4	14 597	86.3
1	2112	12.4	2095	12.4
≥2	206	1.2	230	1.4
<b>Prior breast biopsy</b>				
No	13 167	80.2	13 095	80.3
Yes, 1 biopsy	2377	14.5	2323	14.2
Yes, ≥2 biopsies	867	5.3	897	5.5
<b>Age at the birth of first child, y</b>				
Never pregnant/no term pregnancy	1841	11.1	1909	11.5
<20	2814	17.0	2683	16.2
20–29	10 676	64.3	10 807	65.1
≥30	1273	7.7	1204	7.3
<b>Oophorectomy</b>				
No	12 948	73.1	12 821	72.5
Yes, 1 or part removed	1474	8.3	1462	8.3
Yes, bilateral oophorectomy	3304	18.6	3392	19.2
<b>Prior E-only use, y</b>				
No prior any hormone use	8788	59.4	8627	58.6
<2	1333	9.0	1341	9.1
2–5	1215	8.2	1217	8.3
≥5	3470	23.4	3538	24.0
<b>Prior E+P use, y</b>				
No prior any hormone use	8788	67.5	8627	66.9
<2	1116	8.6	1141	8.9
2–5	1196	9.2	1174	9.1
≥5	1926	14.8	1957	15.2
<b>Selective estrogen receptor modulators</b>				
Tamoxifen (current use)	13	0.08	10	0.06
Raloxifene (current use)	16	0.10	17	0.11

(Table continues)

**Table 1 (Continued).**

Characteristic	CaD (N = 18 176)		Placebo (N = 18 106)	
	No.	%	No.	%
<b>Body mass index, kg/m<sup>2</sup></b>				
<25	4745	26.2	4833	26.8
25–<30	6472	35.8	6483	36.0
≥30	6867	38.0	6695	37.2
<b>Physical activity, MET-h/week</b>				
None	3154	19.1	3170	19.3
>0–3.5	2745	16.6	2669	16.2
>3.5–8.0	3227	19.5	3333	20.3
>8.0–16.5	3613	21.8	3425	20.8
>16.5	3807	23.0	3851	23.4
<b>Alcohol use</b>				
Nondrinker	1863	10.3	1891	10.5
Past drinker	3192	17.7	3209	17.8
<1 drink per month	2529	14.0	2520	14.0
<1 drink per week	3863	21.4	3758	20.9
1–<7 drinks per week	4683	26.0	4706	26.2
≥7 drinks per week	1910	10.6	1900	10.6
<b>Smoking</b>				
Never smoked	9325	51.9	9428	52.6
Past smoker	7255	40.3	7133	39.8
Current smoker	1405	7.8	1356	7.6
<b>NSAID use</b>				
No	15 126	83.2	15 182	83.9
Yes	3050	16.8	2924	16.2
<b>Baseline total vitamin D (supplements + diet), IU</b>				
<200	6827	38.3	6671	37.6
200–<400	3379	19.0	3423	19.3
400–<600	4188	23.5	4295	24.2
≥600	3427	19.2	3364	19.0
<b>Baseline vitamin D supplement use (any)</b>				
No	9620	52.9	9495	52.4
Yes	8556	47.1	8611	47.6
<b>Region of residence at baseline</b>				
Southern (≤37°N)	6159	33.9	6158	34.0
Middle (>37–40°N)	3622	19.9	3612	20.0
Northern (>40°N)	8395	46.2	8336	46.0
<b>Baseline total calcium (supplements + diet), mg</b>				
<800	6104	34.3	6003	33.8
800–<1200	4715	26.5	4655	26.2
≥1200	7002	39.3	7095	40.0

\* CaD = calcium and vitamin D supplementation; GED = general educational development; E = estrogen; P = progestin; MET = metabolic equivalents; NSAID = nonsteroidal anti-inflammatory drug.

supplement group and 18 106 in the placebo group). Breast cancer risk factors were also balanced. Use of tamoxifen and raloxifene was low at entry and remained low throughout the study (Table 1).

Self-reported baseline total calcium and vitamin D intakes were similar in the randomization groups (Table 1), with nonprotocol vitamin D supplement use of 400 IU/day or greater reported by 37.7% of women in the placebo group and 37.1% of women in the supplement group. During the trial, nonprotocol calcium and vitamin D supplement use was similar in the two randomization groups. At year 6, nonprotocol vitamin D supplement use, mostly in multivitamin preparations, was reported by 52.8% of women in the placebo group and 52.0% of women in the supplement group.

During the trial, nonprotocol calcium intake increased by approximately 100 mg daily in both randomization groups.

### Breast Cancers

After a mean follow-up of 7 years, a total of 528 invasive breast cancers were diagnosed in the supplement group and 546 in the placebo group (HR = 0.96, 95% CI = 0.85 to 1.09) (Figure 2; Table 2). In addition, 145 in situ breast cancers were seen in the supplement group and 152 in the placebo group (HR = 0.94, 95% CI = 0.75 to 1.18) (Table 2). A sensitivity analysis censoring follow-up of 6 months after nonadherence found 274 invasive breast cancers in the supplement and 315 in the placebo groups (HR = 0.91, 95% CI = 0.77 to 1.07;  $P = .24$ ). A total of 23 deaths from breast cancer occurred in each randomization group (HR = 0.99, 95% CI = 0.55 to 1.76).

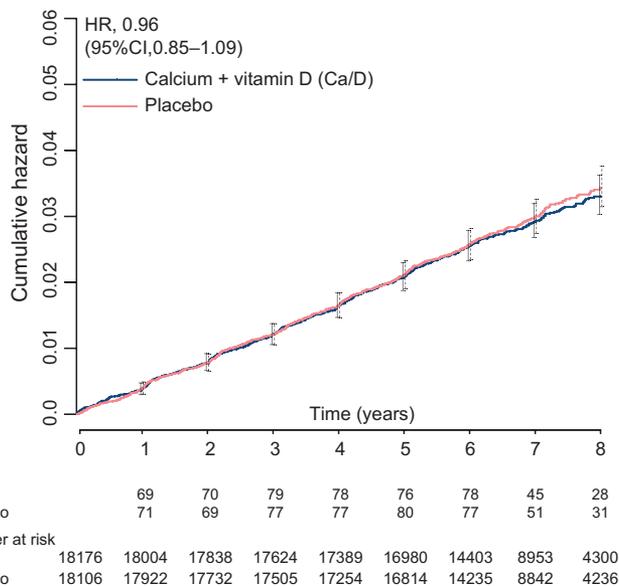
Breast cancer histology was similar in the two randomization groups. There were 68 estrogen receptor–negative invasive cancers in the supplement group and 83 in the placebo group, but this difference was not statistically significant (HR = 0.82, 95% CI = 0.59 to 1.13). The cancers that were diagnosed in the supplement group were somewhat smaller than those in the placebo group (mean = 1.54 vs 1.71 cm in diameter, respectively,  $P = .05$ ) but were of similar stage (Table 2). Mammogram findings were comparable in the randomization groups, both at baseline and throughout the study. After 1 year, mammograms with findings suspicious or highly suggestive of malignancy were seen in 269 (1.5%) of the participants in the placebo group and 272 (1.5%) of those in the supplement group.

### Subgroup Analyses

Supplement influence on breast cancer was assessed in 22 subgroups; 12 of the analyses are shown in Figure 3. Among women in the highest quartile of reported total vitamin D intake (diet plus supplement) at baseline, more breast cancers were seen in the supplement group than in the placebo group (HR = 1.34, 95% CI = 1.01 to 1.78); among women in the lowest baseline vitamin D intake quartile, fewer cancers were seen in the supplement group (HR = 0.79, 95% CI = 0.65 to 0.97) ( $P_{\text{interaction}} = .003$ ).

### Serum Vitamin D Levels

The 25-hydroxyvitamin D levels were obtained at baseline for the nested case–control study from 1067 case patients who developed breast cancer during the trial and 1067 matching control subjects who were breast cancer-free. At baseline, self-reported total vitamin D intake was modestly associated with 25-hydroxyvitamin D levels (Figure 4). There was a somewhat stronger association with 25-hydroxyvitamin D levels for women using only dietary sources (correlation  $r = 0.21$ ,  $P < .001$ ) compared with women using vitamin D supplements as well (correlation  $r = 0.19$ ,  $P < .001$ , with a test of the difference in the two regression lines having a  $P$  value of .03). Individual vitamin D intakes at baseline are shown in relation to 25-hydroxyvitamin D levels in each 25-hydroxyvitamin D quintile in Figure 4. Few individuals reported total vitamin D intakes greater than 1000 IU, even in the highest quintile. The range of vitamin D intakes substantially overlapped in each 25-hydroxyvitamin D quintile, and an average vitamin D intake difference of only 238 IU/day separated women in the low vs high



**Figure 2.** Kaplan–Meier estimates of the cumulative hazard ratio for invasive breast cancer with supplemental calcium plus vitamin D (Ca/D) as compared with placebo. HR, hazard ratio; CI, confidence interval. **Error bars** represent 95% CIs of the estimates at each year, using **solid** and **dashed lines** for the Ca/D and placebo groups, respectively.

25-hydroxyvitamin D quintiles. Although they are potential surrogates for sunlight exposure, 25-hydroxyvitamin D levels were only modestly associated with geographic location (north, middle, or south, defined by °N latitude ( $P = .03$ )). They were, however, statistically significantly associated with recreational physical activity and body mass index (BMI) (both  $P < .001$ ) (Table 3). The 25-hydroxyvitamin D levels were associated with neither breast cancer family history nor prior breast biopsy.

In the nested case–control assessment of 25-hydroxyvitamin D, the mean  $\pm$  SD baseline 25-hydroxyvitamin D level was 50.0  $\pm$  21.0 nmol/L among the 895 participants who were subsequently diagnosed with invasive breast cancer and 52.0  $\pm$  21.1 nmol/L among the 898 control subjects (Table 4). In logistic regression analyses adjusted for age, race and/or ethnicity, latitude of the clinical center, breast cancer family history, prior breast biopsies, HT as estrogen alone or combined with progestin, and HT and DM trial participation, higher baseline hydroxyvitamin D levels were associated with lower breast cancer risk ( $P = .04$ ) (Table 4). However, no association between levels of baseline hydroxyvitamin D and breast cancer risk emerged in analyses that were further adjusted for BMI and physical activity ( $P_{\text{trend}} = .20$ ) (Table 4). In addition, there was no interaction between quintile of baseline 25-hydroxyvitamin D levels, randomization group assignment, and breast cancer risk ( $P_{\text{interaction}} \geq .99$ ) (Table 4). Side effects of the calcium and vitamin D supplement were minimal and have been previously reported (12,13).

### Discussion

In this randomized, double-blind, placebo-controlled trial, daily supplementation with 1000 mg of elemental calcium combined with 400 IU of vitamin D<sub>3</sub> had no effect on breast cancer incidence. Thus, the main findings do not support a causal relationship between calcium and vitamin D supplement use and

**Table 2.** Clinical outcomes incidence (annualized %) by randomization assignment group\*

Outcomes	CaD (N = 18176)		Placebo (N = 18106)		Hazard ratio (95% CI)*	P
	No.	%	No.	%		
<b>Total breast cancer†</b>	668	0.52	693	0.54	0.96 (0.86 to 1.07)	
Invasive	528	0.41	546	0.43	0.96 (0.85 to 1.09)	
In situ	145	0.11	152	0.12	0.94 (0.75 to 1.18)	
Death from breast cancer	23	0.02	23	0.02	0.99 (0.55 to 1.76)	
<b>Tumor size, mean (SD), cm</b>	1.54	1.23	1.71	1.29		.05
No tumor found	1	<0.01	1	<0.01		
Microscopic focus or foci, cm	6	<0.01	14	0.01	0.43 (0.17 to 1.12)	.08
≤0.5	66	0.05	55	0.04	1.17 (0.82 to 1.68)	.38
>0.5–1	133	0.10	107	0.08	1.24 (0.96 to 1.60)	.10
>1–2	179	0.14	197	0.15	0.91 (0.74 to 1.11)	.33
>2–5	74	0.06	90	0.07	0.82 (0.60 to 1.12)	.21
>5	7	0.01	11	0.01	0.66 (0.25 to 1.70)	.39
Missing	62	0.05	71	0.06		
<b>Lymph nodes examined</b>						
No	37	0.03	55	0.04	0.67 (0.44 to 1.01)	.06
Yes	483	0.38	480	0.38	1.00 (0.88 to 1.14)	.98
Missing	8	0.01	11	0.01		
<b>No. of positive lymph nodes</b>						
None	359	0.28	362	0.28	0.99 (0.85 to 1.14)	.87
1–3	90	0.07	78	0.06	1.14 (0.84 to 1.55)	.39
≥4	32	0.02	39	0.03	0.82 (0.51 to 1.31)	.41
Missing	47	0.04	67	0.05		
<b>SEER stage</b>						
Localized	386	0.30	404	0.32	0.95 (0.83 to 1.09)	.49
Regional	127	0.10	121	0.10	1.04 (0.81 to 1.34)	.74
Distant	5	<0.01	9	0.01	0.53 (0.18 to 1.57)	.24
Missing	10	0.01	12	0.01		
<b>Histology</b>						
Ductal	336	0.26	337	0.26	0.99 (0.86 to 1.16)	.94
Lobular	49	0.04	61	0.05	0.80 (0.55 to 1.16)	.24
Ductal and lobular	76	0.06	78	0.06	0.96 (0.70 to 1.32)	.81
Tubular	15	0.01	26	0.02	0.59 (0.31 to 1.11)	.10
Other	49	0.04	37	0.03	1.31 (0.85 to 2.00)	.22
Missing	3	<0.01	7	0.01		
<b>Estrogen receptor assay</b>						
Positive	414	0.32	403	0.32	1.02 (0.89 to 1.17)	.75
Negative	68	0.05	83	0.07	0.82 (0.59 to 1.13)	.22
Borderline	2	<0.01	0			
Missing	44	0.03	60	0.05		
<b>Progesterone receptor assay</b>						
Positive	325	0.25	329	0.26	0.98 (0.84 to 1.15)	.84
Negative	142	0.11	145	0.11	0.97 (0.77 to 1.23)	.82
Borderline	4	<0.01	4	<0.01	0.98 (0.25 to 3.93)	
Missing	57	0.04	68	0.05		

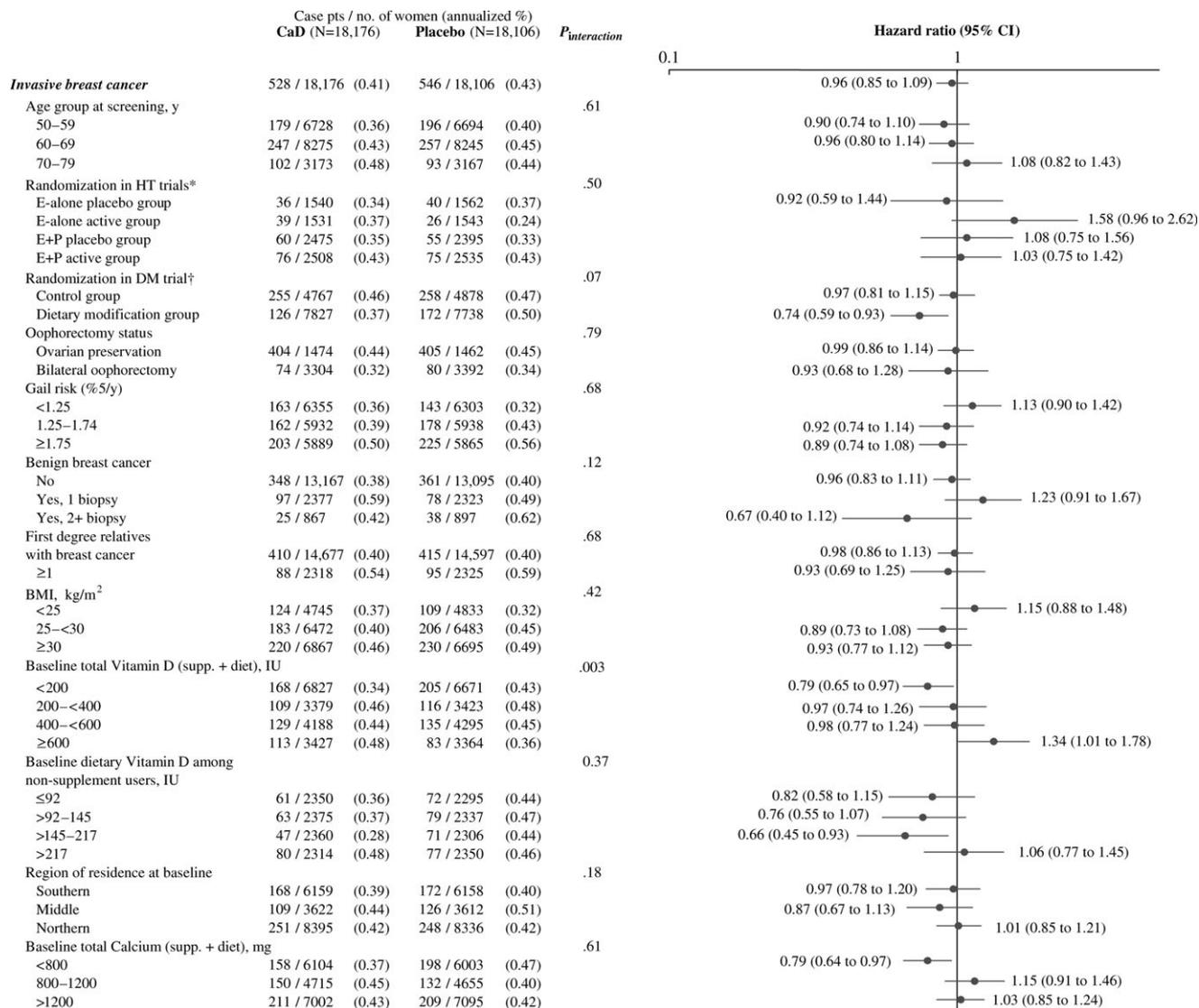
\* Hazard ratios (HRs) and confidence intervals (CIs) are from unweighted Cox proportional hazards models, stratified by age 50–54, 55–59, 60–69, 70–79 years, prevalent disease, hormone therapy randomization assignment (conjugated equine estrogen [CEE] therapy, CEE + medroxyprogesterone acetate [MPA], CEE + MPA placebo, not randomized), and dietary modification randomization assignment (intervention, comparison, not randomly assigned). P values (two-sided) for the comparison of mean tumor size are from an unadjusted t test. CaD = calcium and vitamin D supplementation; SEER = Surveillance, Epidemiology, and End Results. HRs are not reported for “Missing” categories or when the number of cancers is too few to produce a reliable estimate.

† Total breast cancer is the first of either invasive or situ breast cancer.

reduced breast cancer incidence, despite the association observed in some epidemiological studies.

As reviewed (20–22), although some observational studies (4,5,7) support an inverse association between higher vitamin D intakes and lower breast cancer risk in postmenopausal women, others (8–11,23) do not. A recent meta-analysis of observational studies including premenopausal and postmenopausal women reported that a modest reduction of breast cancer incidence was associated with higher intake of vitamin D (≥400 IU/day) of borderline statistical signifi-

cance (24). Similarly, an association between both higher calcium intake (7) and higher calcium levels (25) and lower breast cancer risk in postmenopausal women has been observed in some, but not all (10,23), reports. Studies in postmenopausal women of the relationship between circulating 25-hydroxyvitamin D levels and breast cancer risk have also had mixed results. In three studies (26–28), higher circulating 25-hydroxyvitamin D levels were associated with lower breast cancer risk. However, in a similar number of reports, either no association (11,29,30) or only a borderline association (31)



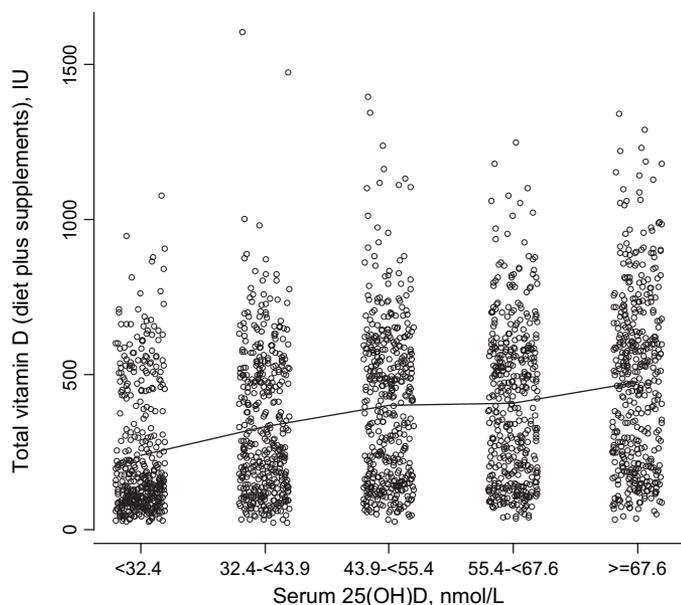
**Figure 3.** Estimated effects of supplemental calcium with vitamin D (CaD) on the risk of invasive breast cancer, according to selected baseline characteristics. Modeling for interaction testing used the continuous form of the following variables: age at screening, body mass index (BMI), Gail risk score, and baseline total calcium and vitamin D intake. Data were missing for some variables. HT = hormone therapy; E =

estrogen; P = progestin; DM = dietary modification. All models were stratified by age (50–54, 55–59, 60–69, 70–79 years), prevalent disease, and randomization in the dietary modification and HT trials. \*Women not randomized in the HT trials are excluded. †Adjusted for age (linear), weight, and baseline percentage of energy from total fat. Women not randomized in the DM trial are excluded. *P* values are two-sided.

was seen between 25-hydroxyvitamin D levels and breast cancer risk. In the current nested case–control study, with 895 case patients and 898 control subjects, no statistically significant association between higher baseline 25-hydroxyvitamin D and subsequent lower breast cancer risk was seen in analyses that adjusted for BMI and physical activity. In the nested case–control analysis that looked at the interaction effects within the trial design, no statistically significant interaction between baseline 25-hydroxyvitamin D levels, random assignment to supplement use, and breast cancer risk emerged, suggesting that even at the highest baseline 25-hydroxyvitamin D level, supplementation with 400 IU/day of D<sub>3</sub> together with calcium was not associated with lower breast cancer risk.

Based on the relatively high threshold of about 75 nmol/L of 25-hydroxyvitamin D, which has been associated with low breast cancer risk in some reports (26,27) and is estimated to require about

1700–2000 IU of supplement daily to achieve (27,28), a higher vitamin D dose than used in this trial has been recommended by some as needed to influence the risk of breast cancer (28,32). Although the dose of vitamin D used in this trial remains an issue (33), when baseline vitamin D intakes were examined across 25-hydroxyvitamin D quintiles in the current trial, the distribution of vitamin D intake in each quintile showed substantial overlap. The difference in reported total vitamin D intake between women with the lowest mean and highest quintiles values for 25-hydroxyvitamin D was, surprisingly, only 238 IU/day of vitamin D, yet the mean ± SD 25-hydroxyvitamin D level in the upper quintile was 81.9 ± 13.2 nmol/L. (The IU refers to the intake of vitamin D by participants, the nmol/L refers to the serum 25-hydroxyvitamin D levels associated with the reported intakes.) A technology assessment of 16 prospective trials of the influence of vitamin D supplementation



**Figure 4.** Self-reported individual vitamin D intake (diet plus supplementation) and serum 25-hydroxyvitamin D levels at baseline. Serum 25-hydroxyvitamin D levels were obtained at baseline entry into the calcium plus vitamin D clinical trial. Results from the 1067 women identified as control subjects from the nested case-control study are shown. Daily intakes of dietary and supplemental vitamin D were determined from self-report. The range of vitamin D intakes substantially overlap in each 25-hydroxyvitamin D quintile, and an average vitamin D intake difference of only 238 IU/day separates women in the low vs high 25-hydroxyvitamin D quintiles. **Line segments** connect the mean vitamin D intake level in each quintile.

(with or without calcium) on 25-hydroxyvitamin D levels (34) also describes considerable heterogeneity between supplement dose and subsequent magnitude of change in 25-hydroxyvitamin D levels. Such results suggest that factors other than dietary and supplement intake of vitamin D likely influence 25-hydroxyvitamin D levels. In fact, although sunlight exposure is a recognized influence on 25-hydroxyvitamin D levels, a substantial genetic influence on such levels has also been reported (35,36).

The relative contribution of factors influencing 25-hydroxyvitamin D levels remains to be defined, especially for higher concentrations found in individuals who do not report high-dose supplement use. Although this mechanism is speculative, a genetic predisposition to both high 25-hydroxyvitamin D levels and low breast cancer risk could appear as a protective effect of vitamin D on breast cancer. Before future clinical trials of high-dose vitamin D regimens to reduce breast cancer risk are implemented, it will be important to demonstrate that the selected vitamin D dose can definitively increase circulatory 25-hydroxyvitamin D levels to the projected target level. Definitive assessment of factors that influence the relationship between vitamin D supplement use and subsequent changes in circulating 25-hydroxyvitamin D levels are therefore a research priority.

Levels of 25-hydroxyvitamin D at baseline were statistically significantly higher among lean women and/or those with more recreational activity than overweight or obese or less active women. Based on the associations of these breast cancer risk factors with 25-hydroxyvitamin D, 25-hydroxyvitamin D could be

a potential mediator of lifestyle influence on breast cancer. Alternatively, lifestyle choices could have led to more sunlight exposure, with higher 25-hydroxyvitamin D levels and lower breast cancer risk as independent processes. The finding that analyses adjusted for BMI and physical activity did not identify an association between baseline 25-hydroxyvitamin D levels and breast cancer risk suggests that the association between 25-hydroxyvitamin D and breast cancer seen in some observational studies could be confounded to some degree by such factors.

Only one of the 22 subgroup analyses we performed demonstrated a statistically significant interaction between randomization group and the selected participant characteristics and suggested a differential calcium plus vitamin D supplement effect on breast cancer incidence according to baseline vitamin D intake. However, in the nested case-control analyses, no statistically significant interactions were observed.

The vitamin D dosage in this trial generally followed recommendations from the Institute of Medicine (37). We cannot assess whether a higher dosage would have changed the outcome of the current study. However, our findings provide some evidence against that hypothesis. Because approximately half of the women were taking an additional 400 IU of nonprotocol vitamin D supplement daily, actual vitamin D supplement intake was greater than 800 IU daily for a substantial number of participants in the supplement group. Nonetheless, no effects on risk of breast cancer overall or in sensitivity analyses that were adjusted for study adherence were observed. Although further study of relationships among calcium plus vitamin D supplement use and breast cancer can be considered, current evidence does not support their use in any dose to reduce breast cancer risk.

Breast cancers in the supplement group were somewhat smaller ( $P = .05$ ) but were of similar stage to those in the placebo group. Because the frequency of abnormal mammograms and rates of mammography screening were similar in the two randomization groups, differential influence on mammographic breast cancer detection does not explain the cancer findings.

Study strengths include the large, diverse study population, the double-blind placebo-controlled design, comprehensive breast cancer risk assessment, serial mammography monitoring, and central adjudication of breast cancers via pathology report review. Although a limitation is that discontinuation rates were higher than optimal, study supplement adherence was comparable to that in most chronic disease prevention trials, with 76% of participants still taking study pills at the end of the trial. Nonetheless, discontinuation of study pills would decrease the difference between the placebo and treated group in vitamin D intake. Because hip fracture was the primary study endpoint, the intervention included calcium as well as vitamin D. The inclusion of calcium could be considered a limitation, given the more modest information supporting calcium's potential relation to breast cancer.

Given the latency of breast cancer, the 7-year duration of the trial also could be questioned. However, raloxifene and tamoxifen, the two agents with a Federal Drug Administration label indication for breast cancer risk reduction, had efficacy demonstrated in trials of about 5-year duration (38,39). In addition, given difficulties in maintaining long-term drug adherence (40,41), any putative pharmacologic intervention that requires

**Table 3.** Baseline serum 25-hydroxyvitamin D levels by variables related to selected breast cancer risk factors and sunlight exposure in 1067 women identified as control subjects for the nested case-control analysis\*

Risk factor	No.	25-hydroxyvitamin D, nmol/L mean (SD)	P	P†
Family history of breast cancer			.95	.76
No	850	51.9 (21.1)		
Yes	160	51.8 (10.5)		
No. of breast biopsies			.28	.20
None	760	51.3 (20.8)		
1	138	52.8 (22.5)		
≥2	55	55.6 (20.9)		
BMI, kg/m <sup>2</sup>			<.001	<.001
<25	311	58.8 (22.2)		
25–29	375	52.2 (19.8)		
≥30	379	46.1 (19.7)		
Expenditure from physical activity, MET-h/week			<.001	<.001
None	175	45.8 (20.0)		
>0–3.5	149	48.2 (20.8)		
>3.5–8.0	207	50.4 (19.2)		
>8.0–16.5	210	53.4 (21.9)		
>16.5	214	58.8 (21.2)		
Region of residence at baseline			.26	.03
Southern (≤37°N)	310	52.9 (21.4)		
Middle (>37–40°N)	241	53.2 (22.4)		
Northern (>40°N)	516	50.9 (20.2)		

\* Blood samples from 1067 women at baseline who remained breast cancer-free identified as control subjects for women who developed breast cancer, matched to corresponding case patients on age, latitude of the clinical center, race/ethnicity, and venipuncture date. Numbers for each risk factor do not sum to the total in the sample because of missing data. BMI = body mass index; MET = metabolic equivalents. P values (two-sided) were calculated from linear regression models.

† Adjusted for age and race/ethnicity.

decades-long and continuous exposure would likely have limited public health implications.

Allowing nonprotocol calcium and vitamin D supplement use during the trial represents another limitation. However, nonprotocol supplement use was closely comparable in the two randomization groups and only about 15% of placebo group women could be considered drop-ins (with nonprotocol vitamin D supplement use

increased by >400 IU daily during the study course). In addition, the difference in calcium and vitamin D dose between randomization groups was sufficient to statistically significantly increase bone mineral density in the whole population and statistically significantly decrease hip fracture in women older than 65 years (12). Finally, this trial cannot separate calcium and vitamin D influence on breast cancer because these agents were used together in the study.

**Table 4.** Odds ratios for invasive breast cancer according to serum 25-hydroxyvitamin D levels and randomization group, as determined in a nested case-control study

Baseline 25-hydroxyvitamin D, nmol/L		Main effect OR (95% CI)†	Calcium + vitamin D		Intervention OR (95% CI)‡
Determinate quintile	Mean (SD)		No. of mpatients/ no. of control subjects	Placebo	
≥67.6	81.9 (13.2)	1.00 (referent)	86/109	76/86	0.89 (0.58 to 1.36)
55.4≤67.6	60.9 (3.5)	1.15 (0.86 to 1.55)	95/87	86/98	1.25 (0.83 to 1.90)
43.9≤55.4	49.2 (3.3)	1.35 (0.99 to 1.82)	102/87	92/84	1.07 (0.70 to 1.62)
32.4≤43.9	38.5 (3.3)	1.17 (0.86 to 1.60)	71/84	102/87	0.69 (0.45 to 1.06)
<32.4	23.6 (5.9)	1.22 (0.89 to 1.67)	94/94	91/82	0.91 (0.60 to 1.39)

\* To convert values for 25-hydroxyvitamin D to ng/mL, multiply by 0.401. CI = confidence interval. The analyses include 895 case patients and 898 control subjects of the original 1067 sample pairs due to missing data for the covariates.

† From an unconditional logistic regression model, adjusted for the matching factors (age, race/ethnicity [white, black, Hispanic, other/unknown]), latitude of clinical center, venipuncture date, and randomization in the hormone therapy (conjugated equine estrogen [CEE] therapy, CEE placebo, estrogen plus progestin therapy, estrogen plus progestin placebo, not randomly assigned) and dietary modification trials (intervention, comparison, not randomly assigned), and body mass index, physical activity (none, >0–3.5, >3.5–8.0, >8.0–16.5, >16.5 MET-h/week), family history of breast cancer (yes or no), history of breast biopsy (none, 1, or 2+), current estrogen plus progestin use (yes or no), and current estrogen-only use (yes or no). The model estimates the main effect of serum 25(OH)D on invasive breast cancer risk.  $P_{\text{trend}} = .20$ . Note:  $P_{\text{trend}} = .04$  without adjustment for body mass index and physical activity.

‡ From an unconditional logistic regression model, adjusted for the same factors listed above, estimating the effect of vitamin D supplementation (CaD) on invasive breast cancer risk by category of serum 25(OH)D.  $P_{\text{interaction}} \geq .99$ , computed from an unconditional logistic model including the above listed adjustment factors, the main effects of calcium and CaD randomization arm, and 25(OH)D as a continuous covariate, and their interaction.

In summary, calcium and vitamin D supplementation in the dosage provided in this trial did not reduce the incidence of invasive breast cancer in postmenopausal women. In addition, 25-hydroxyvitamin D levels were not associated with subsequent breast cancer risk. These findings do not support a relationship between total vitamin D intake and 25-hydroxyvitamin D levels with breast cancer risk.

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