JAMA | Original Investigation

# Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women
## A Randomized Clinical Trial

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**IMPORTANCE** Evidence suggests that low vitamin D status may increase the risk of cancer.

**OBJECTIVE** To determine if dietary supplementation with vitamin $D_3$ and calcium reduces the risk of cancer among older women.

**DESIGN, SETTING, AND PARTICIPANTS** A 4-year, double-blind, placebo-controlled, population-based randomized clinical trial in 31 rural counties (June 24, 2009, to August 26, 2015—the final date of follow-up). A total of 2303 healthy postmenopausal women 55 years or older were randomized, 1156 to the treatment group and 1147 to the placebo group. Duration of treatment was 4 years.

**INTERVENTIONS** The treatment group (vitamin $D_3$ + calcium group) received 2000 IU/d of vitamin $D_3$ and 1500 mg/d of calcium; the placebo group received identical placebos.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the incidence of all-type cancer (excluding nonmelanoma skin cancers), which was evaluated using Kaplan-Meier survival analysis and proportional hazards modeling.

**RESULTS** Among 2303 randomized women (mean age, 65.2 years [SD, 7.0]; mean baseline serum 25-hydroxyvitamin D level, 32.8 ng/mL [SD, 10.5]), 2064 (90%) completed the study. At year 1, serum 25-hydroxyvitamin D levels were 43.9 ng/mL in the vitamin $D_3$ + calcium group and 31.6 ng/mL in the placebo group. A new diagnosis of cancer was confirmed in 109 participants, 45 (3.89%) in the vitamin $D_3$ + calcium group and 64 (5.58%) in the placebo group (difference, 1.69% [95% CI, −0.06% to 3.46%]; $P = .06$). Kaplan-Meier incidence over 4 years was 0.042 (95% CI, 0.032 to 0.056) in the vitamin $D_3$ + calcium group and 0.060 (95% CI, 0.048 to 0.076) in the placebo group; $P = .06$. In unadjusted Cox proportional hazards regression, the hazard ratio was 0.70 (95% CI, 0.47 to 1.02). Adverse events potentially related to the study included renal calculi (16 participants in the vitamin $D_3$ + calcium group and 10 in the placebo group), and elevated serum calcium levels (6 in the vitamin $D_3$ + calcium group and 2 in the placebo group).

**CONCLUSIONS AND RELEVANCE** Among healthy postmenopausal older women with a mean baseline serum 25-hydroxyvitamin D level of 32.8 ng/mL, supplementation with vitamin $D_3$ and calcium compared with placebo did not result in a significantly lower risk of all-type cancer at 4 years. Further research is necessary to assess the possible role of vitamin D in cancer prevention.

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Supplemental content

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Cancer is a major public health burden in the United States.[1] About 40% of the population will have a cancer diagnosis at some point during their lives along with the associated morbidity, effects on quality of life, and health care costs. The cost of cancer care in the United States is estimated to increase from $125 billion in 2010 to $156 billion in 2020.[1] Worldwide, it is estimated that during the next 20 years the annual number of cancer diagnoses will increase from 14 million (in 2012) to 22 million by 2032.[1] Thus, a strategy that would help prevent cancer is highly desirable.

Considerable interest exists in the potential role of vitamin D for prevention of cancer. Garland and Garland first proposed "the Vitamin D Hypothesis" (ie, that vitamin D protects against cancer)[2] in 1980 when they observed that colon cancer mortality rates in the United States were highest in places with the least sunlight. They hypothesized the "sunlight effect" was due to vitamin D. Since then, numerous studies have shown an inverse relationship between risk of cancer and sunlight exposure or serum 25-hydroxyvitamin D (25[OH]D) level, the functional indicator of vitamin D status.[3-7] Although not all clinical studies show this association,[8,9] numerous cell culture and in vivo studies support the possibility of a role of vitamin D in preventing cancer development and progression.[10-15]

The objective of this randomized clinical trial (RCT) was to evaluate the effect of supplementation with vitamin $D_3$ and calcium on risk of incident all-type cancer in healthy older women.

### Key Points

**Question** Does dietary supplementation with vitamin $D_3$ and calcium reduce the risk of cancer among older women?

**Findings** In this randomized clinical trial of 2303 healthy postmenopausal women with a mean baseline serum 25-hydroxyvitamin D level of 32.8 ng/mL, supplementation with vitamin $D_3$ and calcium compared with placebo did not significantly reduce the incidence of all-type cancer over 4 years of follow-up.

**Meaning** Supplementation with vitamin $D_3$ and calcium did not result in a significantly lower risk of cancer among healthy older women.

## Methods

### Trial Design and Enrollment Criteria

This study was approved by the Creighton University institutional review board. The trial protocol and statistical analysis are available in Supplement 1. A data and safety monitoring board (DSMB) of investigators outside the university provided oversight. This was a randomized, double-blind placebo-controlled, population-based study. Postmenopausal women 55 years and older were recruited from the population of independently living rural women in 31 of 93 counties in Nebraska. Recruitment mailings were sent to the target population using lists containing addresses of about 99% of the occupied housing units in the 31 counties. Health care clinicians and directors of public health departments were asked to advertise the study. Advertisements also were placed and talks given in the 31-county area. Potential participants were directed to provide call-back information on a toll-free voicemail. Study staff returned calls and did telephone screening. Eligible patients were scheduled for visit 1 screening; eligible patients were randomized at visit 1. Prior to randomization, nurses gave eligible patients time to read the consent form and to ask questions. Then they asked the volunteers to describe their understanding of the study. All participants signed informed consent.

### Intervention

Participants were randomized by a statistician (P.W.) to 1 of 2 groups by computerized block randomization, using a block size of 8. The treatment group (vitamin $D_3$ + calcium group) received vitamin $D_3$ (cholecalciferol; 2000-IU capsule, once daily) and calcium carbonate (500-mg tablet, 3 times daily) and the placebo group received identical placebos. Only the statistician and a research assistant who had no contact with participants were unblinded to group assignment. Supplements and placebos were made by Tishcon. Participants were asked to limit vitamin D supplementation, outside of the intervention, to 800 IU per day, in keeping with the National Academy of Medicine (NAM; formerly Institute of Medicine) recommended intake level.[16] Participants also were asked by study nurses to limit additional calcium to 1500 mg per day as directed by the investigators and DSMB to be consistent with the previous Creighton cancer and vitamin D study.[17] Study follow-up visits were every 6 months.

### Outcome Measures

The primary outcome was first diagnosis of any type of cancer (excluding nonmelanoma skin cancers), and each participant with a new cancer was counted only once. Prespecified secondary analyses were planned for common specific types of cancer including cancers of the breast, lung, and colon, and lymphoma, leukemia, and myeloma. Other secondary outcomes included hypertension, cardiovascular disease, osteoarthritis, colonic adenomas and diabetes, upper respiratory tract infections, and falls.

At each visit, participants were asked about new diagnoses. If they had been diagnosed with cancer or any tumor or colonic adenoma, medical records were retrieved to verify and date the diagnosis and to validate by pathology reports. Cause of death for participants who died during the study was obtained so that deaths due to cancer were captured. Only the planned secondary analyses for cancer outcomes are reported; the other secondary outcomes will be reported elsewhere.

### Assessments

Baseline serum 25(OH)D level and annual 25(OH)D level response to vitamin $D_3$ were analyzed with the Liaison Analyzer (Diasorin). The Creighton laboratory participates in the Vitamin D External Quality Assessment Scheme (DEQAS) quality assurance system for 25(OH)D assays,[18] and Creighton test samples were consistently close to the international mean.



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Supplements were distributed at each visit, and all bottles and unused supplements were returned at the next visit. Adherence was determined by weighing returned bottles and calculating number of pills taken. Adherence was reported for those who discontinued supplements. Annually, serum calcium levels were measured to monitor for hypercalcemia and creatinine levels for changes in renal function.

Height and weight were measured at baseline and annually. The Block 2005 Food Frequency Questionnaire (Block Dietary Data Systems)[19] was administered at baseline and final visit. Nurses asked participants to self-identify race and ethnicity for purposes of describing the cohort in dissemination of findings. Participants selected their race from the list of US Census Bureau categories: (1) American Indian or Alaska Native, (2) Asian, (3) black or African American, (4) Native Hawaiian or Pacific Islander, (5) white or Caucasian, or (6) do not wish to provide. Participants self-identified their ethnicity by selecting: (1) Hispanic or Latino or (2) not Hispanic or Latino.

## Sample Size Calculations

The planned sample size was based on data from a previous study,[17] in which the overall cancer incidence was 6.9% (20 of 288 participants) over 4 years (or $1 - [1 - 20 / 288]^{1/4} = 1.78\%$ per year) in the placebo group and 2.9% (13 of 446 participants) overall (0.74% per year) in the vitamin $D_3$ + calcium group. The relative risk (RR) (2.9% / 6.9%) was about 40%. A conservative assumption was made that the reduction in cancer incidence in the proposed study might be less than the 60% reduction seen in the previous study; thus, this study was powered to detect a 50% reduction in cancer incidence. With 1000 patients per group, the power for the current study was 94.4% (per equation 4.17 of Fleiss et al[20]) if the annual incidence rates were 2% for the control group and 1% for the treatment group; 86.2% power if the rates were 1.5% for the control group and 0.75% for the treatment group; and 68.5% power if the rates were 1% for the control group and 0.5% for the treatment group.

## Statistical Analysis

Descriptive data of demographic and other variables included means and SDs, medians and interquartile ranges (IQRs), or percentages. Comparisons between the treatment groups at baseline, for supplement compliance and for withdrawals used the Fisher exact test, the $\chi^2$ test of independence, the Wilcoxon rank-sum test (for continuous variables with highly skewed distributions), and the pooled variance estimate *t* test. Time in the study was calculated as time from enrollment until the outcome of interest, death, last visit (for participants who withdrew during the study), or final visit (ninth visit). Time in the study was truncated to 4 years for any study participant with a final visit more than 4 years after baseline. Cancers diagnosed more than 4 years after baseline were excluded.

### Intention-to-Treat Analysis

Prespecified intention-to-treat analyses according to treatment group was performed for cancer of any site and for cancer of the breast. There were too few other specific cancers to have sufficient power to compare the treatment groups. The effect of treatment on cancer diagnosis during the 4 years of the study was evaluated using Kaplan-Meier survival analysis, in which time to first cancer diagnosis was modeled as a function of treatment group. All participants were included in this analysis, except those who withdrew from the study prior to visit 2 without providing any follow-up information. Because this analysis excluded some randomized participants, a post hoc $\chi^2$ test was also performed comparing the proportion affected by cancer in the 2 treatment groups. This analysis included all randomized study participants, and each participant was scored as having a positive or negative result for known cancer. Those with no follow-up were all scored as having a negative result for cancer. In addition, time to first cancer diagnosis was modeled as a function of treatment group using proportional hazards modeling, so that hazard ratios (HRs) could be calculated and so that factors considered to affect cancer risk could be considered for inclusion in the model. Study variables other than treatment group were each evaluated for significant differences between treatment groups and between cancer-affected and unaffected participants. When significant differences were observed, proportional hazards modeling of treatment group association with cancer outcomes was performed with and without adjustment for the other variables. All participants were included in this analysis, except those who withdrew from the study prior to visit 2 without providing any follow-up information were excluded. The primary analysis of prespecified cancer of all sites was the event of interest.

### Post Hoc Analyses

Given the expected time for vitamin D supplementation to increase serum 25(OH)D level and to exert a potential effect on cancer development or progression, a post hoc analysis was performed of cancer diagnosis during years 2 through 4 of the study, which excluded participants who developed cancer or withdrew from the study prior to completing a year of the study. Kaplan-Meier survival analysis was performed, in which time to first cancer diagnosis was modeled as a function of treatment group and time to first cancer diagnosis was also modeled as a function of treatment group using proportional hazards modeling, so that HRs could be calculated.

The study protocol prespecified a secondary nested case-control analysis to test for an association between serum 25(OH)D levels achieved at 1 year and cancer incidence. However, this was changed to a post hoc analysis using Cox proportional hazards models to examine cancer incidence as a function of 25(OH)D while adjusting for potentially important covariates including age, smoking, body mass index (calculated as weight in kilograms divided by height in meters squared), hormone use, and family history (for additional details, see Supplement 2).

In all hypothesis testing, 2-sided tests were performed with *P* value of less than .05 for statistical significance, using SAS (SAS Institute), version 9.4.



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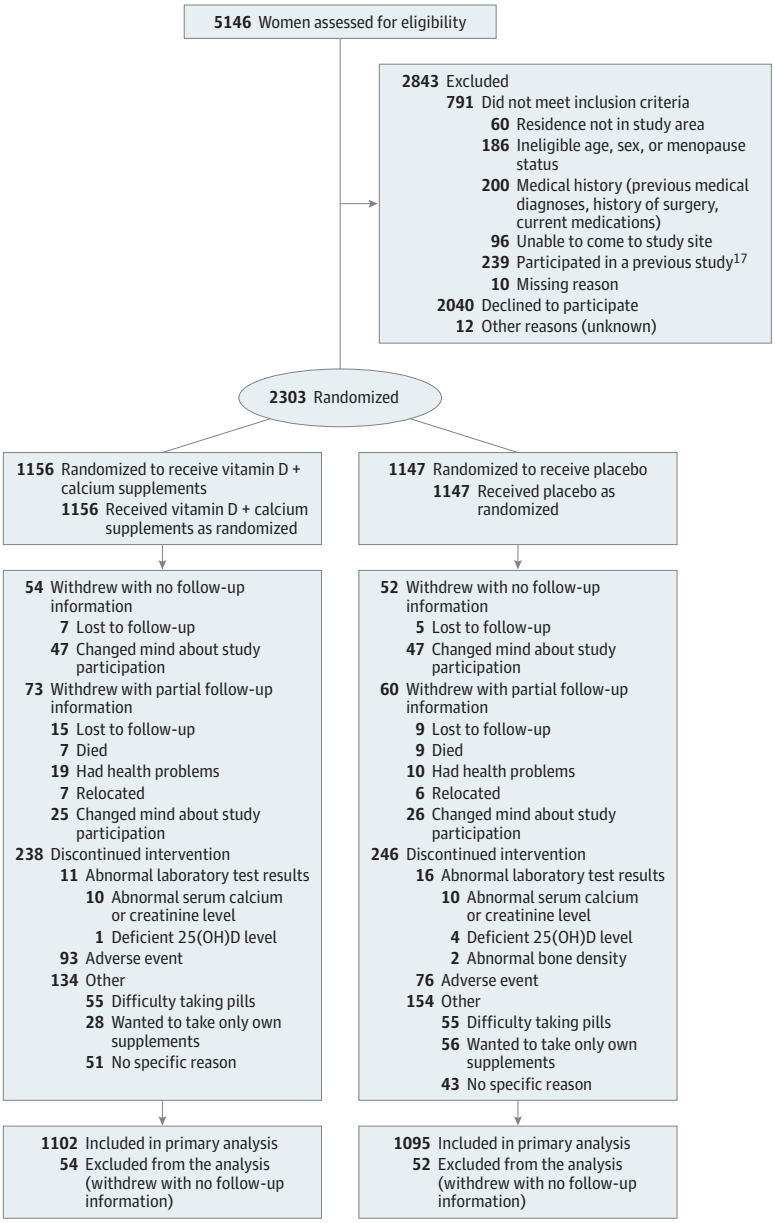
Figure 1. Flow of Participants Through the Study of the Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women




25(OH)D indicates 25-hydroxyvitamin D.

## Results

### Baseline Characteristics

Recruitment occurred from June 2009 to August 2011 with 5146 telephone and visit screens (**Figure 1**). Of 2303 participants randomized, 1156 (50.2%) were allocated to the vitamin $D_3$ + calcium group and 1147 to the placebo group. Of 2303 participants enrolled, 2064 (89.6%; 89.0% of the vitamin $D_3$ + calcium group, 90.2% of the placebo group) completed 4 years of study. Of those not completing the study, 16 participants (7 in the vitamin $D_3$ + calcium group and 9 in the placebo group) died during the study. There were 1102 participants in the vitamin $D_3$ + calcium group and 1095 participants in the placebo group that provided some follow-up. There was no significant difference between groups in the proportion completing the study (difference in proportion, 0.012 [95% CI, −0.013 to 0.037]) or dying while participating in the study (difference in proportion, 0.002 [95% CI, −0.006 to 0.037]).

At baseline, the vitamin $D_3$ + calcium and placebo groups were similar in most relevant variables including age, race, ethnicity, body size, dietary and supplemental calcium and vitamin D, smoking, and estrogen therapy (**Table 1**). The mean age was 65.2 years, and most participants (99.5%) self-identified as non-Hispanic white race. Therapy with estrogen agonists



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Table 1. Baseline Characteristics of Healthy Older Women Receiving Vitamin $D_3$ + Calcium or Placebo Supplementation by Treatment Group

| | Vitamin $D_3$ + Calcium Group | | Placebo Group | |
|---|---|---|---|---|
| | No. of Participants | Mean (SD) | No. of Participants | Mean (SD) |
| Age, y | 1156 | 65.2 (6.9) | 1147 | 65.2 (7.1) |
| Height, cm | 1135 | 162.1 (6.1) | 1123 | 162.0 (6.3) |
| Weight, kg | 1136 | 78.5 (18.0) | 1124 | 79.3 (17.8) |
| BMI | 1134 | 29.9 (6.6) | 1121 | 30.2 (6.5) |
| | No. of Participants | Median (IQR) | No. of Participants | Median (IQR) |
| Calcium supplements, mg/d | 1156 | 600 (5-1050) | 1147 | 600 (0-1000) |
| Vitamin D supplements, IU/d | 1156 | 734 (100-1200) | 1147 | 700 (0-1000) |
| Dietary calcium, mg/d | 1140 | 641 (460-893) | 1116 | 641 (454-892) |
| Dietary vitamin D, IU/d | 1140 | 103 (60-176) | 1116 | 107 (60-173) |
| | | No. of Participants (%) | | No. of Participants (%) |
| Race/ethnicity | | | | |
| White | | 1149 (99.4) | | 1142 (99.6) |
| American Indian or Alaska Native | | 4 (0.4) | | 4 (0.3) |
| Asian, black, unknown | | 3 (0.3) | | 1 (0.1) |
| Hispanic | | 9 (0.8) | | 2 (0.2) |
| Surgical menopause | | 423 (36.6) | | 389 (33.9) |
| Bilateral oophorectomy | | 315 (27.3) | | 280 (24.4) |
| Current smoking | | 75 (6.5) | | 66 (5.7) |
| Never smoking | | 768 (66.4) | | 773 (67.4) |
| Estrogen therapy | | 186 (16.1) | | 168 (14.7) |
| Estrogen agonist or antagonist therapy | | 19 (1.64) | | 38 (3.3) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

Table 2. Mean Values of Serum 25-hydroxyvitamin D at Baseline and at Annual Visits, Vitamin D and Calcium Supplementation Outside of Study Supplements, and Dietary Vitamin D and Calcium Among Healthy Older Women Receiving Vitamin $D_3$ + Calcium or Placebo Supplementation by Treatment Group

| | Vitamin $D_3$ + Calcium Group | | Placebo Group | | Between-Group Difference, Mean (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | No. of Participants | Mean (95% CI), ng/mL | No. of Participants | Mean (95% CI), ng/mL | | |
| **Serum 25-Hydroxyvitamin D Level** | | | | | | |
| Visit 1 (baseline) | 1156 | 33.0 (32.3 to 33.6) | 1146[a] | 32.7 (32.1 to 33.3) | | |
| Visit 3 (12 mo) | 989 | 43.9 (43.2 to 44.7) | 1002 | 31.6 (30.9 to 32.3) | 12.3 (11.3 to 13.3) | <.001 |
| Visit 5 (24 mo) | 966 | 44.3 (43.6 to 45.0) | 966 | 31.7 (31.0 to 32.4) | 12.6 (11.6 to 13.6) | <.001 |
| Visit 7 (36 mo) | 938 | 45.1 (44.3 to 45.9) | 925 | 32.4 (31.7 to 33.1) | 12.7 (11.63 to 13.8) | <.001 |
| Visit 9 (48 mo) | 980 | 42.5 (41.7 to 43.3) | 992 | 30.9 (30.2 to 31.6) | 11.6 (10.6 to 12.7) | <.001 |
| Mean (visit 2 [6 mo] to visit 9) | 1047 | 43.6 (42.9 to 44.3) | 1056 | 31.6 (31.0 to 32.2) | 12.0 (11.1 to 12.9) | <.001 |
| **Outside of Study Supplement Intake (Visit 2 to Visit 9)** | | | | | | |
| Vitamin $D_3$, IU/d | 1099 | 740 (691 to 789) | 1094 | 869 (803 to 934) | −128.1 (−209.5 to 46.6) | .002 |
| Calcium, mg/d | 1099 | 500 (475 to 525) | 1994 | 512 (489 to 536) | −12.0 (−46.0 to 22.0) | .49 |
| **Dietary Intake (Visit 1 to Visit 9)** | | | | | | |
| Vitamin $D_3$, IU/d | 1145 | 127.2 (121.7 to 132.7) | 1128 | 126.8 (121.4 to 132.2) | 0.4 (−7.4 to 8.1) | .93 |
| Calcium, mg/d | 1145 | 680.2 (661.8 to 698.5) | 1128 | 672.1 (654.2 to 690.0) | 8.1 (−17.6-33.7) | .54 |

SI Conversion: To convert 25-hydroxyvitamin D to nmol/L; multiply by 2.496.

[a] One participant's baseline serum 25-hydroxyvitamin D was not available.

and antagonists (such as tamoxifen or raloxifene) during the study, primarily for treatment or prevention of osteoporosis and not for prevention of breast cancer, was more common in the placebo group (difference in proportion, 0.017 [95% CI, 0.004 to 0.03]). Mean baseline 25(OH)D level was 32.8 ng/mL (to convert to nmol/L; multiply by 2.496), and values did not differ significantly between groups; all 25(OH)D level values after baseline were significantly higher in the treatment group



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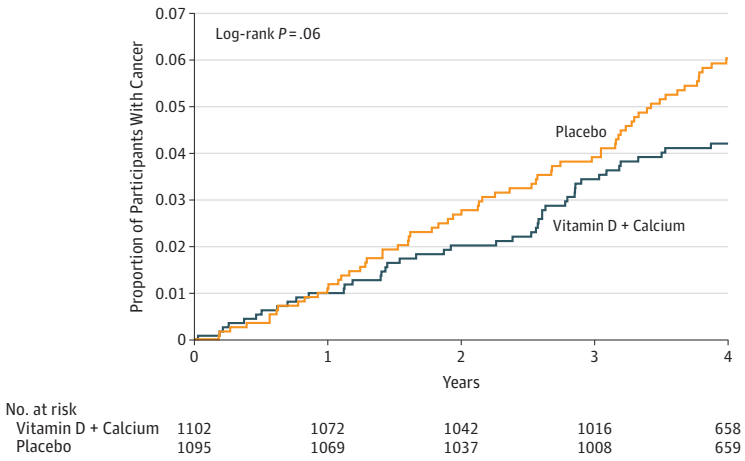
Figure 2. Invasive and In Situ Cancer Incidence Among Healthy Older Women Receiving Vitamin D and Calcium vs Placebo




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Vitamin D + Calcium | 1102 | 1072 | 1042 | 1016 | 658 |
| Placebo | 1095 | 1069 | 1037 | 1008 | 659 |

Figure excludes 54 participants in the treatment group and 52 participants in the placebo group who enrolled but then withdrew without providing any follow-up information. The median duration of follow-up was 4 years in both treatment groups.

(**Table 2**). For example, at 36 months the 25(OH)D level was 45.1 ng/mL in the vitamin $D_3$ + calcium group and 32.4 ng/mL in the placebo group.

Baseline median for vitamin $D_3$ dose was 734 IU/d (IQR, 100-1200) in the vitamin $D_3$ + calcium group and 700 IU/d (IQR, 0-1000) in the placebo group. Mean outside-of-study vitamin $D_3$ and calcium supplement dose for visits 2 through 9 in each group are reported in Table 2, as are dietary intakes for each nutrient. No differences were observed, except in vitamin D supplementation: women in the placebo group took higher amounts of vitamin D supplementation in addition to the study supplements than those in the vitamin $D_3$ + calcium group.

## Intention-to-Treat Analysis

Among the 1156 participants assigned to the vitamin $D_3$ + calcium group, 45 cancers (3.89%) were diagnosed; among the 1147 participants assigned to the placebo group, 64 cancers (5.58%) were diagnosed (between-group difference, 1.69% [95% CI, −0.06% to 3.46%], $P$ = .06). After excluding 54 participants in the vitamin $D_3$ + calcium group and 52 participants in the placebo group who withdrew after randomization with no follow-up, there was no significant difference in cancer incidence between the 2 groups using Kaplan-Meier analysis (log-rank test of equality over strata, $P$ = .06). Kaplan-Meier incidence over 4 years was 0.042 (95% CI, 0.032 to 0.056) in the vitamin $D_3$ + calcium group and 0.060 (95% CI, 0.048 to 0.076) in the placebo group, $P$ = .06; **Figure 2**). In proportional hazards modeling (which included the same events as the Kaplan-Meier analysis, excluded the same participants with no follow-up, and was not adjusted for other covariates), the HR was 0.70 (95% CI, 0.47 to 1.02).

**Table 3** shows the cancer types observed overall, and stratified by study year 1 and years 2 through 4. Breast carcinoma was diagnosed in 19 participants in the vitamin $D_3$ + calcium group and 24 participants in the placebo group (difference in proportion, 0.005 [95% CI, −0.007 to 0.016]). After excluding 54 participants in the treatment group and 52 participants in the placebo group who withdrew after randomization with no follow-up, comparison of time to diagnosis in the 2 groups using Kaplan-Meier analysis showed that the difference in breast cancer was not significant (log-rank test of equality over strata, $P$ = .435). Kaplan-Meier incidence for breast cancer over 4 years was 0.018 (95% CI, 0.011 to 0.028) in the vitamin $D_3$ + calcium group and 0.023 (95% CI, 0.015 to 0.034) in the placebo group. Proportional hazards modeling (which included the same events as Kaplan-Meier analysis and excluded the same participants with no follow-up) showed an HR of 0.79 (95% CI, 0.43 to 1.43). There were too few of the other cancers to analyze.

Four of the 109 participants who were diagnosed with cancer during the study developed a second primary cancer, which were excluded from analysis. The second primary cancers included 2 cancers (1 breast cancer and 1 colon cancer) in the vitamin $D_3$ + calcium group, and 2 cancers (both lymphomas) in the placebo group. Of the first primary cancers, 99 were invasive and 10 were in situ. Table 3 indicates the groups in which the invasive and in situ cancers occurred. Of 194 colonic adenomas identified in 181 participants, 2 cancers were identified as in situ cancers of the colorectum.

By proportional hazards modeling, which included the same cancer events indicated earlier and excluded the same study participants with no follow-up, age at baseline was significantly associated with cancer incidence (HR, 1.05 (95% CI, 1.02 to 1.08), and use of estrogen agonists and antagonists during the study was significantly more common in the placebo group. With age adjustment, the HR associated with treatment was 0.70 (95% CI, 0.48 to 1.02). With adjustment for estrogen agonist and antagonist use, the HR was 0.70 (95% CI, 0.47 to 1.02).

Mean adherence with vitamin $D_3$ or placebo was 75.4% in the vitamin $D_3$ + calcium group and 76.6% in placebo group (mean difference, −1.17 [95% CI, −3.88 to 1.55]); the calcium or placebo adherence was 57.7% in the vitamin $D_3$ + calcium group and 59.4% in the placebo group (mean difference, −1.7 [95% CI, −4.51 to 1.10]). Values included those who discontinued study



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Table 3. Cancer Site for Healthy Older Women With First Diagnosis of Cancer Receiving Vitamin $D_3$ + Calcium or Placebo Supplementation, by Years in the Study

| | Participants With First Diagnosis of Cancer, No. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Year 1 | | | Years 2-4 | | | Years 1-4 | | |
| Cancer Site | Vitamin $D_3$ + Calcium Group | Placebo Group | Total | Vitamin $D_3$ + Calcium Group | Placebo Group | Total | Vitamin $D_3$ + Calcium Group | Placebo Group | Total |
| Breast | 4 | 5 | 9 | 12 | 18 | 30 | 16 | 23 | 39 |
| Breast in situ | 1 | 0 | 1 | 2 | 1 | 3 | 3 | 1 | 4 |
| Colon or rectum | 0 | 0 | 0 | 4 | 4 | 8 | 4 | 4 | 8 |
| Colon or rectum in situ | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 2 | 2 |
| Endometrium | 0 | 1 | 1 | 2 | 2 | 4 | 2 | 3 | 5 |
| Lung | 1 | 0 | 1 | 4 | 2 | 6 | 5 | 2 | 7 |
| Melanoma | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 3 |
| Melanoma in situ | 0 | 0 | 0 | 1 | 2 | 3 | 1 | 2 | 3 |
| Neuroendocrine | 1 | 0 | 1 | 1 | 4 | 5 | 2 | 4 | 6 |
| Ovary | 0 | 0 | 0 | 0 | 5 | 5 | 0 | 5 | 5 |
| Other[a] | 4 | 5 | 9 | 7 | 10 | 17 | 11 | 15 | 26 |
| Other[a] in situ | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 |
| **Total** | **11** | **12** | **23** | **34** | **52** | **86** | **45** | **64** | **109** |

[a] Tumors with 2 or fewer occurrences: anal, biliary tract, bladder, brain, cervix, esophagus, kidney, leukemia, lymphoma, meningioma, myeloma, pancreas, sarcoma, thyroid, vagina, and primary site unknown.

supplements. During follow-up, 304 participants (13.2%; 12.4% of the vitamin $D_3$ + calcium group and 14.0% of the placebo group) stopped taking the vitamin D or placebo supplement, and 474 participants (20.6%; 20.3% of the vitamin $D_3$ + calcium group and 20.8% of the placebo group) stopped taking the calcium or placebo (difference in proportion, 0.017 [95% CI, −0.011 to 0.044] for vitamin $D_3$ supplement; 0.005 [95% CI, −0.028 to 0.038]) for calcium supplement.

There were no serious supplement-related adverse events. Renal calculi were reported by 26 participants, 16 (1.4%) in the vitamin $D_3$ + calcium group and 10 (0.9%) in the placebo group (difference in proportion, 0.005 [95% CI, −0.004 to 0.015]). Eight participants had 1 serum calcium value above normal (6 in the vitamin $D_3$ + calcium group and 2 in the placebo group; difference in proportion, 0.003 [95% CI, −0.002 to 0.010]).

### Post Hoc Analyses

In post hoc analysis, in which participants who withdrew, died, or developed cancer prior to being in the study for 12 months were excluded (excluding 84 participants in the vitamin $D_3$ + calcium group and 78 in the placebo group), a total of 34 participants in the vitamin $D_3$ + calcium group and 52 participants in the placebo group developed cancer during years 2 through 4 ($\chi^2$, 3.17% vs 4.86%, $P$ = .046); difference in proportions, 1.7% (95% CI, 0.1% to 3.4%). In Kaplan-Meier analysis, the difference was significant (log-rank test of equality over strata, $P$ = .047), and in proportional hazards modeling, the HR was 0.65 (95% CI, 0.42 to 0.99) (eFigure 1 in Supplement 2).

In another post hoc analysis, the achieved serum 25(OH)D level was significantly inversely associated with cancer incidence ($P$ = .03, coefficient, −0.017). Compared with 25(OH)D level of 30 ng/mL as baseline, the estimated HR for cancer incidence for 25(OH)D levels between 30 ng/mL and 55 ng/mL was 0.65 (95% CI, 0.44 to 0.97) (eFigure 2 in Supplement 2).

## Discussion

In this RCT involving healthy postmenopausal older women with mean serum 25(OH)D levels of 32.8 ng/mL, supplementation with vitamin $D_3$ and calcium compared with placebo did not result in a significantly lower risk of all-type cancer at 4 years. There was no statistically significant difference between the treatment groups in incidence of breast cancer.

One explanation for lack of statistically significant differences between the treatment groups in all-type cancer incidence is that the study cohort had higher baseline serum 25(OH)D levels compared with the US population. In the US National Health and Nutrition Examination Surveys (NHANES) from 2001 through 2006, an estimated 75% to 80% of the adult population had serum 25(OH)D level values less than 30 ng/mL, and approximately 30% had 25(OH)D level values below 20 ng/mL,[21] the 2 most commonly recommended levels for vitamin D adequacy from the NAM and the Endocrine Society, respectively. In this cohort, the mean baseline serum 25(OH)D level was approximately 33 ng/mL; only 9.6% of baseline 25(OH)D level values were less than 20 ng/mL, and 38.6% were less than 30 ng/mL. Response to change in vitamin D intake, similar to other nutrients, is dependent on an individual's initial nutritional status.[22] Thus, if vitamin D does have any potential effect on cancer prevention, persons with higher levels of serum 25(OH)D (ie, better nutrient status) would be expected to have a lesser effect from supplementation than those with lower baseline levels, at least up to some cut-off level.

Studies of vitamin D supplementation have an advantage over studies of most other nutrients because serum 25(OH)D is available as an intermediate measure (biomarker) of supplement efficacy. Serum 25(OH)D takes into account the known variation in absorption efficiency of vitamin $D_3$ and in



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its enzymatic 25-hydroxylation, and also accounts for total vitamin D intake, including outside-of-study supplements, diet, and sunlight exposure. The higher intake of outside vitamin $D_3$ supplementation in the placebo group in this study cohort (the majority of individuals would be considered to be vitamin D sufficient[23]) might obscure any treatment effect in the intention-to-treat analysis.

The association observed in the post hoc analysis excluding cancers that were diagnosed during year 1 may be related to the possibility that cancers diagnosed early in the study may have been present upon enrollment and that time is needed for vitamin D supplementation to increase serum 25(OH)D level and to exert a potential effect on cancer development or progression. However, this finding, as well as the post hoc observation suggesting an inverse association between serum 25(OH)D levels and cancer, should be considered only exploratory and hypothesis generating, and require assessment in further studies.

Other studies have evaluated the relationship between vitamin D supplementation and cancer. In an RCT of vitamin $D_3$ and calcium supplementation with cancer incidence as a primary outcome from the Women's Health Initiative (WHI),[20] postmenopausal women randomly assigned to daily 1000-mg calcium and 400-IU vitamin D or placebo pills showed no difference in colorectal cancer incidence. However, the intervention dose was only 400 IU per day, and the supplement adherence was only about 50%. The NAM-recommended dietary allowance for vitamin D is 600 IU per day for persons aged 50 to 70 years and 800 IU per day for those 70 years or older. In a nested case-control study of the WHI, there was a statistically significant inverse relationship between baseline serum 25(OH)D level and incidence of colorectal cancer risk (RR, 2.53 [95% CI, 1.49 to 4.32]).[20]

In a previous study by Lappe et al,[17] in which cancer was a secondary outcome, vitamin $D_3$ and calcium supplementation were significantly associated with decreased cancer incidence. In the entire cohort (vitamin $D_3$ and calcium supplementation and placebo groups), which had a mean baseline serum 25(OH)D level of 28.7 ng/mL (SD, 8.1), the RR of developing cancer for the vitamin $D_3$ and calcium group compared with placebo was 0.40 (95% CI, 0.20 to 0.82; $P$ = .01); for the calcium-only group, the RR was 0.53 (95% CI, 0.27 to 1.03, $P$ = .06). Excluding cancers that developed during year 1, the RR for the vitamin $D_3$ and calcium supplementation group was 0.23 (95% CI, 0.09 to 0.60; $P$ = .005), whereas for the calcium-only group, the RR was 0.59 (95% CI, 0.29 to 1.21, $P$ = .15).

In a secondary analysis of a fracture prevention RCT in the United Kingdom, a single dose of 100 000 IU of vitamin D every 4 months had no significant effect on cancer incidence (age-adjusted RR, 1.11 [95% CI, 0.86 to 1.42]).[24] The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial, an RCT of vitamin $D_3$ (800 IU per day) and calcium (1000 mg per day) to prevent fragility fractures, also showed no effect on cancer incidence. Both of these latter studies used vitamin D doses of about 800 IU per day, which is less than the vitamin $D_3$ dose of 2000 IU per day used in this study.

Observational studies showed an inverse association between sunlight and cancer incidence.[4] Meta-analyses showed an association with lower risk of colon cancer in persons with higher 25(OH)D levels,[5,6] and prospective studies found a significant nonlinear inverse association between 25(OH)D level and breast cancer.[7] Other studies, such as the 25(OH)D pooling project,[25] showed no relationship between 25(OH)D level and cancer.[26,27]

In this trial, calcium supplements were included in the intervention to ensure maintenance of adequate calcium intake, primarily because the combination of vitamin D and calcium reduced the incidence of cancer in the previous RCT,[17] whereas the calcium-only group showed no significant effect on cancer incidence. Calcium is important for vitamin D signaling, and it has been shown that antiproliferative effects of 1,25-dihydroxyvitamin D in colorectal cancer cell lines depend on expression of the calcium-sensing receptor.[28] In animal studies, dietary calcium was significantly inversely associated with carcinogenesis of the large bowel.[29] In humans, high calcium intakes have been associated with lower risk of colon cancer[30] and adenomas,[31] and RCTs of calcium have shown decreased risk of adenomas.[32,33] However, a more recent RCT[35] found no effect of calcium, vitamin D, or both on incidence of recurrent adenomas. Whether calcium supplementation affected cancer incidence in this study is not known.

In the vitamin $D_3$ + calcium group supplemented with 2000 IU per day of vitamin $D_3$ along with 1500 mg per day of calcium, neither hypercalcemia nor renal calculi (both confirmed by medical records) occurred more often than would be expected in a population of older women. Renal calculi were reported by 1.4% of the treatment group and 0.9% of the placebo group, which compares with incidence of 0.3% over 4 years among older women in Rochester, Minnesota.[36] The occurrence of hypercalcemia and renal calculi did not differ between treatment groups. In contrast, in the WHI,[37] the incidence of self-reported clinically diagnosed urinary tract stones was higher in the calcium and vitamin D group than in the placebo group (HR, 1.17 [95% CI, 1.02 to 1.34]). When participants with adherence of less than 80% for their assigned treatment were censored, findings were similar.

This study has several strengths. This study was a population-based RCT that used an intervention with a relatively high dose of vitamin $D_3$ that increased mean serum 25(OH)D level, had low participant drop out, measured 25(OH)D level at baseline and annually on all participants, had on-site monitoring every 6 months, and validated cancer outcomes with pathology reports.

This study also has several limitations. The cohort included older women, primarily non-Hispanic white, and no men, which limits generalizability. Allowing members of the placebo group to take their own vitamin D and calcium, not to exceed NAM recommendations, may have biased the analyses by treatment group toward null. The NAM recommendations for minimum vitamin D intake and of 25(OH)D level for skeletal health, and the high prevalence of low vitamin D status and osteoporosis rendered it unethical to ask participants to avoid any supplemental vitamin D and calcium. Furthermore, due to widespread information about the potential



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importance of vitamin D, it would be unfeasible to recruit for a large study in which no participants were permitted to take vitamin D. Sample-size calculations were based on a study cohort with lower baseline 25(OH)D levels than the current cohort and limited the power to find an effect of vitamin $D_3$ supplementation. Another limitation was the post hoc nature of the analysis that excluded cancers diagnosed during year 1 and the analysis that examined the relationship between 25(OH)D levels and cancer.

## Conclusions

Among healthy postmenopausal older women with a mean baseline serum 25-hydroxyvitamin D level of 32.8 ng/mL, supplementation with vitamin $D_3$ and calcium compared with placebo did not result in a significantly lower risk of all-type cancer at 4 years. Further research is necessary to assess the possible role of vitamin D in cancer prevention.

## ARTICLE INFORMATION

**Author Contributions:** Drs Lappe and Watson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Lappe, Travers-Gustafson, Recker, Garland.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Lappe, Watson, Garland, Gorham, Baggerly.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Watson, Baggerly, McDonnell.
*Obtained funding:* Lappe.
*Administrative, technical, or material support:* Lappe.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lappe reports having joined the scientific panel for GrassrootsHealth after this study was under way. GrassrootsHealth is a nonprofit 501(c)(3) organization based in San Diego, California, with public health promotion as its primary endeavor. The focus is on vitamin D testing and education. Dr Lappe has advised GrassrootsHealth on research design and data interpretation, but she is not employed by them, and has never received any funding from them. She has shared data from a previous study for Drs Garland, Gorham, and Baggerly and Ms McConnell to combine with data collected by GrassrootsHealth for analysis and publication. Drs Garland and Gorham both serve on the scientific advisory board for GrassrootsHealth, but they are not employed by GrassrootsHealth and have not received funding from them. Dr Baggerly reports that he is the son of Carole Baggerly, director of GrassrootsHealth. Dr Baggerly has no direct affiliation with GrassrootsHealth—he is not employed by them, nor does he receive any funding from them. Ms McDonnell reports that she is employed by GrassrootsHealth. She was paid by Creighton funds for her analysis work for this article. No other disclosures were reported.

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