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ORIGINAL REPORT

Calcium Plus Vitamin D Supplementation and the Risk of Nonmelanoma and Melanoma Skin Cancer: Post Hoc Analyses of the Women's Health Initiative Randomized Controlled Trial

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ABSTRACT

Purpose
In light of inverse relationships reported in observational studies of vitamin D intake and serum 25-hydroxyvitamin D levels with risk of nonmelanoma skin cancer (NMSC) and melanoma, we evaluated the effects of vitamin D combined with calcium supplementation on skin cancer in a randomized placebo-controlled trial.

Methods
Postmenopausal women age 50 to 79 years (N = 36,282) enrolled onto the Women's Health Initiative (WHI) calcium/vitamin D clinical trial were randomly assigned to receive 1,000 mg of elemental calcium plus 400 IU of vitamin D3 (CaD) daily or placebo for a mean follow-up period of 7.0 years. NMSC and melanoma skin cancers were ascertained by annual self-report; melanoma skin cancers underwent physician adjudication.

Results
Neither incident NMSC nor melanoma rates differed between treatment (hazard ratio [HR], 1.02; 95% CI, 0.95 to 1.07) and placebo groups (HR, 0.86; 95% CI, 0.64 to 1.16). In subgroup analyses, women with history of NMSC assigned to CaD had a reduced risk of melanoma versus those receiving placebo (HR, 0.43; 95% CI, 0.21 to 0.90; $P_{interaction} = .038$), which was not observed in women without history of NMSC.

Conclusion
Vitamin D supplementation at a relatively low dose plus calcium did not reduce the overall incidence of NMSC or melanoma. However, in women with history of NMSC, CaD supplementation reduced melanoma risk, suggesting a potential role for calcium and vitamin D supplements in this high-risk group. Results from this post hoc subgroup analysis should be interpreted with caution but warrant additional investigation.

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INTRODUCTION

Skin cancer is the most common malignancy in the United States, with more than 1 million new diagnoses each year.[1] Over the past 40 years, there has been a dramatic increase in the incidence of both nonmelanoma skin cancer (NMSC) and melanoma, especially among women,[2-4] and the significant morbidity and mortality in advanced stages provide compelling reasons to identify novel chemopreventive agents.[5] Although the etiology of NMSC (basal cell and squamous cell carcinomas) and melanoma is not completely understood, sun exposure is a primary risk factor.[6-9]

Currently, there is considerable interest in possible chemopreventive effects of vitamin D, which has been associated with reduced risk of colon, prostate, and breast cancers.[10-13] In observational studies, calcium supplementation has also been associated with a reduced risk of developing colon polyps,[14] and one small randomized controlled trial showed a significant reduction in total all-cancer incidence with calcium plus vitamin D (CaD) supplementation.[15]

Vitamin D may be important in skin cancer development. Mice lacking the vitamin D receptor have increased numbers of NMSC,[16] and vitamin D treatment decreases the growth of NMSC and melanoma cells in vitro and in mouse models.[17-21] There is evidence in humans that higher serum 25-hydroxyvitamin D (25[OH]D) levels are associated with reduced risk of NMSC[22] and with thinner

melanomas and improved survival from melanoma.[23] However, evidence from randomized controlled trials of vitamin D for skin cancer risk is lacking.

The Women's Health Initiative (WHI) CaD trial, designed to test the hypotheses that dietary CaD supplementation would reduce hip fractures and colorectal cancer in postmenopausal women,[24-26] provided the opportunity to investigate whether CaD supplementation reduces risk of NMSC and melanoma within a randomized placebo-controlled trial.

METHODS

Study Design

Detailed CaD trial methods have been published previously.[24-27] In brief, postmenopausal women age 50 to 79 years enrolled as participants in the WHI dietary modification (DM) and/or hormone therapy (HT) trials were invited to join the CaD supplementation trial at their first and second annual follow-up visits. Key outcomes of the CaD trial were hip fracture (primary end point)[24] and colorectal cancer (secondary end point).[25] To enroll onto the WHI trials, participants had to have a life expectancy of at least 3 years and no history of cancer, except nonmelanoma skin cancer, within the past decade. WHI participants with history of hypercalcemia, kidney stones, corticosteroid, or calcitriol use were ineligible for the CaD trial.

The CaD trial enrolled 36,282 WHI participants between 1995 and 2000; 25,210 (69%) were participating in the DM trial, 16,089 (44%) were in one of the HT trials, and 5,017 (14%) were in both DM and HT trials[24] (Fig 1). Participants were randomly allocated using a permuted block algorithm that assigned them in a double-blind fashion to receive either a twice daily supplement containing 500 mg of elemental calcium and 200 IU of vitamin D3 (n = 18,716) or a placebo identical in appearance (n = 18,106; GlaxoSmithKline, Middlesex, United Kingdom), stratified by age and clinical center. Participants were instructed to take the tablets with meals, ideally morning and evening, to improve absorption. Personal CaD supplementation was also allowed, initially limited to a 600 IU total daily intake of vitamin D but raised to a maximum of 1,000 IU daily in 1999, after 1997 Institute of Medicine recommendations were released.[28] Serum 25(OH)D levels measured 2 years after randomization were 28% higher in a subset of 227 women assigned to receive active supplements compared with 221 assigned to receive placebo pills.[24] Participants' total CaD dietary intake was evaluated using a food frequency questionnaire assessing intake of fortified dairy products, oily fish, and supplements; this was completed at time of randomization in the CaD trial, if available; otherwise, data collected at time of randomization in the HT or DM trials (1 to 2 years before) were used. HT use was also determined at CaD trial initiation; all other baseline variables were obtained at baseline visits for the HT/DM trials. The protocol was approved by the review board of each participating institution. Written informed consent was obtained for each participant at the CaD randomization visit.

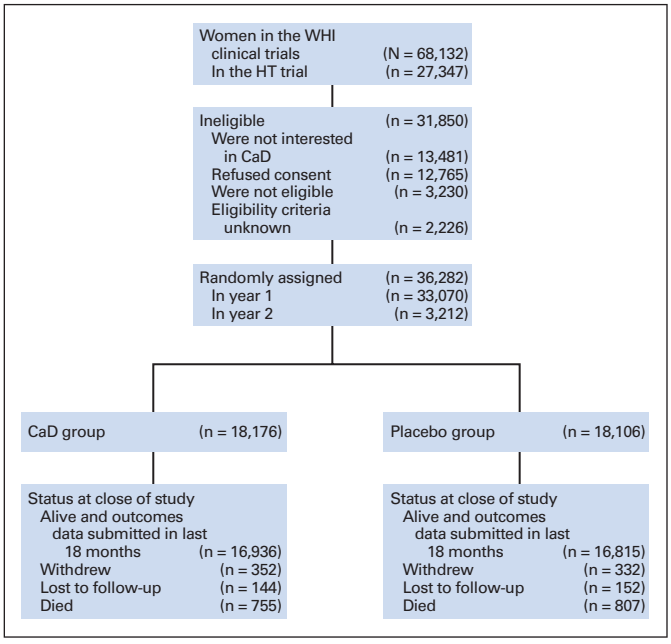

Fig 1. CONSORT diagram of the Women's Health Initiative (WHI) randomized trial of calcium and vitamin D (CaD). HT, hormone therapy. Data adapted.[12]

Retention, Adherence, and Follow-Up

Adherence to study medication was measured by weighing returned pill bottles at annual visits and defined as use of 80% or more of study medication. Adherence rates in the first 3 years of follow-up ranged from 60% to 63%, with another 13% to 21% of participants taking at least 50% of their study pills. By the end of the study, 76% of participants were still taking study medications, with 59% taking 80% or more of their daily pills.[24] Participants were observed for major outcomes, regardless of adherence to study protocol, until death, loss to follow-up, or study closure. Over the course of the study, 980 participants (2.7%) withdrew or were lost to follow-up, and 1,551 participants (4.3%) died.[24] Mean duration of follow-up was 7.0 years, with 16,936 participants (93%) in the CaD group and 16,815 participants (93%) in the placebo group in active follow-up at the end of the trial.

Determining Incident Cases of Skin Cancers

Women were mailed annual questionnaires to report hospitalizations and other health outcomes, including self-reported incident NMSC and melanomas. Reports of incident melanoma were confirmed by physician-adjudicated medical record review, including pathology reports, and coded as invasive, in situ, or borderline.[29] Per protocol, women diagnosed with melanoma fewer than 10 years before enrollment in the HT/DM trials were excluded. In the period between the start of the HT/DM trials and initiation of the CaD trial, 15 women were diagnosed with melanoma; these 15 women are included among women with history of melanoma in our analysis.

Statistical Analysis

Descriptive characteristics and potential risk factors for skin cancer, including race, body mass index (BMI), smoking, geographic region, physical activity (outdoor walking), multivitamin use, and history of skin cancer were compared between the CaD and placebo groups using χ^2 tests with a two-sided P value of less than .05 defined as significant. Modeling analyses used time-to-event methods according to the intention-to-treat principle. Incidences of NMSC and melanoma were compared between the randomization groups using hazard ratios (HRs) with corresponding 95% CIs and Wald statistic P values from Cox proportional hazards models (Figs 2, 3). Kaplan-Meier estimates were used to describe event rates over time. An adherence analysis was also performed as a corollary to the intention-to-treat analysis.

To assess whether the effect of CaD supplementation on NMSC and melanoma risk varied according to baseline risk factors for both types of skin cancer, Cox proportional hazards models were extended to include the variable of interest and interaction with group assignment. HRs for CaD versus placebo within each subgroup are presented along with the P value for the CaD by subgroup interaction. Eight prespecified subgroup analyses were conducted for both NMSC and melanoma outcomes: one, age (50 to 59, 60 to 69, and 70 to 79 years); two, BMI less than 25 kg/m^2, 25 to 29.9 kg/m^2, and 30 kg/m^2 or more; three, low versus high ultraviolet (UV) exposure (as measured by mean annual solar radiation in Langleys and defined as $\leq$ 375 Langleys, low UV exposure $v >$ 375 Langleys, high UV exposure[30]); four, history of NMSC; five, vitamin D intake ($\geq$ 400 $v <$ 400 IU); six, history of melanoma; seven, history of cancer; and eight, white versus black/Hispanic/Asian or Pacific Islander/Native American or Alaskan native/other race. There were too few NMSC and melanoma cases in the nonwhite race categories to conduct subgroup analyses of race/ethnicity. Although subgroups were prespecified before this secondary data analysis, skin cancer was not a primary or secondary end point. Thus, all analyses of skin cancer are considered post hoc. A total of 16

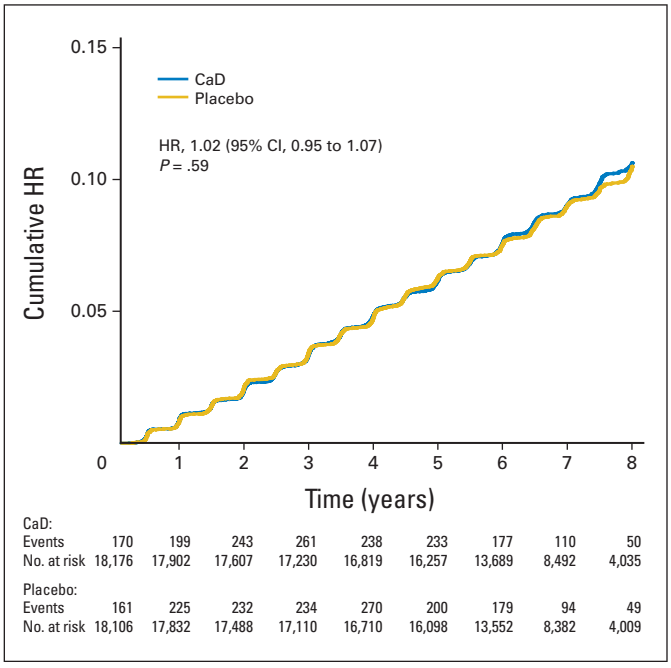

Fig 2. Kaplan-Meier estimates of the cumulative hazard ratio (HR) for nonmelanoma skin cancer with supplemental calcium plus vitamin D (CaD) as compared with placebo.

subgroups were examined; thus, approximately one statistically significant interaction test ($P < .05$) might be expected by chance alone. *P* values are presented without adjustment for multiple testing. All proportional hazards models were also adjusted for age, assignment in the HT (active, placebo, not randomly assigned) and DM (intervention, comparison, not randomly assigned) trials, and outcome prevalent condition (melanoma or NMSC). Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). The

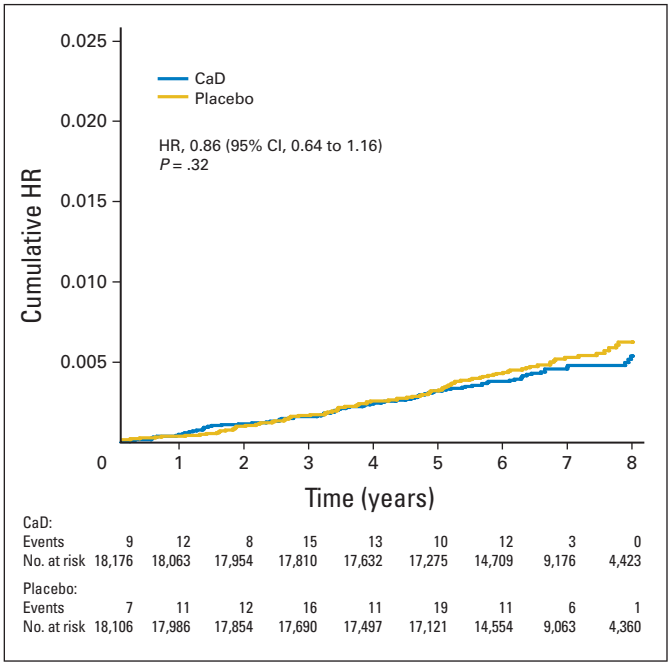

Fig 3. Kaplan-Meier estimates of the cumulative hazard ratio (HR) for melanoma with supplemental calcium plus vitamin D (CaD) as compared with placebo.

WHI investigators and National Institutes of Health sponsors all contributed to the study design and execution. Statistical analyses and data management were conducted at the WHI Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center (Seattle, WA).

RESULTS

Demographics of Participants

Table 1 shows the baseline characteristics of participants in the active CaD (n = 18,176) and placebo (n = 18,106) groups. Demographics, health behaviors, and diet were balanced between randomization groups, as were specified skin cancer risk factors (eg, age, smoking, nonsteroidal anti-inflammatory drug use, history of skin cancer, and sun exposure [measured via regional solar radiation, geography, and outdoor walking]). Total vitamin D intake of 400 IU or more per day was reported by 41.8% of women in the CaD arm and 42.3% of women assigned to placebo ($P = .37$). At year 6, off-protocol CaD supplement use was similar in both randomization groups (CaD arm, 52.0%; placebo group, 52.8%).[24]

NMSCs

After a mean follow-up of 7.0 years, there was no difference between treatment groups in self-reported NMSCs, with a total of 1,683 NMSC cases reported in the active CaD group and 1,655 cases in the placebo group (HR, 1.02; 95% CI, 0.95 to 1.07; Fig 2). Nor did CaD supplementation affect NMSC outcomes within any of the subgroups (ie, by age, BMI, total vitamin D intake, solar radiation [Langleys], history of cancer, history of melanoma, or history of NMSC; Fig 4).

Melanoma

After the mean 7.0-year follow-up, there was no difference in melanoma incidence between groups, with 82 melanomas diagnosed in the active group and 94 in the placebo group (HR, 0.86; 95% CI, 0.64 to 1.16; Fig 3). In prespecified subgroup analysis, women who reported a history of NMSC had 57% fewer melanomas when assigned to active CaD versus placebo (HR, 0.43; 95% CI, 0.21 to 0.90; $P = .026$; $P_{interaction} = .038$; Fig 5). This effect was not seen in women without history of NMSC (HR, 1.02; 95% CI, 0.73 to 1.41). CaD supplementation did not affect melanoma within any of the other subgroups. There were no significant differences in subtypes of melanomas (invasive *v* in situ), whether comparing women randomly assigned to receive CaD versus placebo or based on skin cancer history (Table 2).

Sensitivity Analyses

In analyses restricted to adherent participants (ie, women who took ≥ 80% of study pills during the trial), there was no effect of CaD supplementation on NMSC or melanoma (data not shown).

DISCUSSION

Daily supplementation with 1,000 mg of calcium and 400 IU of vitamin D had no effect on NMSC or melanoma skin cancer incidence in this large randomized double-blinded placebo-controlled trial. One possible reason for the overall null results is that a daily 400-IU dose of vitamin D is inadequate for reducing cancer risk. Since the report of no reduction in colorectal cancer—the key secondary outcome of the

Table 1. Descriptive Characteristics of Participants at Baseline by Random Assignment

Characteristic	CaD No.	CaD %	Placebo No.	Placebo %	*P*
Total No. of participants	18,176		18,106		
Age, years					.997
50-59	6,726	37.0	6,696	37.0	
60-69	8,276	45.5	8,243	45.5	
70-79	3,174	17.5	3,167	17.5	
Race/ethnicity					.446
White	15,051	82.8	15,104	83.4	
Black	1,680	9.2	1,635	9.0	
Hispanic	785	4.3	717	4.0	
American Indian	77	0.4	72	0.4	
Asian/Pacific Islander	370	2.0	351	1.9	
Unknown	213	1.2	227	1.3	
Education					.986
High school/GED or lower	4,286	23.6	4,290	23.7	
School after high school	7,217	39.7	7,156	39.5	
College degree or higher	6,557	36.1	6,545	36.1	
Body mass index, kg/m^2					.334
$<$ 25	4,745	26.1	4,834	26.7	
25 to $<$ 30	6,476	35.6	6,487	35.8	
$\geq$ 30	6,870	37.8	6,692	37.0	
Smoking					.504
Never	9,325	51.3	9,428	52.1	
Past	7,255	39.9	7,133	39.4	
Current	1,405	7.7	1,356	7.5	
NSAID use					.303
Yes	6,249	34.4	6,132	33.9	
No	11,927	65.6	11,974	66.1	
Total vitamin D intake (dietary plus supplements), IU					.372
$<$ 200	6,842	37.6	6,678	36.9	
200 to $<$ 400	3,373	18.6	3,419	18.9	
400 to $<$ 600	4,180	23.0	4,293	23.7	
$\geq$ 600	3,426	18.8	3,363	18.6	
Total calcium intake (dietary plus supplements), mg					.740
$<$ 400	1,318	7.3	1,273	7.0	
400 to $<$ 800	4,790	26.4	4,732	26.1	
800 to $<$ 1,200	4,712	25.9	4,654	25.7	
$\geq$ 1,200	7,001	38.5	7,094	39.2	
Solar radiation of region, Langleys					.999
300-325	5,366	29.5	5,351	29.6	
350	3,920	21.6	3,880	21.4	
375-380	2,012	11.1	2,009	11.1	
400-430	3,018	16.6	3,015	16.7	
475-500	3,860	21.2	3,851	21.3	
US region					.996
Northeast	4,018	22.1	4,001	22.1	
South	4,327	23.8	4,304	23.8	
Midwest	4,429	24.4	4,399	24.3	
West	5,402	29.7	5,402	29.8	
Total outdoor walking energy expenditure, METs/wk					.964
None	6,081	33.5	6,056	33.4	
$\leq$ 3.5	3,491	19.2	3,481	19.2	
3.6-7.0	3,241	17.8	3,233	17.9	
$>$ 7.0	3,733	20.5	3,678	20.3	
History of cancer					.235
Yes	745	4.1	698	3.9	
No	17,431	95.9	17,408	96.1	
History of melanoma cancer					.293
Yes	92	0.5	78	0.4	
No	18,084	99.5	18,028	99.6	
History of nonmelanoma skin cancer					.300
Yes	1,086	6.0	1,129	6.2	
No	17,090	94.0	16,977	93.8	
Hormone use (CaD baseline)*					.237
Never user	5,810	32.0	5,685	31.4	
Past user	3,007	16.5	2,937	16.2	
Current user	9,359	51.5	9,484	52.4	
HT intervention assignment					.740
Not randomly assigned	10,122	55.7	10,071	55.6	
Active	4,039	22.2	4,078	22.5	
Placebo	4,015	22.1	3,957	21.9	
DM intervention assignment					.299
Not randomly assigned	5,582	30.7	5,490	30.3	
Intervention	4,767	26.2	4,878	26.9	
Comparison	7,827	43.1	7,738	42.7	

Abbreviations: CaD, calcium and vitamin D; DM, dietary modification; GED, general educational development; HT, hormone therapy; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

*HT variables calculated for time of CaD randomization and include hormone use from Women's Health Initiatve HT trial.

CaD trial—at the dose tested,[25] some[31,32] have recommended higher intakes of vitamin D for reducing colorectal and other cancers. The daily 400-IU dose of vitamin D3 is estimated to have raised mean serum 25(OH)D levels by approximately 4 ng/mL, which may be inadequate to observe a clinical difference in skin cancers. Indeed, 400 IU per day is 33% lower than the daily adequate intake level of 600 IU recommended in a recent Institute of Medicine consensus statement (November 2010).[33] However, this dose was considered adequate to aid calcium absorption at the inception of the trial in the early 1990s and thus appropriate for testing the primary CaD trial hypothesis that CaD supplementation would reduce hip fracture. Although hip fracture incidence was not, in fact, reduced in the WHI cohort of women age 50 to 79 years at baseline, significant reduction was seen in women age 60 years and older.[24]

Another possible explanation for the null results regarding skin cancer is that the study design allowed off-protocol calcium and/or vitamin D supplementation; women were allowed to take up to 600 IU of vitamin D daily initially and up to 1,000 IU daily from 1999 onward. Therefore, some in the placebo group were taking more vitamin D than some women in the intervention group. However, there is some evidence that active CaD-arm participants had higher overall vitamin D intake than those assigned to receive placebo; in a subset of 227 women assigned to receive active pills versus 221 assigned to receive placebo, serum 25(OH)D levels in women taking active pills were 28% higher than those in women taking placebo pills 2 years after randomization.[24] These 448 women with baseline and year-2 serum 25(OH)D levels were randomly selected and were at least 50% adherent to study medication. The 28% difference in 25(OH)D levels between the two groups is likely to be generalizable to the entire trial, because 84% of all participants were more than 50% adherent to study medications.

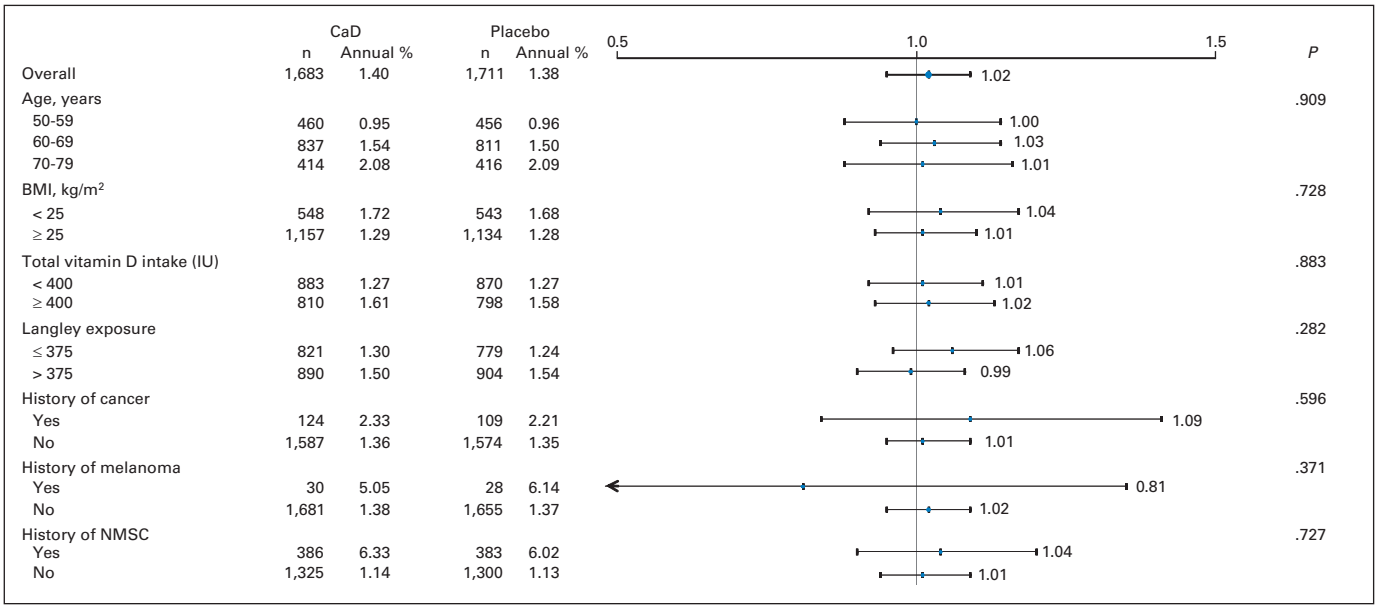

Fig 4. Estimated effects of supplemental calcium with vitamin D (CaD) on risk of nonmelanoma skin cancer (NMSC), according to selected baseline characteristics. All models were adjusted for age, assignment in Women's Health Initiative (WHI) hormone therapy trial (active, placebo, not randomly assigned), assignment in WHI dietary modification trial (intervention, comparison, not randomly assigned), and outcome prevalent condition (NMSC). BMI, body mass index; Langley exposure, average regional solar radiation.

Although the difference in 25(OH)D levels is modest, this substudy confirmed that 400 IU of vitamin D did raise 25(OH)D levels in this trial.

Whether the trial dose was too low or the difference in intake between treatment groups was too small to see an effect of CaD on NMSC, it is of interest that in subgroup analysis, CaD supplementation reduced risk of melanoma by 57% in women with history of NMSC. Additionally, CaD supplementation tended to reduce risk of melanoma in women with higher BMIs (> 25 kg/m^2), with lower baseline vitamin D intake (< 400 IU), and from areas with less sun exposure (< 375 Langleys), although there were no statistically significant interactions of CaD treatment with any of these variables. In the subgroup of women with history of NMSC, the absolute number of melanoma cases in both arms was small: 10 in the CaD arm and 24 in

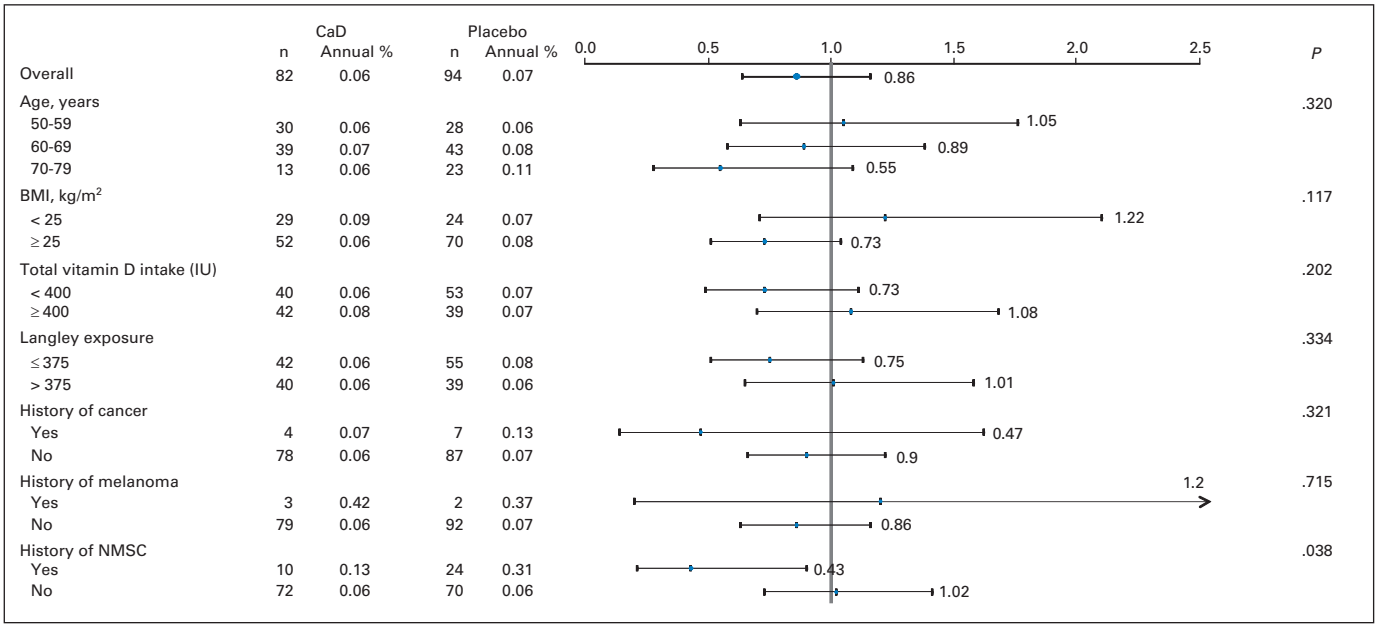

Fig 5. Estimated effects of supplemental calcium with vitamin D (CaD) on risk of melanoma, according to selected baseline characteristics. All models were adjusted for age, assignment in Women's Health Initiative (WHI) hormone therapy trial (active, placebo, not randomly assigned), assignment in WHI dietary modification trial (intervention, comparison, not randomly assigned), and outcome prevalent condition (melanoma). BMI, body mass index; Langley exposure, regional solar radiation; NMSC, nonmelanoma skin cancer.

Table 2. Characteristics of Melanomas by Study Group

Melanoma Subtype	CaD (n = 82) No.	CaD (n = 82) %	Placebo (n = 94) No.	Placebo (n = 94) %
Total invasive melanomas	44	54	58	62
Total in situ melanomas	38	46	36	38
History of NMSC (total)	10		24	
Invasive	5	50	12	50
In situ	5	50	12	50
No history of NMSC (total)	72		70	
Invasive	39	54	46	66
In situ	33	46	24	34
History of melanoma (total)	3		2	
Invasive	2	67	2	100
In situ	1	33	0	0
No history of melanoma (total)	79		92	
Invasive	42	53	56	61
In situ	37	47	36	39

Abbreviations: CaD, calcium and vitamin D; NMSC, nonmelanoma skin cancer.

the placebo arm. Thus, this finding may have resulted by chance, particularly because we examined 16 subgroups in these analyses. However, there is some evidence that vitamin D may affect development of melanoma. Vitamin D reduces UV-induced DNA damage in mice and has antiproliferative and prodifferentiative effects on melanoma cell lines in vitro.[19,34] In humans, previous studies have reported an association between higher 25(OH)D levels and lower Breslow thickness at melanoma diagnosis as well as decreased risk of relapse and death[23] and metastasis.[35] Others have noted a positive relationship between signs of sun damage (and presumably higher vitamin D levels) and decreased death from melanoma.[36] Finally, some[37] but not all[38] studies have shown that higher dietary or supplemental intake of vitamin D is associated with reduced risk of melanoma. Previous WHI and other cohort studies have reported that women with history of NMSC are 2.4 times more likely to develop melanoma than those without history of NMSC.[39-43] Therefore, NMSC may be a marker for participants with more UV-induced DNA damage[6,44-47] and thus higher risk for melanoma.

The possibility that CaD supplementation, or either vitamin D or calcium alone, might prevent melanoma in this high-risk group has important public health implications. Although we cannot rule out a role for calcium in preventing melanoma, we have some evidence that vitamin D may be an important factor in our findings. In exploratory patient case–control analyses of serum 25(OH)D levels measured in 4,868 women for previously reported fracture and breast and colorectal cancer patient case–control studies,[25,26] higher 25(OH)D levels were associated with 50% reduction in melanoma (manuscript in preparation). We hypothesize that raising vitamin D levels may prevent development of melanoma in women at high risk. A possible role for vitamin D supplementation in preventing melanoma in women with a history of NMSC warrants further investigation.

This study has several limitations. First, the WHI CaD trial was designed to examine the effect of a specific dose of CaD supplementation on hip fracture and colorectal cancer. Post hoc analyses of other malignancies may lack statistical power to detect differences between active and placebo groups, and it may be that any potential benefit of CaD supplementation on cancer incidence takes more than 7 years to appear. Second, NMSC outcome was based on particpant self-report, and cases were not adjudicated; however, several studies have found self-reported skin cancer to be highly accurate.[48,49] We lacked information on specific types of NMSC in this study; thus, we cannot determine if there was a differential effect of CaD supplementation on basal cell versus squamous cell carcinoma risk. Additionally, we lacked systematic measurements of 25(OH)D achieved after intervention and cannot determine the relationship between 25(OH)D levels after CaD supplementation and skin cancer risk. Even though women were randomly assigned to receive 400 IU of vitamin D, serum 25(OH)D levels could have varied as a result of genetic or environmental factors affecting vitamin D metabolism.[50,51] Finally, the finding that CaD supplementation reduced risk of incident melanomas in women with a history of NMSC must be interpreted with caution, because the *P* value is modest ($P_{interaction}$ = .038) and may reflect a chance finding given the multiple subgroups tested.

Strengths of this study include its randomized double-blinded design, large well-characterized study population, and long follow-up duration. This study controlled for many potential confounding factors, including diverse geographic regions with differing solar radiation, physical activity, smoking and alcohol status, education, socioeconomic status, and nutrient intake.

Despite the large study population, the number of incident melanomas was small (n = 176), illustrating the size of the cohort needed to detect a chemopreventive effect of any agent in a 7-year period. At this time, it seems unlikely that a randomized trial of the scope needed to examine the effect of calcium or vitamin D (or combined) supplementation on skin cancer risk will be performed, and this trial may provide the best data with which to assess this issue in the near future.

In conclusion, daily supplementation of calcium (1,000 mg) and vitamin D (400 IU) did not reduce incidence of NMSC or melanoma in a large cohort of postmenopausal women age 50 to 79 years. Therefore, our results do not support use of these supplements, at these doses, for preventing skin cancer in older women. However, CaD supplementation seems to have reduced the incidence of melanoma in women with history of NMSC, suggesting a possible role for either vitamin D or calcium, or their combination, in reducing melanoma in this high-risk group. Additional investigations of CaD supplementation to prevent melanoma in women with history of NMSC are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jean Y. Tang, Teresa Fu, Marcia L. Stefanick
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Data analysis and interpretation: Jean Y. Tang, Erin S. LeBlanc, Joann E. Manson, David Feldman, Eleni Linos, Nathalie Zeitouni, Joseph Larson, Marcia L. Stefanick
Manuscript writing: All authors
Final approval of manuscript: All authors

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