ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

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ABSTRACT

BACKGROUND

It is unclear whether supplementation with vitamin D reduces the risk of cancer or cardiovascular disease, and data from randomized trials are limited.

METHODS

We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n–3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events. This article reports the results of the comparison of vitamin D with placebo.

RESULTS

A total of 25,871 participants, including 5106 black participants, underwent randomization. Supplementation with vitamin D was not associated with a lower risk of either of the primary end points. During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; hazard ratio, 0.96; 95% confidence interval [CI], 0.88 to 1.06; P=0.47). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85 to 1.12; P=0.69). In the analyses of secondary end points, the hazard ratios were as follows: for death from cancer (341 deaths), 0.83 (95% CI, 0.67 to 1.02); for breast cancer, 1.02 (95% CI, 0.79 to 1.31); for prostate cancer, 0.88 (95% CI, 0.72 to 1.07); for colorectal cancer, 1.09 (95% CI, 0.73 to 1.62); for the expanded composite end point of major cardiovascular events plus coronary revascularization, 0.96 (95% CI, 0.86 to 1.08); for myocardial infarction, 0.96 (95% CI, 0.78 to 1.19); for stroke, 0.95 (95% CI, 0.76 to 1.20); and for death from cardiovascular causes, 1.11 (95% CI, 0.88 to 1.40). In the analysis of death from any cause (978 deaths), the hazard ratio was 0.99 (95% CI, 0.87 to 1.12). No excess risks of hypercalcemia or other adverse events were identified.

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

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This article was published on November 10, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1809944

Long prescribed to prevent and treat bone-related disorders,[1] supplemental vitamin D has been viewed in recent years as a potential strategy for preventing cancer and cardiovascular disease. In the United States, routine assessment of vitamin D status in patients in primary care settings[2] and the use of vitamin D supplements[3] have increased substantially. Ecologic studies have shown lower rates of death from cancer and cardiovascular disease in regions with greater sun exposure than in areas with less sun exposure.[1,4] Such exposure is necessary for cutaneous synthesis of vitamin D. Laboratory studies have shown the presence of vitamin D receptors in many tissues and have suggested plausible vitamin D pathways that may be related to cancer and cardiovascular disease, and observational studies have shown associations between low serum levels of 25-hydroxyvitamin D and increased risks of cancer and cardiovascular disease.[1,4-6] Nevertheless, it is uncertain whether supplementation with vitamin D prevents cancer or cardiovascular disease, because such results cannot establish causality.[1,4,7,8] For example, observational studies are susceptible to confounding by outdoor physical activity (which correlates with sun exposure), adiposity (which may decrease bioavailability of 25-hydroxyvitamin D), general nutritional status, and other factors that may produce spurious protective associations.[1,4]

Data from large-scale randomized trials (involving ≥10,000 participants) of vitamin D in moderate or high doses and designed with cancer or cardiovascular disease as primary outcomes are lacking. Trials examining such outcomes, typically using secondary or post hoc analyses, have usually shown null results, but the use of low doses of vitamin D, insufficient statistical power, short durations, lack of rigorous end-point adjudication, or a combination of these factors limit conclusions.[1,4] However, meta-analyses[9,10] of randomized trial data suggest a stronger benefit of vitamin D with respect to the rate of death from cancer than to the incidence of cancer. The U.S. Preventive Services Task Force concluded that there are insufficient data to evaluate the effectiveness of supplementation with vitamin D for the prevention of cancer or cardiovascular disease.[7] The Institute of Medicine had previously reached this same conclusion and called for new trials of vitamin D (in amounts at least twice the current recommended dietary allowance of 600 to 800 IU per day for bone health) to clarify the benefit–risk balance.[1] The Vitamin D and Omega-3 Trial (VITAL), a large-scale trial that evaluated high-dose vitamin D, was designed to address these knowledge gaps. Included in the trial population were more than 5000 black participants, for whom the question of the effectiveness of vitamin D is particularly relevant because their cutaneous synthesis of vitamin D in response to solar radiation is lower than that in persons in other racial or ethnic groups. VITAL also evaluated n–3 (omega-3) fatty acids; those results are shown in an accompanying article in the *Journal*.[11]

Methods

Trial Design and Oversight

We conducted this randomized, double-blind, placebo-controlled trial, with a two-by-two factorial design, to examine the benefits and risks of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n–3 fatty acids at a dose of 1 g per day in the primary prevention of cancer and cardiovascular disease among 25,871 men who were 50 years of age or older and women who were 55 years of age or older. The trial protocol has been described elsewhere[4,12] and is available with the full text of this article at NEJM.org.

Participants were recruited throughout the United States, and the groups were balanced according to sex and with a goal to include at least 5000 black participants. Eligible participants had no history of cancer (except nonmelanoma skin cancer) or cardiovascular disease at trial entry, and they were required to agree to limit the use of vitamin D from all supplemental sources, including multivitamins, to 800 IU per day and to complete a 3-month placebo run-in phase. Safety exclusions included renal failure or dialysis, cirrhosis, history of hypercalcemia, or other serious conditions that would preclude participation. Randomization was computer generated within sex, race, and 5-year age groups in blocks of eight.

Baseline questionnaires collected data on risk factors for cancer, cardiovascular disease, and other conditions and included a food frequency questionnaire. Participants received follow-up questionnaires at 6 months and 1 year after randomization and annually thereafter to collect information on adherence to trial regimens, outside use of vitamin D supplements, development of major illnesses, updates on risk factors, and po-

tential side effects of the trial agents. Calendar packs containing the trial capsules of vitamin D or corresponding placebo (and n–3 fatty acids or corresponding placebo) were mailed with questionnaires to the participants.

Blood samples were obtained at baseline during the run-in period from all willing participants — 16,956 of the 25,871 persons who underwent randomization (65.5%). At no cost to the trial, Quest Diagnostics donated and performed serum 25-hydroxyvitamin D assays with the use of liquid chromatography–tandem mass spectrometry on all samples that could be analyzed. Quest had no role in the design of the trial, accrual of the data (other than the assays), analysis of the data (other than assay standards), or preparation of the manuscript. Our trial participated in the vitamin D standardization program of the Centers for Disease Control and Prevention.[13]

The National Institutes of Health, the sponsors of the trial, had a collaborative role in the design and conduct of the trial. Final decisions regarding the data collection, management, and analysis and the review and approval of the manuscript and decision to submit the manuscript for publication resided with trial investigators and the trial research group. The trial was approved by the institutional review board of Partners HealthCare–Brigham and Women's Hospital and was monitored by an external data and safety monitoring board. The trial agents have received Investigational New Drug Approval from the Food and Drug Administration. Pharmavite donated vitamin D and Pronova BioPharma and BASF donated fish oil (Omacor); the companies also donated matching placebos and packaging in the form of calendar packs. None of the donating companies had any role in the design or conduct of the trial, collection or analysis of the data, or preparation or review of the manuscript. The first three authors and the last author had full access to all the trial data and vouch for the completeness and accuracy of the data, for the accuracy of the data analyses, and for the fidelity of the trial to the protocol. All the participants provided written informed consent before enrollment in the trial.

TRIAL END POINTS

The primary end points were invasive cancer of any type and major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes). Secondary cancer end points were incident colorectal, breast, and prostate cancers, and death from cancer. Secondary cardiovascular end points were an expanded composite of major cardiovascular events plus coronary revascularization and the individual components of major cardiovascular events. Participants who reported an end-point event were asked to sign a release for medical records, which were reviewed for confirmation by an end-points committee of physicians who were unaware of the trial-group assignments. Cancer was confirmed on the basis of histologic or cytologic data.[14] Myocardial infarction and stroke were confirmed with the use of established criteria,[15,16] coronary revascularization was confirmed by medical record review, and death from cardiovascular causes was confirmed if there was convincing evidence of a cardiovascular event from all available sources. Analyses included only confirmed end points.

For deaths reported by family members, the next of kin was asked for permission to obtain medical records and a copy of the death certificate. Alternatively, the latter was obtained from the state vital records bureau. The end-points committee reviewed the records to assign the cause of death. If records were unavailable (or participants were lost to follow-up), the National Death Index (NDI) Plus was searched for cause of death according to the death-certificate information. Deaths were defined with the use of all these sources; a secondary analysis of cause-specific deaths required medical records or other adjudication of cause of death beyond NDI coding.

STATISTICAL ANALYSIS

Analyses of effect were based on the intention-to-treat principle (all participants who underwent randomization were included). The trial was designed to have a greater than 85% power to detect observed hazard ratios of 0.85 and 0.80 for the primary end points of cancer and cardiovascular disease, respectively.[4] Initial analyses compared baseline characteristics of participants according to trial regimen with the use of t-tests or chi-square tests. Primary analyses compared the main effects of vitamin D on cancer and cardiovascular disease with the use of Cox proportional-hazards models that were controlled for age, sex, and randomization group in the n–3 fatty acid portion of the trial (n–3 fatty acid group or placebo group). Person-time was counted from randomization to

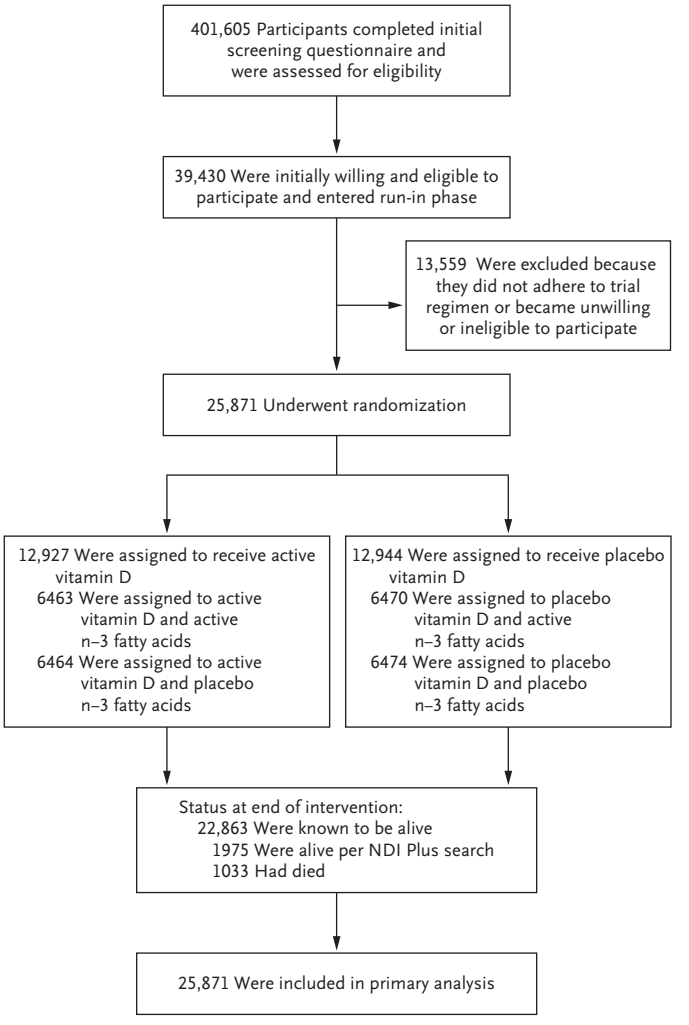

Figure 1. Screening, Randomization, and Follow-up of the Participants.
NDI denotes National Death Index.

the end point, to death, or to the end of the trial on December 31, 2017. Cumulative-incidence plots and interactions with time were used to examine whether effects varied over time. Prespecified analyses of the primary outcomes excluding events that occurred during the first year and the first 2 years of follow-up assessed latent effects. Adherence effects were estimated by censoring follow-up data when the participant discontinued trial capsules or began taking more than 800 IU per day of outside vitamin D.

Possible variations in the effect according to race or ethnic group, age, sex, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), baseline 25-hydroxyvitamin D level, concurrent randomization to the n–3 group, outside use of vitamin D supplements, and baseline risk factors for cancer and cardiovascular disease were specified a priori. However, there was no control for multiple hypothesis testing, and no formal adjustment was made to the P values or confidence intervals. Thus, results regarding secondary and exploratory end points, as well as those regarding subgroups, should be interpreted with caution. The incidence of potential side effects according to randomly assigned group was also compared.

RESULTS

TRIAL PARTICIPANTS

Randomization to receive vitamin D, n–3 fatty acids, both active agents, or both placebos took place from November 2011 through March 2014. The trial intervention ended as planned on December 31, 2017, which yielded a median follow-up of 5.3 years (range, 3.8 to 6.1). A total of 401,605 persons were screened for eligibility to participate, and 25,871 persons ultimately underwent randomization (Fig. 1).

Table 1 shows baseline characteristics of the trial participants (further details are provided in Table S1 in the Supplementary Appendix, available at NEJM.org). Of the 25,871 participants, 51% were women. The mean age of the participants was 67.1 years. The cohort was racially diverse and included 71% self-declared non-Hispanic white participants and 20% black participants; the rest were members of other racial or ethnic groups. Characteristics of the participants were balanced between the two groups.

Among the 15,787 participants who had blood samples that could be analyzed, the mean (±SD) serum total 25-hydroxyvitamin D level at baseline was 30.8±10.0 ng per milliliter (77 nmol per liter); 12.7% had levels below 20 ng per milliliter (50 nmol per liter), and 32.2% had levels from 20 to less than 30 ng per milliliter (50 to <75 nmol per liter). In a subgroup of 1644 participants with repeat measurements after 1 year, mean 25-hydroxyvitamin D levels increased from 29.8 ng per milliliter (74 nmol per liter) at baseline to 41.8 ng per milliliter (104 nmol per liter) at 1 year (a 40% increase) in the vitamin D group and changed minimally (mean, −0.7 ng per milliliter [−2 nmol per liter]) in the placebo group. Base-

Table 1. Characteristics of the Participants at Baseline, According to Randomized Assignment to Vitamin D or Placebo.*

Characteristic	Total (N=25,871)	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)
Female sex — no. (%)	13,085 (50.6)	6547 (50.6)	6538 (50.5)
Age — yr	67.1±7.1	67.1±7.0	67.1±7.1
Race or ethnic group — no./total no. (%)†			
Non-Hispanic white	18,046/25,304 (71.3)	9013/12,647 (71.3)	9033/12,657 (71.4)
Black	5106/25,304 (20.2)	2553/12,647 (20.2)	2553/12,657 (20.2)
Nonblack Hispanic	1013/25,304 (4.0)	516/12,647 (4.1)	497/12,657 (3.9)
Asian or Pacific Islander	388/25,304 (1.5)	188/12,647 (1.5)	200/12,657 (1.6)
Native American or Alaskan native	228/25,304 (0.9)	118/12,647 (0.9)	110/12,657 (0.9)
Other or unknown	523/25,304 (2.1)	259/12,647 (2.0)	264/12,657 (2.1)
Body-mass index‡	28.1±5.7	28.1±5.7	28.1±5.8
Current smoking — no./total no. (%)	1836/25,485 (7.2)	921/12,729 (7.2)	915/12,756 (7.2)
Hypertension treated with medication — no./total no. (%)	12,791/25,698 (49.8)	6352/12,834 (49.5)	6439/12,864 (50.1)
Current use of cholesterol-lowering medication — no./total no. (%)	9524/25,428 (37.5)	4822/12,700 (38.0)	4702/12,728 (36.9)
Diabetes — no./total no. (%)	3549/25,828 (13.7)	1812/12,903 (14.0)	1737/12,925 (13.4)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. There were no significant differences between the groups with regard to the baseline characteristics.
† Race and ethnic group were reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 2.4% of the participants.

line 25-hydroxyvitamin D levels varied according to age, sex, race or ethnic group, and BMI (Fig. S1A in the Supplementary Appendix), but most groups had 25-hydroxyvitamin D levels close to, or above, 40 ng per milliliter (100 nmol per liter) after 1 year of supplementation with vitamin D (Fig. S1B in the Supplementary Appendix).

The mean rate of response to questionnaires was 93.1%, and follow-up regarding mortality was greater than 98% over the 5.3-year follow-up period. The mean rate of adherence to the trial regimen (the percentage of participants who reported taking at least two thirds of the trial capsules) was 82.0% in the vitamin D group and 80.3% in the placebo group during this time (Table S2 in the Supplementary Appendix). At 2 years, the prevalence of outside use of vitamin D (>800 IU per day) was 3.8% in the vitamin D group and 5.6% in the placebo group; at 5 years, the rates were 6.4% and 10.8%, respectively. These results probably reflect outside screening during the trial for 25-hydroxyvitamin D levels and the initiation of supplementation in some participants who had low levels.

CANCER

The primary end point of invasive cancer of any type developed in 1617 participants, with similar event rates in the vitamin D group and the placebo group (793 and 824 participants with cancer, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.88 to 1.06; P=0.47) (Table 2). No significant differences between the two groups were observed with regard to the incidence of breast, prostate, or colorectal cancer. During follow-up, 341 participants died from cancer, with 154 such deaths in the vitamin D group and 187 in the placebo group (hazard ratio, 0.83; 95% CI, 0.67 to 1.02).

The cumulative incidence of invasive cancer of any type (Fig. 2A and Table 2) and death from cancer (Table 2, and Fig. S2D in the Supplementary Appendix) did not differ significantly between the two groups. No significant differences between the two groups were observed with regard to preplanned analyses of the primary end point of cancer, excluding the first 1 and 2 years of follow-up. However, the test for proportionality over time was significant for the rate of death

Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to Vitamin D or Placebo, in Intention-To-Treat Analyses.*

End Point	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
	no. of participants with event		
Cancer			
Primary end point: invasive cancer of any type	793	824	0.96 (0.88–1.06)
Breast cancer	124	122	1.02 (0.79–1.31)
Prostate cancer	192	219	0.88 (0.72–1.07)
Colorectal cancer	51	47	1.09 (0.73–1.62)
Death from cancer	154	187	0.83 (0.67–1.02)
Cardiovascular disease			
Primary end point: major cardiovascular event†	396	409	0.97 (0.85–1.12)
Cardiovascular event in expanded composite end point‡	536	558	0.96 (0.86–1.08)
Myocardial infarction	169	176	0.96 (0.78–1.19)
Stroke	141	149	0.95 (0.76–1.20)
Death from cardiovascular causes	152	138	1.11 (0.88–1.40)
Other cardiovascular end point§			
PCI	182	188	0.97 (0.79–1.19)
CABG	73	98	0.75 (0.55–1.01)
Death from myocardial infarction	24	15	1.60 (0.84–3.06)
Death from stroke	19	23	0.84 (0.46–1.54)
Death from any cause	485	493	0.99 (0.87–1.12)
Analyses excluding the first 2 yr of follow-up			
Invasive cancer of any type	490	522	0.94 (0.83–1.06)
Death from cancer	112	149	0.75 (0.59–0.96)
Major cardiovascular event	274	296	0.93 (0.79–1.09)
Death from any cause	368	384	0.96 (0.84–1.11)

* Analyses were from Cox regression models that were controlled for age, sex, and n–3 fatty acid randomization group. Analyses were not adjusted for multiple comparisons.
† This end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.
‡ This end point was a composite of major cardiovascular events and coronary revascularization (percutaneous coronary intervention [PCI] or coronary-artery bypass grafting [CABG]).
§ These events were not prespecified as primary or secondary outcomes.

from cancer. In both an analysis that excluded 1 year of follow-up and an analysis that excluded 2 years of follow-up, neither of which was specified in the protocol, the rate of death from cancer was significantly lower with vitamin D than with placebo (hazard ratio, 0.79 [95% CI, 0.63 to 0.99], and hazard ratio, 0.75 [95% CI, 0.59 to 0.96], respectively). In analyses restricted to 153 deaths from cancer in patients with medical records or other adjudication of the cause of death beyond the NDI coding, the hazard ratios were 0.72 (95% CI, 0.52 to 1.00) over the total follow-up period and 0.63 (95% CI, 0.43 to 0.92) after the first 2 years were excluded. Preliminary analyses of cancer stage at diagnosis showed slightly fewer advanced cancers, metastatic cancers, or both among patients assigned to vitamin D than among those assigned to placebo, but differences were not significant (data not shown). The cumulative incidence rates of site-specific cancers and of death from cancer (prespecified secondary end points) are shown in Figure S2 in the Supplementary Appendix.

Results of prespecified subgroup analyses are

presented in Table 3. The findings suggest that BMI may have modified the effect of vitamin D on cancer.

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

During follow-up, there were 805 major cardiovascular events (myocardial infarction, stroke, or cardiovascular death), with events in 396 participants in the vitamin D group and 409 participants in the placebo group (hazard ratio, 0.97; 95% CI, 0.85 to 1.12; P=0.69) (Table 2). Supplementation with vitamin D also did not affect the risk of secondary cardiovascular end points (Table 2). There were no significant differences between the two groups with respect to the cumulative incidence of major cardiovascular events (Fig. 2B) and no significant effect modification according to baseline characteristics or randomization to the n–3 fatty acid intervention (Table 3) or according to traditional cardiovascular risk factors (Table S3 in the Supplementary Appendix). There were 978 deaths from any cause; the numbers of these deaths were similar in the vitamin D group and the placebo group (485 and 493 deaths, respectively; hazard ratio, 0.99; 95% CI, 0.87 to 1.12). Analyses that censored data for nonadherence did not materially alter the results. No meaningful change in the rates of major cardiovascular events or death from any cause occurred after data from the first 2 years of follow-up were excluded (Table 2).

ADVERSE EVENTS

There were no significant differences between the two groups with respect to incident diagnoses of hypercalcemia, kidney stones, or gastrointestinal symptoms (Table S4 in the Supplementary Appendix).

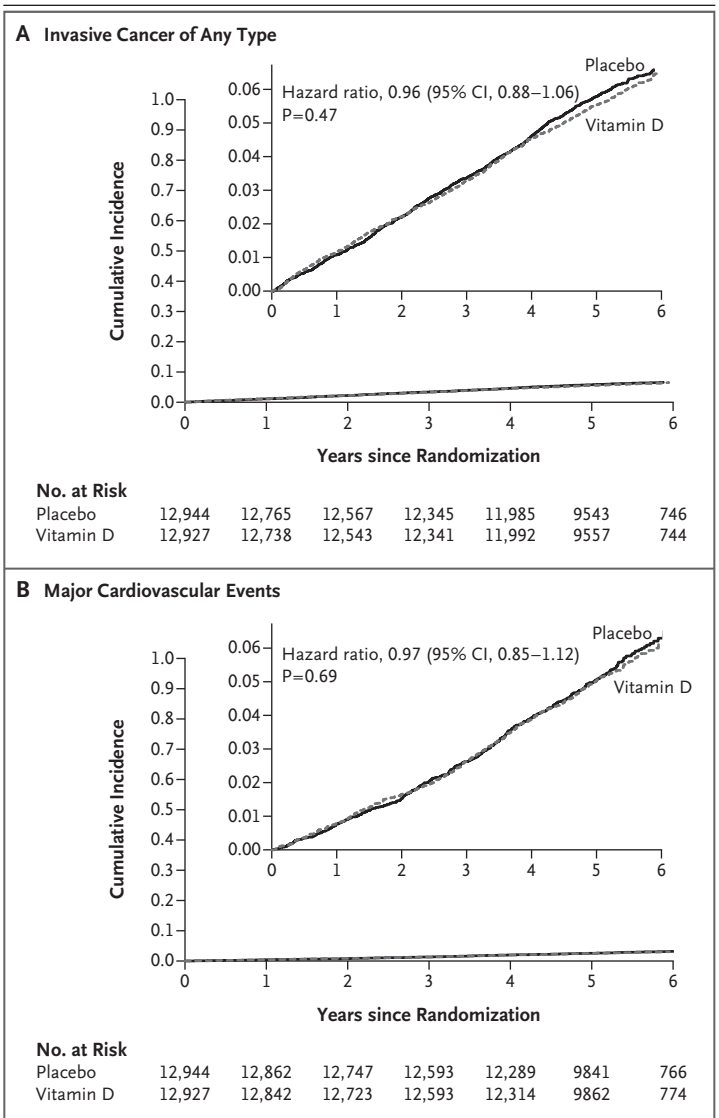

Figure 2. Cumulative Incidence Rates of Invasive Cancer of Any Type and Major Cardiovascular Events, According to Year of Follow-up, in the Vitamin D Group and Placebo Group.

Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the n–3 fatty acid portion of the trial (intention-to-treat analyses). The insets show the same data on an enlarged y axis.

DISCUSSION

In this large primary-prevention trial, supplementation with vitamin D_3 (at a dose of 2000 IU per day) did not lead to a significantly lower incidence of invasive cancer of any type or a composite of major cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes) than placebo. The intervention also did not lead to a lower incidence of total deaths from cancer or a lower incidence of breast, prostate, or colorectal cancer than placebo.

Effects did not vary according to baseline serum 25-hydroxyvitamin D levels. The use of vitamin D did not lead to a significant difference in any of the secondary cardiovascular end points or in the rate of death from any cause in the overall cohort or in subgroups.

In analyses excluding early follow-up data, there was also no significant between-group difference in the incidence of invasive cancer of any type or

Table 3. Hazard Ratios of the Primary Outcomes According to Subgroup, Comparing the Vitamin D Group with the Placebo Group.*

Subgroup	No. of Participants	Invasive Cancer of Any Type				Major Cardiovascular Events			
		Vitamin D	Placebo	Hazard Ratio (95% CI)	P Value for Interaction	Vitamin D	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of participants with event				*no. of participants with event*			
Age	25,871				0.73				0.31
<Median of 66.7 yr	12,859	302	322	0.95 (0.81–1.11)		140	131	1.07 (0.85–1.36)	
≥Median of 66.7 yr	13,012	491	502	0.98 (0.86–1.11)		256	278	0.93 (0.78–1.10)	
Sex	25,871				0.38				0.57
Male	12,786	452	488	0.93 (0.82–1.06)		223	223	1.01 (0.84–1.21)	
Female	13,085	341	336	1.02 (0.87–1.18)		173	186	0.93 (0.76–1.14)	
Race†	25,304				0.21				0.37
Non-Hispanic white	18,046	626	632	0.99 (0.89–1.11)		280	301	0.93 (0.79–1.10)	
Black	5,106	98	126	0.77 (0.59–1.01)		69	76	0.91 (0.65–1.26)	
Other	2,152	53	52	1.03 (0.70–1.51)		32	24	1.36 (0.80–2.31)	
Body-mass index	25,254				0.002				0.66
<25	7,843	206	278	0.76 (0.63–0.90)		117	115	1.07 (0.83–1.38)	
25 to <30	10,122	338	323	1.04 (0.90–1.21)		152	162	0.93 (0.74–1.16)	
≥30	7,289	228	199	1.13 (0.94–1.37)		120	120	0.98 (0.76–1.26)	
Body-mass index category	25,254				0.026				0.89
<Median of 27.1	12,582	361	421	0.86 (0.75–0.99)		189	193	0.99 (0.81–1.21)	
≥Median of 27.1	12,672	411	379	1.08 (0.94–1.24)		200	204	0.97 (0.80–1.18)	
Baseline serum 25-hydroxyvitamin D	15,787				0.99				0.75
<20 ng/ml	2,001	58	63	0.97 (0.68–1.39)		34	34	1.09 (0.68–1.76)	
≥20 ng/ml	13,786	459	464	0.98 (0.86–1.12)		218	216	1.00 (0.83–1.21)	
Baseline serum 25-hydroxyvitamin D category	15,787				0.57				0.42
<Median of 31 ng/ml	7,812	251	252	1.02 (0.86–1.21)		128	139	0.94 (0.74–1.20)	
≥Median of 31 ng/ml	7,975	266	275	0.95 (0.80–1.12)		124	111	1.09 (0.84–1.41)	

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Baseline vitamin D use‡	25,871			0.64					0.71
Yes	11,030	370	376	0.99 (0.86–1.14)		165	164	1.00 (0.81–1.25)	
No	14,841	423	448	0.94 (0.83–1.08)		231	245	0.95 (0.79–1.14)	
Randomization in the n–3 fatty acids portion of trial	25,871				0.56				0.56
Placebo group	12,938	385	412	0.94 (0.82–1.08)		210	209	1.01 (0.83–1.22)	
Active-agent group	12,933	408	412	0.99 (0.87–1.14)		186	200	0.93 (0.76–1.14)	

* Analyses were from Cox regression models that controlled for age, sex, and n–3 fatty acid randomization group (intention-to-treat analyses). Analyses were not adjusted for multiple comparisons. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.5.
† Race was reported by the participants.
‡ Data shown are for use of out-of-trial vitamin D supplements at baseline (restricted to ≤800 IU per day from all sources combined, including individual supplements and multivitamins).

major cardiovascular events. A post hoc analysis of the rate of death from cancer suggested a possible benefit with respect to the rate of total deaths from cancer after exclusion of early follow-up data, based on an unadjusted 95% confidence interval that does not include 1.

The results of subgroup analyses raise the possibility of differential effects on cancer incidence according to BMI, with normal-weight participants who received vitamin D having a lower incidence than those who received placebo. However, these analyses should be considered hypothesis-generating, in the context of the negative findings for the primary outcome measures and given that they are not adjusted for multiple comparisons.

Because of its size and long duration (≥5 years), our trial had sufficient power to examine the effect of high-dose vitamin D on the risk of cancer and cardiovascular events. Previous vitamin D trials testing doses of 400 to 1100 IU per day administered with or without calcium have suggested, in aggregate, no significant benefit with respect to the incidence of cancer but a significant benefit with respect to the rate of death from cancer. A 2014 meta-analysis of four such trials[17-20] yielded summary relative risks of 1.00 (95% CI, 0.94 to 1.06) for the incidence of cancer and 0.88 (95% CI, 0.78 to 0.98) for the rate of death from cancer.[9] Another meta-analysis showed similar results.[10] Two trials of high-dose vitamin D have recently been completed. One 4-year trial[21] that tested daily vitamin D (2000 IU) plus calcium (1500 mg) against placebo for cancer prevention in 2303 women in Nebraska showed a suggestive but nonsignificant 30% lower incidence of cancer in association with the active intervention. The 3.3-year Vitamin D Assessment Study (ViDA),[22] which tested monthly vitamin D (100,000 IU) against placebo for prevention of cardiovascular disease in 5110 participants in New Zealand, reported null results for cancer outcomes. However, these trials had shorter durations and fewer deaths from cancer than our trial, as well as few black participants. Also, ViDA used intermittent bolus dosing, which is associated with nonphysiological fluctuations in blood levels of vitamin D.[23]

Data from laboratory studies and studies in animals support mechanisms whereby vitamin D may inhibit carcinogenesis and slow tumor progression, including promotion of cell differentiation,

inhibition of cancer-cell proliferation, and antiinflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects.[1,24] Vitamin D may decrease tumor invasiveness and the propensity to metastasize, leading to a reduced rate of death from cancer.[24] Among patients with cancer, higher 25-hydroxyvitamin D levels at diagnosis or treatment have been linked to longer survival.[9] Observational studies suggest that vitamin D may confer greater protection against death from cancer than against the initial development of clinically evident cancer, albeit with benefits with regard to both end points,[5] with the strongest inverse relationships between 25-hydroxyvitamin D levels and colorectal cancer.[25-27] The power of our trial for analyses of site-specific cancers was limited. In addition, given the long latency for cancer development, extended follow-up is necessary to fully ascertain potential effects.

The observed lack of benefit of vitamin D supplementation for cardiovascular outcomes in our trial is consistent with results of previous trials of vitamin D,[17,20,28-33] even at moderate or high doses.[32] Most recently, in ViDA, the rate of cardiovascular disease was not lower among participants who received monthly administration of high-dose vitamin D than among those who received placebo.[31] Neither our trial nor ViDA[31] showed that vitamin D was associated with a reduced rate of death from any cause; lower-dose vitamin D trials have shown neutral effects or at most modest reductions in this end point.[33-35] However, detection of a decreased rate of death from any cause, if present, may require longer follow-up.

Previous research points to possible mechanisms through which supplementation with vitamin D might reduce the risk of cancer among normal-weight but not overweight or obese participants. Parathyroid hormone appears to be suppressed at lower 25-hydroxyvitamin D levels in overweight and obese persons,[36] which would be consistent with obesity-related hormonal dysregulation leading to less benefit of supplementation. Alternatively, because of volumetric dilution[37] or decreased bioactivity of vitamin D, overweight and obese persons may require higher doses to derive a benefit with respect to cancer, analogous to body-size differences in aspirin dosage requirements.[38] However, in our trial, there was only slight variation in the mean 25-hydroxyvitamin D level in response to the tested dose according to BMI group (Fig. S1B in the Supplementary Appendix). Finally, supplementation with vitamin D is unlikely to affect all mechanistic pathways linking obesity with numerous cancers.[39] These hypothesis-generating issues require further investigation.

The finding of a possible vitamin D–associated benefit with regard to the incidence of cancer among black participants — a group with lower vitamin D requirements for bone health than white persons (lower fracture risk despite lower 25-hydroxyvitamin D levels than white persons)[1] — may imply that the most favorable vitamin D status may vary according to organ system and tissue. We speculate that the possible trial regimen–associated effects on cancer incidence among normal-weight participants and suggestive effects among black participants, which contrast with the null cardiovascular findings in these groups, may be explained by different vitamin D requirements for these outcomes.

In observational studies, the 25-hydroxyvitamin D levels associated with lowest risks tend to be above 30 ng per milliliter (75 nmol per liter) for cancer (at least colorectal cancer)[26] but between 20 and 25 ng per milliliter for cardiovascular disease.[6] Thus, vitamin D requirements for cardiovascular health may have already been met for most participants. Although neither our trial nor ViDA showed a significant cardiovascular benefit of vitamin D among participants with low 25-hydroxyvitamin D levels at baseline, it remains possible that a trial involving persons with extremely low vitamin D levels (i.e., well below the 20 ng per milliliter recommended for bone health[1]) would show stronger effects on risk. However, maintaining participants in a vitamin D–deficient state and circumventing real-world clinical care for 5 years would be neither ethical nor feasible.

Our trial has many strengths, including a large general population sample with racial, ethnic, and geographic diversity; daily vitamin D dosing; high rates of follow-up and adherence to the trial regimen; rigorously adjudicated end points; baseline and follow-up blood samples from many participants; and achieved mean 25-hydroxyvitamin D levels in the targeted range. Ancillary studies addressing treatment effects on diabetes, heart failure, cognition, autoimmune disorders, and other outcomes will inform the overall benefit–risk balance of high-dose supplementation. Our trial also has limitations. The median dura-

tion of follow-up was 5.3 years. The trial tested only one dose of vitamin D. Trials[40] are ongoing to add information regarding other doses, although some are using bolus dosing. A 2-year postintervention follow-up of our cohort is ongoing to capture latency effects and increase statistical power to assess end points.

In summary, daily supplementation with high-dose vitamin D for 5 years among initially healthy adults in the United States did not reduce the incidence of cancer or major cardiovascular events.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Health and Human Services or the National Institutes of Health.

Supported by grants (U01 CA138962 and R01 CA138962) from the National Cancer Institute, the National Heart, Lung, and Blood Institute, the Office of Dietary Supplements, the National Institute of Neurological Disorders and Stroke, and the National Center for Complementary and Integrative Health. The ancillary studies are supported by grants from multiple institutes, including the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Mental Health, and others.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial investigators, staff, and participants for their dedication and commitment to the trial.

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