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Research Article

Prospective Population-Based Study of the Association between Serum 25-Hydroxyvitamin-D Levels and the Incidence of Specific Types of Cancer

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Abstract

Background: Observational studies have suggested an inverse association between vitamin D status and cancer. We investigated the prospective associations between vitamin D status and the total and specific type of cancer in three cohorts from the general Danish population.

Methods: A total of 12,204 individuals 18 to 71 years old were included. The level of 25-hydroxyvitamin D was measured at baseline, and information about cancer was obtained from the Danish Cancer Registry.

Results: During the 11.3-year median follow-up time, there were 1,248 incident cancers. HRs [95% confidence intervals (CI)] per 10 nmol/L higher baseline vitamin D level were: for all cancers (HR = 1.02; 95% CI, 0.99–1.04), all cancers excluding non-melanoma skin cancer, NMSC (HR = 1.00; 95% CI, 0.97–1.03), head and neck cancer (HR = 0.97; 95% CI, 0.84–1.12), colorectal cancer (HR = 0.95; 95% CI, 0.88–1.02), cancer of bronchus and lung (HR = 0.98; 95% CI, 0.91–1.05), breast cancer (HR = 1.02; 95% CI, 0.96–1.09), cancer of the uterus (HR = 1.10; 95% CI, 0.95–1.27), prostate cancer (HR = 1.00; 95% CI, 0.93–1.08), cancer of the urinary organs (HR = 1.01; 95% CI, 0.90–1.14), NMSC (HR = 1.06; 95% CI, 1.02–1.10), and malignant melanoma (HR = 1.06; 95% CI, 0.95–1.17).

Conclusions: Apart from a significantly higher risk for NMSC with higher vitamin D status, we found no statistically significant associations between vitamin D status and total or specific cancers.

Impact: Our results do not indicate that there is an impact of vitamin D on total cancer incidence. *Cancer Epidemiol Biomarkers Prev; 23(7); 1220–9. ©2014 AACR.*

Introduction

Vitamin D is a fat soluble vitamin produced in sun-exposed skin and can be ingested from the diet and dietary supplements. In addition to its traditional role in bone metabolism and remodeling, vitamin D has numerous biologic functions ranging from antiproliferative and antiangiogenic effects to modulation of the immune system (1). The vitamin D receptor is found in most cells of the body and many tissues can convert vitamin D to its active form (1). Vitamin D insufficiency and deficiency are common worldwide and are associated with a number of common diseases, such as cardiovascular risk factors (e.g., hyperlipidemia and albuminuria), diabetes, cardiovascular disease, and mortality (1–7).

The role of vitamin D in cancer is largely unresolved. Cancer is a broad group of diseases resulting from unregulated cell growth. Six main features of cancer cells have been suggested: self-sufficiency of growth signals, evasion of apoptosis, insensitivity to antigrowth signals, sustained angiogenesis, limitless replicative potential, and tissue invasion and metastasis (8). Through its ability to induce apoptosis and prevent angiogenesis and migration in malignant cells, vitamin D could play an important role in some of the common pathways of cancer (1).

From a public health point of view, both the impact of vitamin D status on specific cancer types and the impact of vitamin D on the total incidence of cancer are important. In observational studies, vitamin D deficiency was associated with an increased risk of cancers, such as colorectal cancer (9), lung cancer (10), and breast cancer (11). Also, a recent meta-analysis by Yin and colleagues found a moderate inverse association between vitamin D status and total cancer incidence and mortality (12).

We investigated the prospective association between vitamin D status, as assessed by serum 25-hydroxyvitamin D (25-OH-D), and the specific type of cancer according to The International Classification of Disease in three cohorts from the general Danish population.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Materials and Methods

Ethics statement

Participants gave their informed written consent. The studies were approved by the Ethics Committee of Copenhagen and the Danish Data Protection Agency, and the recommendations of the Declaration of Helsinki were followed.

Study populations

We included the population-based studies, Monica10, Inter99, and Health2006, all recruited from the Danish Central Personal Register as random samples of the population in the southern part of the former Copenhagen County. The Monica10 study (1993–1994) included 2,656 individuals, which was 64.3% of the 4,130 individuals that were invited, between 40 and 71 years old (13).

The Inter99 study was conducted between 1999 and 2001 and included examination of 6,784 individuals aged 30 to 60 years from the general population (14). The baseline participation rate was 52.5%. The Inter99 study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) performed to investigate the effects of lifestyle intervention on cardiovascular disease (14). Only participants with a Northern European origin (Danish, Norwegian, Swedish, Icelandic, or Faroese nationality) were included in the current study (N = 6,405).

In the Health2006 study, 7,931 Danish citizens aged 18 to 69 years and born in Denmark were invited to participate in a health examination (15). A total of 3,471 (43.8%) individuals were examined between 2006 and 2008. In the present study, we included 2,649, 6,146, and 3,409 participants from the Monica10, the Inter99, and the Health2006 studies, respectively, with measurements of vitamin D status, yielding a total of 12,204 persons. The three studies included questionnaires, physical examinations, and blood tests.

Vitamin D measurements

Measurements of serum 25-OH-D in the Monica10 study were performed by the IDS-SYS 25-Hydroxy Vitamin D method with the IDS-iSYS Multi-Discipline System (IDS Nordic A/S; ref. 16). In the Inter99 study, measurements of 25-OH-D were done by high-performance liquid chromatography as previously described (17). In the Health2006 study, 25-OH-D was measured by immunoassay using Cobas e411 (Roche Diagnostics; ref. 18).

Registry-based diagnoses

All residents in Denmark have a unique and permanent personal civil registration number that allows data linkage from national registers on an individual level. Participants were followed until July 11, 2011. Information on fatal and nonfatal cancers was obtained from the Danish Cancer Registry (19, 20) according to the International Classification of Diseases (ICD). Reporting to the Cancer Registry has been mandatory since 1987. From 1943 to 1978, the Registry was classified according to the modified ICD-7, and starting in 1978, the diagnoses were coded in accordance with the ICD-10 (19). Information on deaths and emigration status was obtained from the Danish Civil Registration System (21). The grouping of codes used for ICD-10 is not unambiguously translated to ICD-7 codes (or vice versa). However, as we are only using ICD-7 codes for excluding people who had cancer before the study, and since most of these cases are, in fact, ICD-10 coded, the inconsistency is likely to be negligible.

Our classification of the main types of cancer (our end points) according to the ICD-7 and the ICD-10 codes is displayed in Table 1. For each cancer type, we excluded the persons with a history of that particular cancer at baseline in the regression analyses.

Other covariates

Questionnaires were used to obtain the following: information on education/vocational training [no education (only basic education), education beyond basic including students]; intake of fish (<twice a week, ≥twice a week); physical activity during leisure time (sedentary, light, or moderate/vigorous); smoking habits (never smoked, ex-smoker, occasional smoker, current smoker <15 g/day; 15–<25 g/day, or ≥25 g of tobacco/day; 1 cigarette = 1 g, 1 cheroot = 2 g, 1 cigar = 3 g, pipe = stated in g); and alcohol

Table 1. Classification of the main cancer types according to ICD-7 and ICD-10 codes

	ICD-7	ICD-10
All cancers	140–205	C00-C97
All cancers excluding NMSC	140–205 excluding 191	C00-C97 excluding C44
Head and neck cancer	140–148, 160–161	C00-C14, C30-C32
Colorectal cancer	153–154	C18-C20
Malignant neoplasm of the bronchus and lung	162	C34
Breast cancer	170	C50
Cancer of the uterus	172–174	C54-C55
Prostate cancer	177	C61
Malignant neoplasms of the urinary organs	180–181	C64-C68
Malignant melanoma	190	C43
NMSC	191	C44

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consumption (0, >0–7, >7–14, or >14 drinks per week). Weight and height were measured with no shoes and light clothes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Statistical analyses

Analyses were performed using SAS, version 9.2 (SAS Institute Inc.). *P* values were two-tailed, and statistical significance was defined as $P < 0.05$. Descriptive characteristics (number) and vitamin D status (mean and SD) of the study participants according to the study population are presented and compared with the Kruskal–Wallis test in Table 2. Table 3 shows the distribution of cancers (% and number) and corresponding vitamin D status (mean and SD) according to the three cohorts and overall.

In Tables 4 and 5, the associations between vitamin D status and incidence of type-specific cancer are shown. For each regression analysis, only participants for which we had complete information for all considered variables were included (complete case analysis). Vitamin D status was used both as a continuous variable and in season-specific quartiles (divided before pooling of data, with the lowest quartile used as reference; ref. 22). We pooled the data from the three population-based studies. Persons with the cancer of interest before the baseline examination were excluded from the analyses. In the Cox regression analyses, we used age as the underlying time and delayed entry where participants entered the analysis at the baseline age and exited the analysis at their event or censoring age. The first model was adjusted for study and gender. The second model was further adjusted for education, time of year when the blood sample was drawn (March–May, June–August, September–November, or December–February), physical activity, smoking habits, alcohol intake, intake of fish, and BMI. P_{trend} was the *P* value for a linear trend across quartiles. Only women were included for the analysis of breast and uterine cancers. Likewise, only men were included in the analysis of prostate cancer. There were no interactions between study population and vitamin D status, so there was no evidence of vitamin D having differential effects in the different study populations. The assumption that there was a linear relationship between vitamin D status and cancer was tested by adding vitamin D status squared and checking for significance.

In additional analyses, we excluded persons who developed a cancer of interest in the first two years after examination. Therefore, participants started to contribute risk time at baseline + two years (Supplementary Table S1). We also stratified the analyses by gender and BMI, respectively (Supplementary Table S2). In the analyses stratified by BMI, we excluded persons with BMI < 18.5 kg/m^2.

In further analyses, we used Stata, version 12.1 (StataCorp LP) for meta-analyses of the study-specific estimates of the association between vitamin D status and cancer using both fixed and random effects models, and the results are summarized in Fig. 1. Heterogeneity between the studies was assessed by the I^2 test.

Results

Vitamin D levels were highest in the Monica10 study and lowest in the Health2006 study, with the Inter99 study showing intermediate levels. In addition, vitamin D levels were highest in the summer and autumn. Levels were highest in individuals with normal BMIs and were lower in both underweight and overweight individuals. Likewise, physically active participants had higher vitamin D levels than those that were physically inactive. Abstinent individuals had lower vitamin D status than nonabstinent (Table 2).

The overall mean (SD) vitamin D levels among individuals with a history of cancer before baseline ($N = 471$), incident ($N = 1{,}248$), and no cancer ($N = 10{,}485$) were 53.7 (27.6), 57.4 (27.0), and 51.8 (26.5) nmol/L, respectively. The vitamin D levels according to study population are shown in Tables 2 (history of cancer) and 3 (no cancer and incident cancer). Almost 11% of those without cancer before baseline developed some type of cancer during the follow-up (Table 3). The most frequent cancer, non-melanoma skin cancer (NMSC), affected 3.3% of the persons, followed by breast cancer (1.4%), colorectal cancer (1.2%), prostate cancer (1.1%), and cancer of bronchus and lung (1.0%; Table 3). The least abundant cancers included in this study were malignant melanoma (0.5%), cancer of the urinary organs (0.4%), head and neck cancer (0.4%), and cancer of the uterus (0.2%; Table 3).

The mean baseline vitamin D status was 57.4 nmol/L among persons developing any type of cancer during follow-up. Having a mean vitamin D status below this value were, in ascending order, persons developing head and neck cancer, person without incident cancer and persons with colorectal cancer, breast cancer, cancer of bronchus and lung, and all cancers excluding NMSC. Having a mean vitamin D status above the mean of any cancer were persons developing malignant melanoma, prostate cancer, NMSC, cancer of the urinary organs, and cancer of the uterus (Table 3).

The overall person-years at-risk was 120,680 years for all cancers. The median follow-up time was 11.3 years: 16.8, 11.5, and 4.0 years in the Monica10, Inter99, and Health2006 studies, respectively. The overall HR [95% confidence interval (CI)] for total cancer incidence was HR = 1.02 (95% CI, 0.99–1.04) per 10 nmol higher vitamin D status in the fully adjusted model (Table 5). For all cancers excluding NMSC, we found that HR = 1.00 (95% CI, 0.97–1.03). We found a statistically significant positive association between vitamin D status and NMSC, with an HR = 1.06 (95% CI, 1.02–1.10) per 10 nmol/L higher baseline vitamin D status in both the partly and the fully adjusted model (Table 5). The association between vitamin D status and development of colorectal cancer was statistically significant, with an HR = 0.93 (95% CI, 0.87–1.00) for a 10 nmol/L higher vitamin D status in the partly adjusted model, but was not significant in the fully adjusted model, although the estimate only changed little. On the other hand, the statistically insignificant inverse association between vitamin D status and head and neck

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Table 2. Baseline characteristics and vitamin D status according to study population ($N = 12,204$)

	Monica10			Inter99			Health2006		
	N	25-OH-D, nmol/L Mean (SD)	*P*[b]	*N*	25-OH-D, nmol/L Mean (SD)	*P*[b]	*N*	25-OH-D, nmol/L Mean (SD)	*P*[b]
Gender									
Male	1,329	65.8 (28.2)		3,006	50.6 (25.8)		1,531	43.1 (21.3)	
Female	1,320	63.7 (25.9)	0.187	3,140	52.6 (27.3)	0.005	1,878	45.3 (23.5)	0.0134
Age, y									
≤45	726	65.9 (29.0)		2,780	52.1 (26.6)		1,313	43.2 (24.3)	
45–55	740	66.6 (28.2)		2,422	51.2 (26.3)		847	42.8 (20.7)	
≥55	1,183	62.9 (24.9)	0.025	944	51.2 (27.3)	0.249	1,249	46.6 (21.6)	<0.001
Season, blood test									
March–May	419	52.3 (20.3)		1,814	46.3 (24.3)		821	40.1 (21.4)	
June–August	611	78.5 (30.7)		1,387	58.6 (32.8)		750	51.0 (20.9)	
September–November	1,150	66.7 (25.5)		1,601	58.8 (24.3)		1,047	48.4 (24.1)	
December–February	469	53.2 (20.7)	<0.001	1,344	43.1 (20.1)	<0.001	791	37.1 (20.1)	<0.001
Level of education[a]									
Basic	677	60.3 (25.3)		918	51.2 (27.3)		445	46.6 (24.1)	
Above basic	1,971	66.3 (27.5)	<0.001	5,033	51.8 (26.4)	0.258	2,913	44.0 (22.3)	0.054
BMI, kg/m^2									
<18.5	26	62.7 (28.9)		66	53.5 (27.4)		62	43.7 (25.3)	
18.5–24.9	1,202	67.2 (28.3)		2,621	53.5 (27.3)		1,570	47.0 (23.6)	
25–29.9	1,008	64.8 (26.2)		2,396	51.5 (25.9)		1,238	43.7 (21.8)	
≥30	413	57.5 (24.2)	<0.001	1,059	47.1 (25.9)	<0.001	537	38.1 (19.2)	<0.001
Physical activity									
Sedentary	550	59.7 (27.7)		1,243	48.4 (25.3)		611	39.7 (23.3)	
Light	1,478	63.7 (26.1)		3,779	51.8 (26.6)		2,053	44.1 (21.4)	
Moderate/vigorous	573	72.5 (27.8)	<0.001	1,016	55.1 (27.8)	<0.001	707	49.0 (23.9)	<0.001
Fish, weekly intake									
<Twice	2,119	64.9 (27.5)		3,454	51.3 (26.6)		688	44.4 (26.1)	
≥Twice	344	68.1 (25.3)	0.009	2,670	52.0 (26.6)	0.353	2,678	44.4 (22.1)	0.739
Smoking, g/d									
Never smoker	693	65.7 (26.6)		2,147	52.7 (26.5)		1,409	42.5 (21.1)	
Former smoker	727	67.4 (25.4)		1,572	53.8 (27.1)		1,102	43.3 (20.5)	
Current smoker, <15	494	64.6 (27.8)		633	50.8 (25.4)		308	48.8 (23.8)	
Current smoker, <25	553	62.3 (28.4)		1,116	48.2 (26.0)		340	48.6 (27.1)	
Current smoker, ≥25	150	57.9 (28.4)		419	48.2 (27.9)		108	47.7 (30.0)	
Occasional smokers	24	59.7 (27.1)	<0.001	218	50.6 (24.5)	<0.001	109	49.3 (28.0)	<0.001
Alcohol, drinks/wk									
0	358	59.5 (25.9)		546	50.0 (29.0)		199	40.1 (24.0)	
≤7	1,099	63.7 (25.6)		2,661	52.1 (26.7)		1,494	42.7 (21.5)	
≤14	572	69.6 (26.3)		1,298	52.2 (25.1)		705	47.1 (21.8)	
>14	599	65.6 (30.3)	<0.001	1,430	51.0 (26.6)	0.024	705	48.3 (23.0)	<0.001
History of cancer									
No	2,518	64.5 (27.0)		5,989	51.6 (26.6)		3,226	44.3 (22.6)	
Yes	131	69.1 (28.4)	0.063	157	50.9 (27.3)	0.675	183	45.2 (22.6)	0.577

[a]Education beyond basic.
[b]Kruskal–Wallis test.

cancer in the partly adjusted model changed when adjusted for smoking habits: the HR changed from 0.88 (Table 5, model 1) to 0.97 (Table 5, model 2) per 10 nmol/L higher vitamin D status. Except for the abovementioned associations, we found no statistically significant associations between baseline vitamin D status and other types of cancers. In general, the CIs were relatively narrow for many of the cancers (Tables 4 and 5). When we excluded

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Table 3. Distribution of incidences of cancers and corresponding vitamin D status according to study population

	Overall		Monica10		Inter99		Health2006	
Cancer type	n(%)	Mean (SD) 25-OH-D, nmol/L	n(%)	Mean (SD) 25-OH-D, nmol/L	n(%)	Mean (SD) 25-OH-D, nmol/L	n(%)	Mean (SD) 25-OH-D, nmol/L
No incident cancer	10,485(89.4)	51.8 (26.5)	1,952(77.5)	64.4 (27.3)	5,437(90.8)	51.6 (26.5)	3,096(96.0)	44.1 (22.5)
All cancers	1,248(10.6)	57.4 (27.0)	566(22.5)	65.0 (26.0)	552(9.2)	51.6 (27.1)	130(4.0)	49.1 (22.9)
All cancers excl. NMSC	951(8.0)	56.6 (26.8)	465(18.1)	63.2 (25.6)	388(6.4)	50.7 (27.0)	98(3.0)	48.2 (24.1)
Head and neck cancer	44(0.4)	47.6 (33.0)	17(0.6)	72.1 (37.7)	24(0.4)	30.6 (17.0)	3(0.1)	44.0 (13.6)
Colorectal cancer	153(1.2)	54.0 (22.6)	82(3.1)	58.2 (19.5)	58(0.9)	48.3 (25.2)	13(0.4)	53.3 (24.9)
Cancer, bronchus and lung	126(1.0)	56.4 (24.9)	84(3.2)	59.5 (22.5)	36(0.6)	52.4 (29.5)	6(0.2)	36.5 (16.5)
Cancer of the breast	174(1.4)	56.0 (26.8)	64(2.4)	63.4 (25.7)	81(1.3)	53.9 (28.7)	29(0.9)	45.9 (19.2)
Cancer of the uterus	27(0.2)	61.7 (26.9)	11(0.4)	75.2 (27.7)	16(0.3)	52.5 (22.8)	0 (0)	NA
Prostate cancer	133(1.1)	60.5 (28.6)	64(2.4)	68.4 (24.6)	52(0.9)	52.4 (27.3)	17(0.5)	55.2 (38.7)
Cancer, urinary organs	48(0.4)	61.3 (25.3)	30(1.1)	65.1 (26.6)	12(0.2)	57.3 (26.6)	6(0.2)	49.8 (10.5)
Malignant melanoma	56(0.5)	59.4 (27.9)	18(0.7)	70.1 (24.1)	30(0.5)	58.5 (29.6)	8(0.2)	39.2 (17.8)
NMSC	398(3.3)	60.4 (27.0)	157(6.1)	71.1 (25.5)	196(3.2)	53.6 (26.9)	45(1.4)	52.6 (20.6)

NOTE: Since some persons develop more than one cancer, the percentages do not add up.
Abbreviation: NA, not applicable.

individuals who developed the cancer of interest in the first two years after baseline (Supplementary Table S1), the results were similar. There were no major changes when we stratified by gender and BMI, respectively (Supplementary Table S2). The association between vitamin D status and NMSC were, however, no longer statistically significant for persons with BMI ≤ 25 kg/m^2.

The results from meta-analyses of the study-specific estimates are summarized in Fig. 1. They were very similar to the individual-based analyses (Table 5). As in the individual-based analyses, there was a statistically significant higher risk of NMSC with higher vitamin D status. Although there were signs of heterogeneity across studies in some of the outcomes, the estimates change little. At most, the estimate differed between 0.95 (Table 5) and 0.99 (Fig. 1) for vitamin D and colorectal cancer when using the random effects model.

Discussion

We explored the association between vitamin D status and total and specific cancers in the same populations. We found a statistically significant positive association between vitamin D status and the incidence of NMSC. Except for this, there were no statistically significant associations between vitamin D status and total cancer as well as specific cancers in the fully adjusted models. However, the inverse associations between vitamin D status and colorectal cancer and head and neck cancer were statistically and borderline significant, respectively, in the partly adjusted models.

Regarding other general population studies on vitamin D status and total cancer incidence, the results were inconclusive. Ordonez-Mena and colleagues found no statistically significant association between vitamin D status and the incidence of total cancer in a general German population cohort, except in subgroup analyses (23). Thus, there was a significantly increased overall cancer risk for low vitamin D status among men, the non-obese, and individuals reporting low fish consumption, and for high vitamin D status among non-smokers and non-obese individuals (23). Afzal and colleagues performed an analysis on 9,791 participants from the Copenhagen City Heart study and found an HR = 1.06 (95% CI, 1.02–1.11) for a 50% reduction in vitamin D for all cancers (24). Yin and colleagues, however, recently summarized the results from prospective studies of vitamin D and cancer in a meta-analysis and found a moderate inverse association between vitamin D status and total cancer incidence [risk ratio (RR) = 0.89; 95% CI, 0.81–0.97], and mortality (RR = 0.83; 95% CI, 0.71–0.96) per 50 nmol/L higher vitamin D status (12).

Although NMSCs are the most common form of cancer, accounting for about one-third of all cancers worldwide, they are often excluded from cancer statistics because they are easily treated and are almost always cured, often in a short, outpatient procedure. It is worth noting that we chose to exclude carcinoma *in situ* in general and performed analyses both with and without NMSCs in the analyses. Neither the analyses on all cancers nor the analyses on all cancers excluding NMSC showed statistically significant associations with vitamin D status.

The observed positive association between vitamin D status and NMSC may be explained by the fact that vitamin D status is a marker for UV exposure. Our results are in agreement with a study by Eide and colleagues who

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Table 4. Association between vitamin D quartiles and incidence of specific types of cancer

	Events (individuals)	Model 1[b] HR (95% CI), *P*	Model 2[c] HR (95% CI), *P*
All cancers	1,134 (10,709)		
2nd vitamin D quartile[a]		0.98 (0.83–1.16)	1.00 (0.84–1.18)
3rd vitamin D quartile[a]		0.99 (0.84–1.17)	1.01 (0.85–1.20)
4th vitamin D quartile[a]		1.06 (0.90–1.25), $P_{trend} = 0.451$	1.10 (0.93–1.29), $P_{trend} = 0.285$
All cancers excluding NMSC	860 (10,866)		
2nd vitamin D quartile[a]		0.90 (0.74–1.08)	0.93 (0.77–1.12)
3rd vitamin D quartile[a]		0.90 (0.74–1.09)	0.95 (0.78–1.15)
4th vitamin D quartile[a]		0.91 (0.75–1.10), $P_{trend} = 0.356$	0.98 (0.81–1.19), $P_{trend} = 0.898$
Head and neck cancer	38 (11,130)		
2nd vitamin D quartile[a]		0.41 (0.17–0.99)	0.47 (0.19–1.15)
3rd vitamin D quartile[a]		0.60 (0.27–1.32)	0.79 (0.35–1.77)
4th vitamin D quartile[a]		0.31 (0.11–0.84), $P_{trend} = 0.029$	0.45 (0.16–1.26), $P_{trend} = 0.198$
Colorectal cancer	141 (11,119)		
2nd vitamin D quartile[a]		0.83 (0.52–1.34)	0.84 (0.52–1.35)
3rd vitamin D quartile[a]		1.05 (0.67–1.64)	1.04 (0.66–1.64)
4th vitamin D quartile[a]		0.82 (0.51–1.32), $P_{trend} = 0.651$	0.82 (0.51–1.35), $P_{trend} = 0.666$
Cancer, bronchus, and lung	110 (11,133)		
2nd vitamin D quartile[a]		1.08 (0.66–1.76)	1.27 (0.77–2.08)
3rd vitamin D quartile[a]		0.82 (0.49–1.39)	1.10 (0.65–1.87)
4th vitamin D quartile[a]		0.63 (0.36–1.11), $P_{trend} = 0.068$	0.91 (0.51–1.62), $P_{trend} = 0.700$
Breast cancer	159 (5606)		
2nd vitamin D quartile[a]		1.04 (0.67–1.62)	1.06 (0.68–1.64)
3rd vitamin D quartile[a]		0.87 (0.55–1.37)	0.90 (0.57–1.43)
4th vitamin D quartile[a]		1.05 (0.68–1.61), $P_{trend} = 0.984$	1.11 (0.71–1.71), $P_{trend} = 0.821$
Cancer of the uterus	25 (5670)		
2nd vitamin D quartile[a]		1.42 (0.32–6.37)	1.37 (0.31–6.17)
3rd vitamin D quartile[a]		3.06 (0.83–11.29)	2.67 (0.71–10.00)
4th vitamin D quartile[a]		2.86 (0.77–10.57), $P_{trend} = 0.059$	2.32 (0.62–8.75), $P_{trend} = 0.145$
Prostate cancer	121 (5,451)		
2nd vitamin D quartile[a]		0.74 (0.44–1.25)	0.72 (0.42–1.22)
3rd vitamin D quartile[a]		0.99 (0.60–1.62)	0.96 (0.58–1.59)
4th vitamin D quartile[a]		0.93 (0.56–1.53), $P_{trend} = 0.920$	0.91 (0.54–1.52), $P_{trend} = 0.982$
Cancer, urinary organs	46 (11,124)		
2nd vitamin D quartile[a]		1.57 (0.66–3.76)	1.69 (0.70–4.07)
3rd vitamin D quartile[a]		1.48 (0.61–3.57)	1.60 (0.65–3.90)
4th vitamin D quartile[a]		1.24 (0.50–3.10), $P_{trend} = 0.752$	1.47 (0.58–3.75), $P_{trend} = 0.508$
NMSC	369 (10,972)		
2nd vitamin D quartile[a]		1.21 (0.88–1.65)	1.18 (0.86–1.61)
3rd vitamin D quartile[a]		1.42 (1.05–1.93)	1.35 (0.99–1.83)
4th vitamin D quartile[a]		1.53 (1.14–2.07), $P_{trend} = 0.003$	1.43 (1.05–1.93), $P_{trend} = 0.015$

(Continued on the following page)

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Table 4. Association between vitamin D quartiles and incidence of specific types of cancer (Cont'd)

	Events (individuals)	Model 1[b] HR (95% CI), *P*	Model 2[c] HR (95% CI), *P*
Malignant melanoma	55 (11,100)		
2nd vitamin D quartile[a]		0.56 (0.22–1.43)	0.52 (0.21–1.33)
3rd vitamin D quartile[a]		1.42 (0.69–2.96)	1.24 (0.60–2.60)
4th vitamin D quartile[a]		1.42 (0.68–2.95), $P_{trend} = 0.110$	1.18 (0.56–2.48), $P_{trend} = 0.275$

[a]The 1st quartile is used as the reference. The number of events (n) and number of persons (N) in each quartile (n_{q1}/, N_{q1}, n_{q2}/N_{q2}, n_{q3}/N_{q3}, n_{q4}/N_{q4}) was: for all cancers (272/2,666, 281/2,693, 278/2,684, 303/2,666), all cancers excluding NMSC (221/2,695, 213/2,737, 210/2,722, 216/2,712), head and neck cancer (16/2,768, 7/2,792, 10/2,799, 5/2,771), colorectal cancer (36/2,765, 33/2,789, 40/2,792, 32/2,773), cancer of bronchus and lung (30/2,771, 34/2,791, 26/2,799, 20/2,772), breast cancer (40/1,393, 40/1,320, 35/1,398, 44/1,495), cancer of the uterus (3/1,409, 4/1,331, 9/1,417, 9/1,513), prostate cancer (30/1,358, 26/1,455, 33/1,377, 32/1,261), cancer of the urinary organs (8/2,765, 14/2,791, 13/2,797, 11/2,771), NMSC (70/2,740, 87/2,747, 102/2,762, 110/2,723), and malignant melanoma (12/2,761, 7/2,784, 18/2,795, 18/2,760).
[b]Adjusted for study and gender.
[c]Further adjusted for education, season, physical activity, smoking habits, alcohol intake, intake of fish, and BMI.

found that not only was an increased baseline vitamin D status significantly associated with an increased risk of NMSC, but also that the association was attenuated on less exposed body sites, indicating that UV exposure is a likely confounding factor (25). Supporting this view is a study by Tang and colleagues, who performed *post hoc* analyses

Table 5. Association between a 10 nmol/L higher vitamin D status and incidence of specific types of cancer

	Events (individuals included)	Model 1[a] HR (95% CI), *P*	Model 2[b] HR (95% CI), *P*
All cancers	1,134 (10,709)		
Per 10 nmol/L higher vitamin D		1.01 (0.99–1.03), $P = 0.31$	1.02 (0.99–1.04) $P = 0.16$
All cancers excluding NMSC	860 (10,866)		
Per 10 nmol/L higher vitamin D		0.99 (0.96–1.02), $P = 0.40$	1.00 (0.97–1.03), $P = 0.94$
Head and neck cancer	38 (11,130)		
Per 10 nmol/L higher vitamin D		0.88 (0.77–1.02), $P = 0.08$	0.97 (0.84–1.12), $P = 0.69$
Colorectal cancer	141 (11,119)		
Per 10 nmol/L higher vitamin D		0.93 (0.87–1.00), $P = 0.05$	0.95 (0.88–1.02), $P = 0.16$
Cancer, bronchus and lung	110 (11,133)		
Per 10 nmol/L higher vitamin D		0.96 (0.89–1.04), $P = 0.29$	0.98 (0.91–1.05), $P = 0.55$
Breast cancer	159 (5,606)		
Per 10 nmol/L higher vitamin D		1.01 (0.95–1.08), $P = 0.67$	1.02 (0.96–1.09), $P = 0.53$
Cancer of the uterus	25 (5,670)		
Per 10 nmol/L higher vitamin D		1.09 (0.96–1.25), $P = 0.19$	1.10 (0.95–1.27), $P = 0.21$
Prostate cancer	121 (5,451)		
Per 10 nmol/L higher vitamin D		1.02 (0.96–1.09), $P = 0.52$	1.00 (0.93–1.08), $P = 0.95$
Cancer, urinary organs	46 (11,124)		
Per 10 nmol/L higher vitamin D		1.01 (0.90–1.12), $P = 0.93$	1.01 (0.90–1.14), $P = 0.86$
NMSC	369 (10,972)		
Per 10 nmol/L higher vitamin D		1.06 (1.02–1.10), $P = 0.003$	1.06 (1.02–1.10), $P = 0.007$
Malignant melanoma	55 (11,100)		
Per 10 nmol/L higher vitamin D		1.06 (0.96–1.16), $P = 0.23$	1.06 (0.95–1.17), $P = 0.29$

NOTE: Complete case analysis. Individuals with a history of the cancer of interest at baseline were excluded.
[a]Adjusted for study and gender (age is underlying time axis).
[b]Further adjusted for education, season during which blood was drawn, physical activity, smoking habits, alcohol intake, intake of fish, and BMI.

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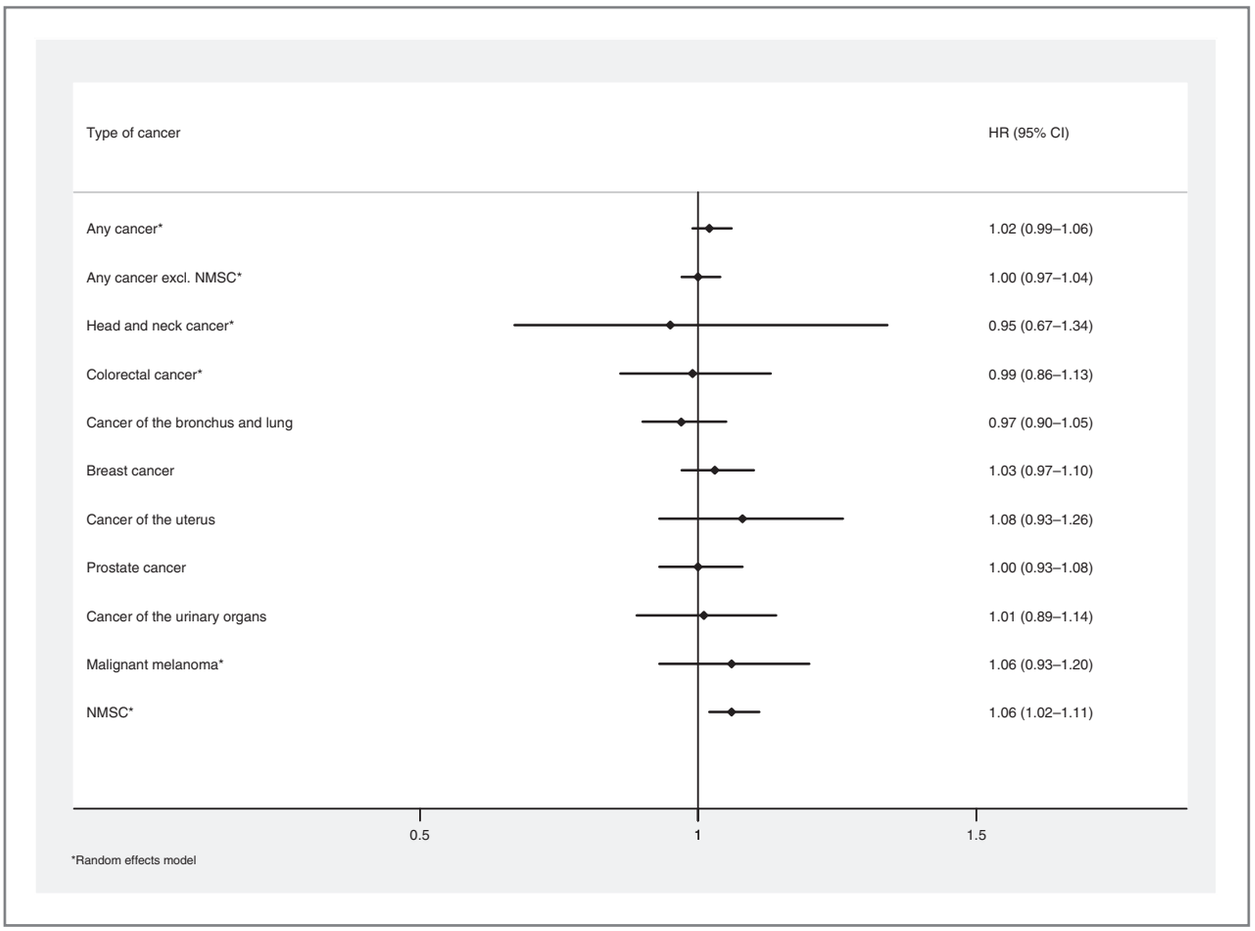

Figure 1. Meta-estimates of the study-specific estimates of the association between a 10 nmol/L higher vitamin D status and risk of cancer.

of the women's health initiative randomized controlled trials (RCT) and found that vitamin D plus calcium supplementation did not reduce the overall incidence of NMSC (26).

A meta-analysis on vitamin D and colorectal cancer by Ma and colleagues revealed an inverse association between blood 25-OH-D levels and the risk of colorectal cancer (9). They included nine prospective studies with objective measurements of vitamin D levels and the risk for colorectal, colon, or rectal cancer, which yielded a pooled risk ratio of 0.74 (95% CI, 0.63–0.89) for a 10 ng/mL higher vitamin D. In comparison, we found an HR = 0.95 (95% CI, 0.88–1.02) for a 10 nmol/L higher vitamin D status.

Our results for vitamin D and head and neck cancer are partially in line with a study by Orell-Kotikangas and colleagues, who investigated 57 patients with head and neck cancer and found subnormal vitamin D levels in a significant proportion of the patients (27). However, a study by Meyer and colleagues of 522 patients with head and neck cancer revealed that vitamin D status before treatment did not influence the disease outcomes (28).

Our results for vitamin D and prostate cancer are in agreement with previous studies. In a meta-analysis, Yin and colleagues summarized the evidence from existing longitudinal studies on the association between vitamin D and the risk of prostate cancer. Yin and colleagues included 11 original reports and found a summary OR of 1.03 (95% CI, 0.96–1.11) per 10 ng/mL higher vitamin D. They concluded that vitamin D status is not associated with the incidence of prostate cancer based on the available evidence.

A meta-analysis on 25-OH-D levels and breast cancer by Yin and colleagues found no statistically significant association in the cohort studies measuring vitamin D status at baseline before cancer diagnosis (29), whereas a meta-analysis of case-control studies by Chen and colleagues found a statistically significant lower risk of breast cancer for the women in the highest vitamin D quartile when compared with the lowest (30). A recent meta-analysis of prospective studies reported a dose–response relationship with a statistically significant 3.2% reduction in breast cancer risk per 10 ng/mL increment in serum 25-OH-D concentration (31). In

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comparison, we found no statistically significant association between vitamin D status and incident breast cancer.

The strengths of our study include the large random sample of the Danish population many of whom have low vitamin D levels (17) and the longitudinal population-based design minimizing risk of reverse causation (i.e., that the disease modifies lifestyle and vitamin D status); a long-term follow-up and the use of standardized registry-based diagnoses with almost no individuals lost to follow-up; and the available prospectively collected information on several important potential confounders, which allowed us to minimize confounding. To further reduce the risk of reverse causation, we performed additional analyses, where we excluded individuals that developed the cancer of interest in the first two years after the initial examination. Another strength of our study is that we included three cohorts with baseline data from two decades.

The limitations of the study include the different methods of measuring vitamin D levels in the merged studies, the risk of residual confounding inherent in an observational study, and the single vitamin D measurement, which likely loses predictive power over time. Also, the types of cancer in the main groups may not share the same potential vitamin D-dependent pathway. The vitamin D levels differed between the studies, which could have been due to evaporation during storage. Therefore, we chose to use vitamin D both as a continuous variable and in season-specific quartiles, classified before pooling of the data. We included meta-analyses of the study-specific estimates. Also, we may have lacked ability to detect small to medium effect sizes. The relatively low participation in some of the included cohorts may result in selection bias and limit the generalizability of the results. Of note, however, another similar Danish study using registry-based outcomes with almost complete follow-up of participants, but with lower baseline participation than in the present study was shown not to be biased by baseline nonparticipation (32). We used complete case analysis for missing covariates in the present study due to the simplicity and comparability across analyses. An alternative approach would be multiple imputations. A study by White and Carlin examined bias and efficiency of multiple imputation compared with complete case analysis for missing covariates (33). On the basis of theoretical results and simulation studies of different scenarios including uni- and bivariate analyses with covariates missing completely at random and at random, respectively, they concluded that none of the methods was universally applicable although the multiple imputation method seemed appropriate across a wider range of settings. In general, both methods were valid when covariates were missing completely at random.

Regarding RCTs, a recent meta-analysis by Bjelakovic and colleagues reported a significantly decreased cancer mortality in a total of 44,492 person from 4 trials using vitamin D_3 supplementation (34). They estimated the quality of the evidence as moderate quality which means that further research is likely to change the estimate and to affect the confidence in the estimate. In particular, the validity of results may be questionable because a large number left the trials before completion. Also, more RCTs are needed in younger, healthy persons and in elderly with no apparent vitamin D deficiency. In comparison, a systematic review by Lazzeroni and colleagues reported a statistically nonsignificant lower risk of cancer mortality in the supplementation group (35), possible due to several things. First, the studies were neither designed, nor sufficiently powered, to investigate the cancer end points. Second, most studies supplemented with both calcium and vitamin D, thus preventing distinguishing between the calcium and the vitamin D effects and raising the possibility that combination therapy is required to prevent cancer. In view of existing evidence from RCTs, Lazzeroni and colleagues suggested that vitamin D could be a risk marker for cancer rather than a risk factor (35). In support of this, Thuesen and colleagues previously reported that vitamin D status was significantly associated with several known cancer-related risk factors (17). There are several ongoing phase II and III RCTs investigating the effect of vitamin D supplementation alone and when combined with calcium on total and different cancers (35).

Currently, the evidence regarding a potential role for vitamin D in the prevention of cancer is inconclusive (36). We found no statistically significant associations between vitamin D status and incidence of total or specific cancers, except for the statistically significant positive association between vitamin D status and the incidence of NMSC. Our results do not indicate that there is an impact of vitamin D on total cancer incidence. However, since cancer is a class of several diseases rather than a single one, vitamin D could be beneficial for the prevention of some cancers while having no or even a detrimental effect on others. We are still awaiting the results of large RCTs to help elucidate this point.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: T. Skaaby, B.H. Thuesen, A. Linneberg
Development of methodology: T. Skaaby
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.L.N. Husemoen, C. Pisinger, T. Jørgensen, A. Linneberg
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Skaaby, L.L.N. Husemoen, B.H. Thuesen, T. Jørgensen, A. Linneberg
Writing, review, and/or revision of the manuscript: T. Skaaby, L.L.N. Husemoen, B.H. Thuesen, C. Pisinger, T. Jørgensen, N. Roswall, S.C. Larsen, A. Linneberg
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Study supervision: L.L.N. Husemoen, A. Linneberg

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