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Serum 25-Hydroxyvitamin D and Cancer Mortality in the NHANES III Study (1988–2006)

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Abstract

Vitamin D has been hypothesized to protect against cancer. We followed 16,819 participants in NHANES III from 1988 through 2006, expanding upon an earlier NHANES III study (1988–2000). Using Cox proportional hazard regression models, we examined risk related to baseline serum 25-hydroxyvitamin D (25(OH)D) for total cancer mortality, in both sexes, and by racial/ethnic groups, as well as for site-specific cancers. Because serum was collected in the south in cooler months and the north in warmer months, we examined associations by collection season (“summer/higher latitude” and “winter/lower latitude”). We identified 884 cancer deaths during 225,212 person-years. Overall cancer mortality risks were unrelated to baseline 25(OH)D status in both season/latitude groups, and in non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans. In men, risks were elevated at higher levels (e.g., for ≥ 100 nmol/L, RR=1.85 (95% CI=1.02–3.35) compared to <37.5 nmol/L). Although risks were unrelated to 25(OH)D in all women combined, risks significantly decreased with increasing 25(OH)D in the summer/higher latitude group (for ≥ 100 nmol/L, RR=0.52 (95% CI=0.25–1.15) compared to <37.5 nmol/L, P-trend=0.03, based on continuous values). We also observed a suggestion of an inverse association with colorectal cancer mortality (P-trend=0.09) and a positive association with lung cancer mortality among males (P-trend=0.03). Our results do not support the hypothesis that 25(OH)D is associated with reduced cancer mortality. Although cancer mortality in females was inversely associated with 25(OH)D in the summer/higher latitude group, cancer mortality at some sites was increased among men with higher 25(OH)D. These findings argue for caution before increasing 25(OH)D levels to prevent cancer.

Keywords

vitamin D; neoplasms mortality; risk factors; cohort studies; male; female; seasons

Introduction

Substantial public health and scientific attention have focused on the hypothesized protective effects of vitamin D on cancer incidence and mortality. Vitamin D status may protect against

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cancer mortality either by reducing incidence and/or by improving cancer survival. A number of commentators on vitamin D have argued that vitamin D supplementation could substantially reduce cancer mortality without imposing major financial costs or adverse effects.(1,2) Some have also suggested that low levels of vitamin D may contribute to the higher cancer mortality observed in blacks.(3–5)

Tissues in numerous organs express the vitamin D receptor,(6) which is activated by the hormonal or active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D)), a nuclear transcription factor that may mediate several anti-neoplastic effects, including reduced cell proliferation and increased differentiation.(2) The active metabolite is converted from the inactive metabolite, 25-hydroxyvitamin D (25(OH)D), in several tissues throughout the body. (7) In epidemiologic studies, vitamin D status is measured by circulating levels of 25(OH)D, rather than 1,25(OH)2D, because circulating 25(OH)D integrates both ultraviolet radiation and dietary intake sources of vitamin D; the enzymatic tools to convert 25(OH)D to 1,25(OH)2D appear to be present in numerous tissues;(7) and 1,25(OH)2D is tightly regulated in the blood (unlike 25(OH)D)(2) and thus may not reflect vitamin D levels relevant to other tissues.

To our knowledge, very few analytic epidemiologic studies have examined the prospective relationship between circulating 25(OH)D and total cancer mortality, and these few have shown mixed results.(8–10) The primary purpose of this paper is to examine the prospective relationship between serum 25(OH)D and total cancer mortality among men and women combined, as well as in men and women separately in NHANES III. We expand a prior study of vitamin D and cancer in this nationally representative cohort of non-institutionalized people. (8) The current study includes 884 cancer deaths, incorporating an additional 348 cases (65% increase above the earlier analysis), over an additional six years of follow-up, through 2006, and thus allows greater opportunity to examine risk by sex and racial/ethnic groups and for site-specific cancer outcomes.

Methods

The methods used in this study are largely the same as those used in the previous analysis of vitamin D and cancer mortality in NHANES III.(8) We present them below, noting when the current analysis differs in key respects from the earlier study.

Study Population

The NHANES III survey, which was conducted between 1988 and 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), was designed to examine the health and nutritional status of the non-institutionalized US population.(11) In addition to providing representative estimates for the total non-institutionalized population, the survey was designed to provide separate estimates for three major racial/ethnic groups: non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans, and over-sampled the latter two populations. Data were collected by interview and physical examinations (conducted in Mobile Examinations Centers (MEC)), including blood sampling for measurement of 25(OH)D and other serum constituents. All procedures were approved by the NCHS Institutional Review Board, and all subjects provided written informed consent.

We restricted eligibility to those who were age 17 years and older and who had completed the MEC exam (n=17,705). Those who had no 25(OH)D measurement (n=875), or had unknown mortality status (n=11) were excluded, resulting in a cohort of 16,819.

Measurement of 25(OH)D

Detailed information on the assay used to measure 25(OH)D has been provided elsewhere. (12) Briefly, levels of the serum 25(OH)D metabolite were assayed with a radioimmunoassay (RIA) kit (DiaSorin, Stillwater, MN) during the baseline survey or shortly thereafter. The coefficient of variation (CV) was based on pooled batch Quality Control samples analyzed in duplicate across all batches. The CV was 10–25% (average 17.6%) for lower 25-OHD values (20–62.5 nmol/L) and 12–18% (average 15%), for higher values (85–147.5 nmol/L).

Because of the larger case numbers, we were able to use a lower categorical cut-point, 37.5 nmol/L, than in the prior study. Categorical 25(OH)D cut-points were set at 37.5, 50, 62.5, 80, and 100, which reflect alternative cut-points for insufficiency in the absence of agreement about sufficient or optimal levels. (12,13) Subgroup analyses included fewer cut-points because of smaller case numbers.

Sample Collection

Data were collected in different seasons (1988–1994) based generally on latitude, with southern collections undertaken in the cooler months (November–March), and northern collections, in warmer months (April–October). (12) Thus, season and latitude, both of which are related to 25(OH)D levels, are linked in the dataset, which limits the opportunity to assess each independent of the other. We refer to the two groups as “winter/lower latitude” and “summer/higher latitude.”

Endpoint Ascertainment

Follow-up of the cohort continued from the baseline physical examination until December 31, 2006. Mortality outcomes based on the NHANES III Linked Mortality file (ICD-10) (with 113 underlying causes of death), were ascertained through probabilistic linkage with the National Death Index (NDI). Cancer deaths were coded by NDI using the classification ICD-10. ICD-10 codes for cancer sites were as follows: C33–C34 (lung, trachea, and bronchus); C18–C21 (colon, rectum, and anus); C15, C16, C22, C25 (other digestive system, i.e., esophagus, stomach, liver, pancreatic cancer); C50 (breast); C61 (prostate); C82–C85, C91–C95 (non-Hodgkin lymphoma/leukemia); and C00–C14, C17, C23–C24, C26–C32, C37–C41, C43–C49, C51–C52, C54–C60, C62–C65, C67–C80, C88, C90, C97 (for a combined grouping of other cancers, including buccal, larynx, melanoma, gynecological sites, kidney, bladder, brain, multiple myeloma).

Survival follow-up continued until the event of interest, an underlying cause of death due to cancer. For persons who died of other diseases or were not known to have died, follow-up was censored at the date of death or December 31, 2006, whichever was earlier.

Statistical Analysis

Chi-square tests and multiple linear regression were used to assess associations between baseline demographic and health-related characteristics and serum 25(OH)D level. Cox proportional hazards regression analysis was used to compute multiple-variable adjusted relative risks (RR) with 95% confidence intervals (CIs) for total and site-specific cancer mortality by categorical level of 25(OH)D, with age (beginning at baseline) as the timeline. (14) The proportional hazards assumption was assessed by testing the interaction between the attained age (<70; ≥70) during the study with continuous 25(OH)D serum levels. The interaction was not statistically significant for men and women combined or for men. Although the interaction for women was significant, it did not reflect a qualitative difference by attained age, i.e., risks declined in younger women and were relatively flat in older women.

We examined total cancer mortality in each of the two season/latitude groups and by sex, as in the earlier report on vitamin D and NHANES III.(8) We also assessed risk for each sex by latitude/seasonal group because of a borderline significant interaction between 25(OH)D and latitude/seasonal group in women and to provide parallel results in men. In addition, we examined total cancer mortality by ethnic/racial subpopulations (non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans), particularly because of the hypotheses about the potentially protective effects of 25(OH)D on blacks.(3–5) To assess further whether 25(OH)D levels contribute to racial differences in cancer mortality, we examined mortality risk by race, with and without adjusting for 25(OH)D circulating levels.

We also examined site-specific mortality for lung, colorectal, other digestive disease, breast, and prostate cancers based on suggested associations reported previously.(1,15–18) We reviewed mortality for the combination of non-Hodgkin's lymphoma (NHL) and leukemia because of small case numbers and because experimental and epidemiologic studies suggest a possible association between 25(OH)D or UV radiation and hematopoietic cancers.(19–24)

We included several covariates in the multivariate model that are highly related to cancer mortality and that were included in the earlier analysis.(8); these were sex, race/ethnicity, and smoking (never, former, current < 20 pack-years, ≥ 20 pack-years, unknown pack-years). We also considered the following covariates: body mass index (BMI) (<25; 25–<30; ≥30 kg/m²; unknown); latitude; education (self-reported years of schooling (categorically)); levels of physical activity (self-reported activity compared to others of the same age and sex); alcohol and calcium intake (both based on a single 24-hours recall and the USDA food composition database)(25); and total body fat (derived using bioelectrical impedance analysis data)(26). However, when these covariates were included in the models, key outcomes, i.e., total cancer mortality in men and in women (by season/latitude group), as well as female breast, colorectal, male lung, and male other digestive cancers, did not substantively change (i.e., the direction of the results was the same and the significance of the results was either unchanged or if significant, sometimes became borderline significant). We nonetheless adjusted for BMI because BMI has often been included in analytic studies of 25(OH)D and cancer.(10,27–30)

Trend tests were based on modeling the measured values of 25(OH)D as continuous (for maximum statistical power). Statistical significance was determined by a two-sided $p < 0.05$. To explore effect modification, we examined stratified analyses and multiplicative interaction (using continuous 25(OH)D values) by creating product terms. The data were analyzed using the SUDAAN (release 9.0.1; Research Triangle Institute, Research Triangle Park, NC) to account for the complex sample design of NHANES III including the sample weights that were used to account for the unequal probability of selecting individuals and for survey non-response.(31)

Results

We identified 884 deaths due to cancer during 225,212 person-years of follow-up (mean follow-up=13.4 years) in this expanded NHANES III study. Of the 884 deaths, 355 were in the winter/lower latitude group (an additional $n=149$ deaths over the earlier report) and 529, in the summer/higher latitude group (an additional $n=199$ deaths).

The cohort mean 25(OH)D levels by month in the summer/higher latitude group were: 67.3 nmol/L (April); 71.9 (May); 74.5 (June); 83.1 (July); 82.4 (August); 80.8 (September); 75.0 (October). In the winter/lower latitude, they were: 71.3 (November); 67.8 (December); 63.6 (January); 63.2 (February); and 62.4 (March).

Table 1 shows the baseline associations between demographic and health-related characteristics and serum 25(OH)D categories. Lower circulating levels were more common among women, non-Hispanic blacks, and Mexican-Americans.

There was no association between 25(OH)D and total cancer mortality in the combined total population of both season/latitude groups ($P_{\text{trend}}=0.43$) (table 2), as in the earlier report.(8) There was also no association in either the winter/lower or summer/higher latitude subpopulations of the population of men and women combined. When we examined the association between circulating 25(OH)D at baseline and total mortality risk during the additional follow-up period (2000–2006), we also observed no association with risk (data not shown).

We then examined the association separately by sex. In men, there was no statistically significant trend in the season/latitude groups combined ($P_{\text{trend}}=0.09$), although there were statistically significant elevated risks in the two highest categories [≥ 80 – <100 nmol/L: $RR=1.66$, 95% (CI= 1.06 to 2.61); ≥ 100 nmol/L: $RR= 1.85$ (CI= 1.02 to 3.35)]. In the winter/lower latitude group, the trend was not statistically significant. It was, however, statistically significant in the summer/higher latitude group ($P_{\text{trend}}= 0.045$). There was no interaction between the two season/latitude groups and trend with 25(OH)D ($P_{\text{interaction}}=0.46$).

In women, there was no statistically significant trend with 25(OH)D in the combined season/latitude groups or in the winter/lower latitude group. The trend, however, was statistically significant, and declining, in the summer/higher latitude subpopulation ($P_{\text{trend}}=0.03$). Compared to the reference category (<37.5 nmol/L) cancer mortality risks were about one-half in the highest category (≥ 100 nmol/L). The test for interaction between the two female season/latitude groups and trend with 25(OH)D was of borderline significance ($P_{\text{interaction}}=0.05$).

Because of the expanded case numbers, we also considered racial/ethnic groups separately by sex (table 3). In non-Hispanic white men and white women, as in all men and women, there was no statistically significant trend in both season/latitude groups combined.

In both non-Hispanic black men and black women, there was also no statistically significant trend in risk. Risks for both, however, were higher at 25(OH)D categories above 37.5 nmol/L. We also assessed the risk for total cancer mortality associated with being non-Hispanic black in comparison to being non-Hispanic white before and after adjusting for circulating 25(OH)D. We found no decrease in the higher risk associated with being non-Hispanic black (risk of total cancer mortality without covariate of circulating 25(OH)D, $RR= 1.37$ (95% CI: 1.08–1.73) ; and after including the covariate continuous 25(OH)D, $RR= 1.44$ (95% CI: 1.15–1.81)). In both Mexican-American men and women there was no statistically significant trend in total cancer mortality risk.

We also analyzed the association between circulating 25(OH)D and risk of mortality for particular cancer sites (table 4). We found no association between 25(OH)D and lung cancer mortality in men and women combined or in women, but there was an adverse statistically significant trend in risk for men ($P_{\text{trend}}=0.03$), with nearly two-fold risks in the highest category (≥ 100 nmol/L). There was also no statistically significant risk trend for colorectal cancer mortality, but risks were non-statistically significantly lower in all categories ≥ 50 nmol/L and substantially so, at ≥ 100 nmol/L, $RR=0.35$ (95% CI= 0.11 to 1.14). Risks generally declined both in men and in women, although not to a statistically significant extent. With regard to mortality for other digestive cancers, there was no apparent trend in risk for both sexes combined or for women. The trend was statistically significant and adverse for men ($P_{\text{trend}}=0.01$). There was also no statistically significant trend for female breast or prostate cancer mortality risk, but risks were highest at the reference level (< 50 nmol/L) for breast cancer and lowest at the reference level for prostate cancer risk. There was also no apparent

risk trend for NHL/leukemia mortality, nor for mortality for all other cancers, regardless of whether the sexes were combined or assessed separately.

We also examined associations between 25(OH)D and many of the key mortality outcomes (total cancer mortality by sex and latitude/seasonal group; non-Hispanic black male and female total cancer; female breast cancer; colorectal cancer; male lung cancer; and male other digestive cancers), after excluding self-reported prevalent non-skin cancers (n=126) at baseline. The results, which are presented in Supplemental Table 1, are similar to those when self-reported baseline cancer cases are not excluded.

Discussion

Prior to the current study, to our knowledge, the association between circulating 25(OH)D and total cancer mortality had been examined in three study populations,(8–10,32–34) with mixed results. In an earlier NHANES III study of circulating vitamin D, total cancer mortality was not associated with baseline 25(OH)D in the entire population, men, women, or ethnic/racial subpopulations.(8) Similarly, a population-based, presumably Caucasian, Norwegian study of circulating 25(OH)D found no significant association with total cancer mortality in smokers and in non-smokers, but specific risks were not reported by gender.(9) A substantially smaller German study of Caucasian patients referred for coronary angiography, with only 95 cancer deaths, found a major reduction in fatal cancer risk in those with the highest circulating vitamin D levels, but the medical characteristics of the study population limit the generalizability of the findings.(10,33) The current NHANES III study has substantially more cancer cases than earlier studies, and permits examination by gender, and racial/ethnic groups, and some specific cancer sites.

Here we observed no association between serum 25(OH)D and overall cancer mortality in the total population, in men or in women with both season/latitude groups combined.(8) However, there was some suggestion that the association may differ between the sexes. For example, in men, our results suggested that serum 25(OH)D > 80 nmol/L may increase risk of overall cancer mortality. Specifically, the RR was significant in the two highest categories (>80–100 and ≥ 100 nmol/L) when season/latitude groups were combined, and there was a significant adverse trend in the summer/higher latitude group when season/latitude was analyzed separately. However in women, results suggested either no association (season/latitude groups combined and winter/lower latitude group) or that there was an inverse relationship (summer/higher latitude group).

The divergent findings for overall mortality may stem from sex differences observed for some of the cancer site-specific analyses. An adverse trend was seen for lung cancer mortality in men, but not in women. Epidemiologic data on lung cancer and 25(OH)D is limited, but another prospective study(18) that examined serum 25(OH)D and lung cancer incidence in Finland found a significant interaction between 25(OH)D and sex, with an inverse association in women. The Finnish study did not find elevated lung cancer risks in men, but the number of male cases was small (n=97) and only 25 had 25OHD values > 52 nmol/L, so presumably there were few cases above the 100 nmol/L cut-point where substantially elevated risks were seen in the NHANES III study. The authors of the Finnish study speculate that sex-dependent hormones may affect lung cancer etiology,(18) and presumably could interact with 25(OH)D status. Sex hormones may also play a role in lung cancer prognosis, and thus mortality.(35) In addition, men and women differ in the histological distribution of lung cancers;(35) but because our case information derived from death certificates, we could not assess whether histology contributed to the sex pattern of our results. Although adjusting for pack-years in more detail did not materially reduce the strength of the associations in men, it is possible that residual confounding by smoking contributed to the finding, particularly smoking outdoors. In addition,

uncontrolled socioeconomic or occupational exposures may have contributed to the results, such as, for example, work environments that combine UV exposure and potential lung carcinogens (e.g., shipbuilding, construction, and painting).(36)

Also noteworthy were the elevated risks for mortality of other digestive cancers (pancreatic, esophageal, stomach and liver cancer) seen in men, but not in women. Three studies have reported an elevated risk of pancreatic cancer related to higher 25(OH)D status, including, a prospective study in Finnish male smokers,(37) the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial study for those living in northern latitudes in the U.S. (although not in the full PLCO study) (38), and the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP).(39) Although neither the PLCO nor the VDPP found an interaction by sex, the association was greater and statistically significant in the highest category in VDPP (≥ 100 vs $50 < 75$ nmol/L) in men compared to women (RR=2.33 (95% =1.24–4.36) vs. 1.46 (0.47–4.61)). Another prospective study in China found higher levels of serum 25(OH)D related to esophageal squamous cell carcinoma incidence in men, but not in women.(40) There was no association with gastric cancer incidence in either sex in that study.(40) But in the VDPP, circulating 25(OH)D was associated with significantly increased risk of upper gastrointestinal cancer incidence in never smokers and in Asians.(41) Thus, the limited epidemiologic data on these cancers suggests elevated risks for some cancer sites in this category, particularly for men in some studies. Nonetheless, the results in the present study may be viewed as suggestive in light of the small case numbers.

Results for some other cancer site-specific analyses did not appear to differ by sex, however. For example, the association with colorectal cancer mortality was inverse in both men and in women, although it was not statistically significant when sexes were combined (P-trend=0.09) or when analyzed separately by sex. Nonetheless, the generally falling risks with rising 25(OH)D levels is consistent with the earlier finding,(8) as well as a large number of epidemiological studies on colorectal cancer incidence.(42,43)

Neither the earlier or present study found a significant trend in breast cancer risk related to 25(OH)D, although both suggest declining risks with increased levels. With 53 breast cancer deaths, however, the case numbers continue to be small for detecting an association. To date the evidence for an inverse prospective breast cancer relationship with one-time measures of circulating 25(OH)D, as in this account, is not strong,(42,44): one study suggested an inverse association in some subpopulations,(45) whereas others found no association.(46–48) These studies, however, involve breast cancer incident cases rather than deaths, and thus may relate to breast cancers that may differ in histology or stage from breast cancer deaths.

It is also of interest that there was an inverse association with 25(OH)D for women in the summer/higher latitude group, although there was no overall cancer relationship in women for both seasonal/latitude groups combined. One can speculate about factors contributing to the disparate associations by seasonal/latitude group. If, for example, peak values of 25(OH)D are particularly relevant to risk, measures in the “summer” would be most informative. It is also possible that low levels measured in higher latitudes in the “summer” constitute a particularly stable reference category given the low likelihood that those with insufficient levels in the “summer” increase their 25(OH)D status in colder months.

There has been substantial scientific interest in whether low 25(OH)D contributes to the elevated cancer and other disease risks characterizing African-Americans (3–5,15), but to date, there have been few prospective studies of measured, circulating 25(OH)D and cancer risk in African-Americans to address this hypothesis.(49) The present analysis, although based on relatively small numbers, helps fill this gap. We found no statistically significant trend in cancer mortality risk related to 25(OH)D levels in non-Hispanic black men or women. Total cancer

mortality risks were, in fact, lowest in non-Hispanic black men and women with 25(OH)D levels in the lowest category, <37.5 nmol/L. Moreover, the fact that the risk of total cancer mortality for non-Hispanic blacks compared to that of non-Hispanic whites was not reduced by adjusting for serum 25(OH)D levels also fails to support the hypothesis that low 25(OH)D levels in African-Americans contribute to racial cancer disparities. Thus, our results caution against assuming a beneficial relationship, and points to the possibility that risks might rise with elevated levels of 25(OH)D.

The strengths of the present study include that 25(OH)D was based on measured, circulating 25(OH)D in a population that is representative of the civilian, U.S. population. As a diverse population, we could explore relationships with 25(OH)D and cancer mortality in non-Hispanic blacks as well as Mexican-Americans, unlike most cohort studies. Because of the extensive collection of information on participants in NHANES III, a wide range of covariates was available.

Limitations of the study principally include the small numbers of cases for subgroup analyses and the collection of data in a manner in which geographic region is confounded by season. It is, however, reassuring that we did see the generally expected gradient for mean 25(OH)D level by month, although the gradient might be sharper had latitude not played a role in the timing of collections. The study also relied on a single measure of 25(OH)D as a surrogate for long-term exposure. We note that a recent study of long-term variation in circulating 25(OH)D showed relatively stable measures over several years, although blood collections for any given individual occurred in the same month each year, and thus did not address potential variability across seasons.⁽⁵⁰⁾ These limitations diminish the opportunity to detect associations; they do not, as far as we can determine, contribute to biases that would inflate potential associations. However, it is possible that the numerous comparisons undertaken in the analyses may have contributed to some significant findings due merely to chance.

The mean follow-up of the study, 13.4 years, is relatively lengthy, but is not clearly a limitation. The overall relationship between 25(OH)D and total cancer mortality in the two genders for the two periods (1988–2000; 2001–2006) was not substantially different, with some attenuation in risk in men in the later period. Serum assays of 25(OH)D for all cohort members were undertaken during the baseline survey or shortly thereafter, which reduces the risk of samples degrading differentially over time. Finally, because there is no consensus on the etiological relevant time for 25(OH)D's potentially cancer preventive effects, the optimal follow-up period is unknown.

The fact that we did observe statistically significant adverse associations in men is noteworthy given the interest in undertaking intervention trials that employ high levels of vitamin D supplements in healthy persons.⁽⁴²⁾ Supplements of 2000 IU or more, which have been advocated by some groups⁽⁴²⁾ (and discussed for intervention trials), could markedly raise 25(OH)D blood levels.⁽⁵¹⁾ Substantial increases in 25(OH)D may pose increased harms if, as these data suggest, some increases in 25(OH)D relate to increased risks for particular outcomes.

In sum, we found no overall relationship between 25(OH)D and cancer mortality risk in the general population, nor in the ethnic/racial groups, including non-Hispanic blacks. We did observe an inverse association with colorectal cancer mortality in the general population which, although not statistically significant, is consistent with findings in the prior study, and with the mainstay of the epidemiologic literature. Some of our results suggested that the relationship between 25(OH)D and overall cancer mortality and at some selected sites may vary by sex. For example, an adverse trend between increasing serum 25(OH)D and overall cancer mortality, and death due to lung cancer and some digestive cancers was seen in men. On the other hand, we found a significant trend toward falling risk of overall cancer mortality with

increasing 25(OH)D levels in women in one season/latitude group. More work is needed to explore possible divergent associations with vitamin D by sex, and, identify biological mechanisms that might contribute to such differences. These results suggest that the relationships between 25(OH)D and cancer may be more complex than has been thought, and advise caution before encouraging vitamin D supplementation to further the goal of preventing cancer, particularly in men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CV	Coefficient of Variation
ICD	International Classification of Diseases
MEC	Mobile Examination Center
NCHS	National Center for Health Statistics
NHANES	National Health and Nutritional Examination Survey
25(OH)D	25-hydroxy-vitamin D
1,25(OH)2D	1,25 dihydroxy-vitamin D

References

1. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *AmJPublic Health* 2006;96(2):252–261.
2. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266–281. [PubMed: 17634462]
3. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. *Cancer Epidemiol Biomarkers Prev* 2006;15(12):2467–2472. [PubMed: 17132768]
4. Egan KM, Signorello LB, Munro HM, Hargreaves MK, Hollis BW, Blot WJ. Vitamin D insufficiency among African-Americans in the southeastern United States: implications for cancer disparities (United States). *Cancer Causes Control* 2008;19(5):527–535. [PubMed: 18219582]
5. Grant WB. Differences in vitamin-D status may explain black-white differences in breast cancer survival rates. *Journal of the National Medical Association* 2008;100(9):1040. [PubMed: 18807432]
6. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80 Suppl(6):1689S–1696S. [PubMed: 15585789]
7. Zehnder D, Bland R, Williams MC, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *JClinEndocrinolMetab* 2001;86(2):888–894.
8. Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst* 2007;99(21):1594–1602. [PubMed: 17971526]
9. Hutchinson MS, Grimnes G, Joakimsen RM, Figenschau Y, Jorde R. Low serum 25-hydroxyvitamin D levels are associated with increased all-cause mortality risk in a general population: the Tromso study. *European journal of endocrinology / European Federation of Endocrine Societies* 2010;162(5):935–942. [PubMed: 20185562]

10. Pilz S, Dobnig H, Winklhofer-Roob B, et al. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev* 2008;17(5): 1228–1233. [PubMed: 18463400]
11. Vital Health Statistics. Hyattsville, MD: NCHS; 1994. National Center for Health S. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–1994. Report No.: DHHS Publication Number (PHS) 94-1308
12. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone* 2002;30(5):771–777. [PubMed: 11996918]
13. Heaney RP. The Vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol* 2005;97(1–2):13–19. [PubMed: 16026981]
14. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *AmJEpidemiol* 1997;145(1):72–80.
15. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* 2005;16(2):83–95. [PubMed: 15868450]
16. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup Environ Med* 2002;59(4):257–262. [PubMed: 11934953]
17. Grant WB, Garland CF. Evidence supporting the role of vitamin D in reducing the risk of cancer. *JInternMed* 2002;252(2):178–179.
18. Kilkkinen A, Knekt P, Heliovaara M, et al. Vitamin D status and the risk of lung cancer: a cohort study in Finland. *Cancer Epidemiol Biomarkers Prev* 2008;17(11):3274–3278. [PubMed: 18990771]
19. Freedman DM, Zahm SH, Dosemeci M. Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma: composite (threefold) case-control study. *BMJ* 1997;314(7092):1451–1455. [PubMed: 9167561]
20. Hartge P, Lim U, Freedman DM, et al. Ultraviolet radiation, dietary vitamin D, and risk of non-Hodgkin lymphoma (United States). *Cancer Causes Control* 2006;17(8):1045–1052. [PubMed: 16933055]
21. Smedby KE, Hjalgrim H, Melbye M, et al. Ultraviolet radiation exposure and risk of malignant lymphomas. *JNatlCancer Inst* 2005;97(3):199–209.
22. Hu S, Ma F, Collado-Mesa F, Kirsner RS. Ultraviolet radiation and incidence of non-Hodgkin's lymphoma among Hispanics in the United States. *Cancer EpidemiolBiomarkers Prev* 2004;13(1): 59–64.
23. Hughes AM, Armstrong BK, Vajdic CM, et al. Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. *IntJCancer* 2004;112(5):865–871.
24. Luong QT, Koeffler HP. Vitamin D compounds in leukemia. *JSteroid BiochemMolBiol* 2005;97(1–2):195–202.
25. U.S.Department of Agriculture ARS. Survey nutrient databases for NHANES III, Phase 1(1993) and Phase 2 (1995). Riverdale, MD: 1993.
26. Looker AC. Body fat and vitamin D status in black versus white women 1. *JClinEndocrinolMetab* 2005;90(2):635–640.
27. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *NEnglJMed* 2006;354(7):684–696.
28. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst* 2007;99(14):1120–1129. [PubMed: 17623801]
29. Ahn J, Peters U, Albanes D, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst* 2008;100(11):796–804. [PubMed: 18505967]
30. Vitamin D and Calcium: Systematic Review of Health Outcomes: AHRQ. 2009
31. Korn, EL.; Graubard, BI. Analysis of Health Surveys. New York: Wiley; 1999. p. 160-165.
32. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Archives of internal medicine* 2008;168(15):1629–1637. [PubMed: 18695076]

33. Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. *Anticancer Res* 2009;29(9):3699–3704. [PubMed: 19667167]
34. Freedman DM, Fuhrman B, Graubard BI, Chang SC. Vitamin D and cancer mortality. *Cancer Epidemiol Biomarkers Prev* 2009;18(1):359. author reply -60. [PubMed: 19124522]
35. Carey MA, Card JW, Voltz JW, et al. It's all about sex: gender, lung development and lung disease. *Trends in endocrinology and metabolism: TEM* 2007;18(8):308–313. [PubMed: 17764971]
36. Consonni D, De Matteis S, Lubin JH, et al. Lung cancer and occupation in a population-based case-control study. *Am J Epidemiol* 2010;171(3):323–333. [PubMed: 20047975]
37. Stolzenberg-Solomon RZ, Vieth R, Azad A, et al. A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res* 2006;66(20):10213–10219. [PubMed: 17047087]
38. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, Anderson KE, Hollis BW, Silverman DT. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. *Cancer Res* 2009;69(4):1439–1447. [PubMed: 19208842]
39. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010;172(1):81–93. [PubMed: 20562185]
40. Chen W, Dawsey SM, Qiao YL, et al. Prospective study of serum 25(OH)-vitamin D concentration and risk of oesophageal and gastric cancers. *British journal of cancer* 2007;97(1):123–128. [PubMed: 17551495]
41. Abnet CC, Chen Y, Chow WH, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010;172(1):94–106. [PubMed: 20562192]
42. IARC. Vitamin D and cancer. Geneva: International Association for Research on Cancer; 2008.
43. Jenab M, Bueno-de-Mesquita HB, Ferrari P, et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations: a nested case-control study. *BMJ* 2010;340:b5500. [PubMed: 20093284]
44. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: Serum vitamin D and breast cancer risk. *Eur J Cancer*. 2010 Epub ahead of print.
45. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14(8):1991–1997.
46. Freedman DM, Chang SC, Falk RT, et al. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2008;17(4):889–894. [PubMed: 18381472]
47. Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst* 2008;100(22):1581–1591. [PubMed: 19001601]
48. McCullough ML, Stevens VL, Patel R, et al. Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. *Breast Cancer Res* 2009;11(4):R64. [PubMed: 19715600]
49. Woolcott CG, Wilkens LR, Nomura AM, et al. Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;19(1):130–134. [PubMed: 20056631]
50. Hofmann JN, Yu K, Horst RL, Hayes RB, Purdue MP. Long-term variation in serum 25-hydroxyvitamin D concentration among participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol Biomarkers Prev* 2010;19(4):927–931. [PubMed: 20332255]
51. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr* 2008;87(6):1952–1958. [PubMed: 18541590]

Table 1

Baseline demographic and health-related characteristics of study participants by serum 25 (OH)D levels (nmol/l) level. Third National Health and Nutritional Examination Survey (NHANESIII), 1988–1994.[†]

	<37.5 N=2689	37.5<50 N=3056	50<62.5 N=3143	62.5<80 N=3713	80<100 N=2521	≥100 N=1697
Sample Size (%)	9.2	13.1	16.2	24.4	19.8	17.3
Serum 25 (OH) levels [‡] (nmol/L)	29.7	44.4	56.6	71.3	89.1	121.9
Age [‡] (years)	44.5	45.8	45.9	44.1	42.5	38.9
Sex (%) [¶]						
Men (N=7905)	6.0	10.2	15.7	25.3	23.1	19.8
Women (N=8914)	12.2	15.8	16.6	23.5	16.9	15.0
Race (%) [¶]						
Non-Hispanic White (N=6837)	5.0	10.2	14.8	26.0	22.9	21.2
Non-Hispanic Black (N=4657)	33.8	26.3	18.5	13.3	5.9	2.3
Mexican-American (N=4639)	12.4	18.4	23.1	25.3	14.0	6.9
Other (N=686)	14.4	20.4	21.6	23.4	13.2	7.2
Education, post Secondary (%)	33.4	36.8	35.9	42.3	41.0	44.1
Latitude [‡]	36.9	37.6	38.1	38.8	39.1	39.5
Smoking Status (%) [¶]						
Never (N=8614)	9.5	13.1	17.1	25.2	18.9	16.2
Former (N=3972)	7.5	12.2	15.3	24.8	23.2	16.9
Current, <20 packyrs (N=2966)	10.4	14.7	14.4	21.8	18.3	20.5
Current, ≥20 packyrs (N=815)	11.0	12.6	18.9	23.5	17.7	16.2
Current, unknown packyrs (N=452)	7.5	12.4	13.3	26.0	20.7	20.2
Alcohol [‡] (g/day)	10.4	8.4	8.3	9.2	10.9	14.9
BMI [‡] (kg/m ²)	27.9	27.7	27.3	26.3	25.7	24.7
Total Body Fat [‡] (kg)	26.5	25.7	24.1	22.5	21.1	18.8
Level of physical activity (same or more active than others same age/gender) %	67.6	73.5	75.6	76.8	79.6	81.4
Ever walk a mile, jog, swim, or bike in last month (%)	48.5	54.9	59.3	66.0	69.7	74.6
Vitamin D from food [‡] (mcg/day)	3.2	4.0	4.5	5.2	5.7	6.0
Calcium from food [‡] (mg/day)	623.2	695.3	802.2	871.5	937.1	997.9

Serum vitamin A [‡] (umol/l)	<37.5 N=2689	37.5<=50 N=3056	50<62.5 N=3143	62.5<80 N=3713	80<100 N=2521	>=100 N=1697
	1.8	1.9	2.0	2.1	2.1	2.2

[‡] All estimates are weighted.
[‡] Mean value.
[¶] Percentages sum across rows.

Table 2

Relative Risks (RR) and 95% Confidence Intervals (CI) between baseline serum 25(OH)D levels (nmol/L) and total cancer mortality by seasonal subpopulation and gender in the NHANES III study, 1988–2006.*

Cancer Mortality		Serum 25(OH) vitamin D levels (nmol/L)						P-trend
		<37.5	37.5<50	50<62.5	62.5<80	80<100	≥100	
Men and Women Combined								
Season/ Latitude combined								
No. cases	116	174	165	200	139	90		
RR	1.00	1.04	1.23	1.19	1.12	1.15		
95% CI	0.77–1.41		0.89–1.69	0.86–1.65	0.80–1.57	0.79–1.68	0.43	
Winter/ Lower latitude								
No. Cases	55	79	57	78	54	32		
RR	1.00	1.30	1.20	1.67	1.31	1.50		
95% CI	0.77–2.19		0.64–2.26	0.98–2.86	0.77–2.23	0.74–3.02	0.23	
Summer/ Higher latitude								
No. Cases	61	95	108	122	85	58		
RR	1.00	0.91	1.19	1.02	1.03	1.02		
95% CI	0.63–1.32		0.78–1.82	0.67–1.54	0.66–1.63	0.63–1.45	0.67	
Men	<37.5	37.5<50	50<62.5	62.5<80	80<100	≥100		
Season/Latitude combined								
No. Cases	47	95	90	122	90	69		
RR	1.00	1.66	1.43	1.52	1.66	1.85		
95% CI	0.98–2.80		0.90–2.26	0.82–2.80	1.06–2.61	1.02–3.35	0.09	
Winter/ Lower latitude								
No. Cases	25	51	31	52	33	23		
RR	1.00	2.58	1.14	1.99	1.42	1.94		
95% CI	1.37–4.87		0.48–2.70	0.86–4.13	0.74–2.72	0.69–5.45	0.55	
Summer/Higher latitude								
No. Cases	22	44	59	70	57	46		
RR	1.00	1.28	1.55	1.33	1.76	1.84		
95% CI	0.51–3.23		0.81–2.99	0.53–3.53	0.87–3.57	0.85–3.98	0.045	
Women	<37.5	37.5<50	50<62.5	62.5<80	80<100	≥100		

Cancer Mortality	Serum 25(OH) vitamin D levels (nmol/L)							P-trend
	<37.5	37.5-50	50-62.5	62.5-80	80-<100	≥100		
Season/ Latitude combined								
No. Cases	69	79	75	78	49	21		
RR	1.00	0.85	1.25	1.11	0.86	0.64		
95% CI		0.59-1.22	0.82-1.90	0.69-1.79	0.50-1.46	0.35-1.18		0.29
Winter/ Lower latitude								
No. Cases	30	28	26	26	21	9		
RR	1.00	0.74	1.27	1.44	1.28	1.01		
95% CI		0.36-1.51	0.51-3.18	0.61-3.38	0.50-3.24	0.26-3.90		0.42
Summer/Higher latitude								
No. Cases	39	51	49	52	28	12		
RR	1.00	0.88	1.18	0.99	0.70	0.52		
95% CI		0.54-1.43	0.65-2.12	0.52-1.87	0.34-1.44	0.25-1.10		0.03

* Adjusted for age, race/ethnicity, smoking history (never, former/current<20 packyrs, ≥20 packyrs, current-unknown packyrs), BMI (<25, 25-30, ≥30 kg/m², missing), using Cox proportion hazards regression. Trend was based on 25(OH)D as a continuous variable. Categories were selected to reflect alternative cut-points of 25(OH)D insufficiency and the full range of 25(OH)D values.,

Table 3

Relative Risks (RR) and 95% Confidence Intervals (CI) between baseline serum 25(OH)D levels (nmol/L) and total cancer mortality by race/ethnicity and gender in the NHANES III study, 1988–2006.*

Racial/Ethnic Group	<50	50–62.5	62.5–80	80–<100	≥100	P-trend
Non-Hispanic White Men						
No. Cases	37	41	71	65	53	
RR	1.0	0.95	1.04	1.23	1.21	0.09
95% CI		0.58–1.56	0.59–1.82	0.79–1.94	0.73–2.00	
Non-Hispanic White Women						
No. Cases	52	44	60	31	15	
RR	1.0	1.60	1.29	0.93	0.71	0.18
95% CI		1.06–2.43	0.82–2.05	0.56–1.56	0.38–1.33	
Non-Hispanic Black Men						
No. Cases	28	47	51	20		
RR	1.0	1.66	1.10	1.28		
95% CI		1.05–2.63	0.63–1.91	0.59–2.80		0.70
Non-Hispanic Black Women						
No. Cases	30	32	24	12		
RR	1.0	1.67	1.12	1.84		
95% CI		0.94–2.90	0.64–1.94	0.76–4.45		0.32
Mexican-American Men						
No. Cases	30	19	24	20		
RR	1.0	0.79	1.33	0.64		
95% CI		0.33–1.92	0.59–3.03	0.27–1.52		0.49
Mexican-American Women						
No. Cases	30	18	5	8		
RR	1.0	0.87	0.32	0.72		
95% CI		0.36–2.07	0.15–69	0.18–2.82		0.39

* Adjusted for age, race/ethnicity, smoking history (never, former/current<20 packyrs, ≥20 packyrs, current-unknown packyrs), BMI (<25, 25–<30, ≥30 kg/m², missing), using Cox proportion hazards regression. Trend was based on 25(OH)D as a continuous variable. Categories were selected to reflect alternative cut-points of 25(OH)D insufficiency and the full range of 25(OH)D values.

Relative Risks (RR) at 95% Confidence Intervals (CI) between baseline serum 25(OH)D levels (nmol/L) and site-specific cancer mortality in the NHANES III study, 1988–2006.*

Table 4

	<50	50–<80	80–<100	≥100	P-Trend
Lung Cancer[†] (Men and Women)					
No. Cases	86	90	42	34	
RR (95% CI)	1.0	1.09 (0.75–1.57)	0.99 (0.58–1.70)	1.50 (0.90–2.52)	0.15
Men					
No. Cases	52	52	30	31	
RR (95% CI)	1.0	0.93 (0.58–1.49)	1.19 (0.74–1.92)	1.87 (1.04–3.34)	0.03
Women					
No. Cases	34	38	15		
RR (95% CI)	1.0	1.35 (0.73–2.48)	0.64 (0.23–1.79)		0.34
Colorectal Cancer[‡] (Men and Women)					
No. Cases	38	34	14	9	
RR (95% CI)	1.0	0.56 (0.29–1.09)	0.61 (0.26–1.47)	0.35 (0.11–1.14)	0.09
Men					
No. Cases	22	23	16		
RR (95% CI)	1.0	0.61 (0.24–1.57)	0.71 (0.25–1.99)		0.26
Women					
No. Cases	16	11	17		
RR (95% CI)	1.0	0.55 (0.21–1.45)	0.37 (0.11–1.27)		0.23
Other Digestive Cancers[§] (Men and Women)					
No. Cases	36	51	31		
RR (95% CI)	1.0	1.69 (0.77–3.74)	1.31 (0.61–2.81)		0.15
Men					
No. Cases	20	29	23		
RR (95% CI)	1.0	1.72 (0.76–3.88)	1.61 (0.75–3.47)		0.01
Women					
No. Cases	16	22	8		
RR (95% CI)	1.0	1.72 (0.58–5.10)	0.99 (0.31–3.11)		0.47
Female Breast					

	<50	50–<80	80–<100	≥100	P-Trend
No. Cases	24	19	10		
RR (95% CI)	1.0	0.94 (0.40–2.20)	0.65 (0.18–2.38)		0.56
Prostate Cancer					
No. Cases	16	38	20		
RR (95% CI)	1.0	1.39 (0.70–2.76)	1.23 (0.50–3.05)		0.84
NHL/Leukemia (Men and Women)					
No. Cases	17	25	16		
RR (95% CI)	1.0	0.92 (0.44–1.92)	1.10 (0.40–2.98)		0.96
Miscellaneous Cancers[¶] (Men and Women)					
No. Cases	73	108	53		
RR (95% CI)	1.0	1.66 (1.06–2.60)	1.36 (0.71–2.59)		0.90
Men					
No. Cases	28	58	28		
RR (95% CI)	1.0	1.04 (0.50–2.16)	0.83 (0.33–2.29)		0.40
Women					
No. Cases	45	50	25		
RR (95% CI)	1.0	2.15 (1.12–4.15)	1.85 (0.74–4.64)		0.39

* Adjusted for age, gender, race/ethnicity, smoking history and BMI, using Cox proportional hazards regression.

[†] Includes cancers of the lung, trachea and bronchus.

[‡] Includes colorectal and anal cancer mortality.

[§] Includes esophageal, stomach, liver, pancreatic cancer.

[¶] Includes cancers of the buccal cavity, larynx, melanoma, gynecological sites, kidney, bladder, brain, multiple myeloma, and others.