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Serum Vitamin D and Risk of Pancreatic Cancer in the Prostate, Lung, Colorectal, and Ovarian Screening Trial

Rachael Z. Stolzenberg-Solomon[1], **Richard B. Hayes**[2], **Ron L. Horst**[3], **Kristin E. Anderson**[4], **Bruce W. Hollis**[3], and **Debra T. Silverman**[2]

[1]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Rockville, Maryland [2]Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Rockville, Maryland [3]Heartland Assays, Inc., Iowa State University, Ames, Iowa [4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota

Abstract

Experimental evidence suggests that vitamin D has anti-carcinogenic properties; however, a nested case-control study conducted in a population of male Finnish smokers found that higher 25-hydroxyvitamin D [25(OH)D], the best indicator of vitamin D status as determined by the sun and diet, was associated with a significant 3-fold increased risk for pancreatic cancer. We conducted a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Screening Trial cohort of men and women 55 to 74 years of age at baseline to test whether prediagnostic serum 25(OH)D concentrations were associated with pancreatic cancer risk. Between 1994 and 2006, 184 incident cases of pancreatic adenocarcinoma occurred (follow-up to 11.7 years). Two controls (n = 368) who were alive at the time the case was diagnosed were selected for each case and matched by age, race, sex, and calendar date of blood draw (to control for seasonal variation). We calculated odds ratios (OR) and 95% confidence intervals (95% CI) using conditional logistic regression, adjusting for smoking and body mass index. Vitamin D concentrations were not associated with pancreatic cancer overall (highest versus lowest quintile, >82.3 versus <45.9 nmol/L: OR, 1.45; 95% CI, 0.66–3.15; P trend = 0.49). However, positive associations were observed among subjects with low estimated annual residential solar UBV exposure, but not among those with moderate to high annual exposure (P interaction = 0.015). We did not confirm the previous strong positive association between 25(OH)D and pancreatic cancer; however, the increased risk among participants with low residential UVB exposure is similar.

Introduction

For most people, more than 90% of their vitamin D status is produced endogenously from exposure of the skin to solar UVB light (280–320 nm) synthesizing cutaneous production of precursors to 25-hydroxyvitamin D [25(OH)D; refs. 1–4]. Dietary sources of vitamin D

Requests for reprints: Rachael Stolzenberg-Solomon, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, 6120 Executive Boulevard, Suite 320, Rockville, MD 20852. Phone: 301-594-2939; Fax: 301-496-6829; rs221z@nih.gov.

Disclosure of Potential Conflicts of Interest

R.L. Horst is the president and chief executive officer of Heartland Assay, Inc. B.W. Hollis is a consultant to DiaSorin Corp, which conducted the assays for this analysis. The other authors disclosed no potential conflicts of interest.

include cholecalciferol (D_3) that occurs naturally in some animal foods (i.e., fatty saltwater fish, liver, and egg yolk), ergocalciferol (D_2) from plants used in pharmaceutical preparations, and fortified foods (D_2 and D_3) such as milk and margarine (5). Dietary sources, however, are relatively weak predictors of vitamin D status (6). 25(OH)D is the major circulating vitamin D metabolite and the best indicator of vitamin D exposure and status as determined by the sun and diet (7). Some ecological studies have shown residing in geographic areas with greater sun exposure is correlated with lower death rates for pancreatic cancer in Caucasian (3,4,8), Japanese (2,9), and African-American (1) populations. Several factors associated with reduced 25(OH)D status, such as age, obesity, and African-American ethnicity (10), have also been associated with pancreatic cancer. These observations have contributed to the hypothesis that higher vitamin D status may be related to lower pancreatic cancer risk.

There is experimental evidence suggesting that vitamin D may have anticarcinogenic properties, including for exocrine pancreatic cancer (11–17). Extrarenal synthesis of 1,25 α-dihydroxyvitamin D [$1,25(OH)_2D$], the hormonally active vitamin D form, is involved in autocrine and paracrine regulation of cell differentiation, proliferation, apoptosis, and angiogenesis, processes implicated in carcinogenesis (5). Expression of $25(OH)D_3$-1α-hydroxylase, the enzyme that catalyses 25(OH)D to $1,25(OH)_2D$, has been observed in pancreatic duct cells, and normal and adenocarcinomatous tissue (18–20). Pancreatic cancer cell line growth is inhibited by $25(OH)D_3$ (19,20). 1,25 Vitamin D analogues inhibit pancreatic cancer cell proliferation, induce differentiation, and promote apoptosis *in vitro* (11,12) and inhibit pancreatic tumor growth *in vivo* (16,17). Pancreatic islet cells possess vitamin D receptors (VDR) and express $25(OH)D_3$-1α-hydroxylase (21) and *in vitro* evidence supports the involvement of vitamin D in the regulation of insulin synthesis, binding, and responsiveness (22,23). Endocrine pancreatic function may have implications in pancreatic carcinogenesis because diabetes and higher glucose and insulin concentrations have been linked to pancreatic cancer development in epidemiologic (24–26) and experimental studies (27). Therefore, it is possible that 25(OH)D status could affect pancreatic function and play a role in pancreatic cancer etiology.

The results from recent epidemiologic studies examining associations between vitamin D intake, predicted 25(OH)D status score, or biochemically measured 25(OH)D status and pancreatic cancer, however, have been conflicting. Two prospective studies suggested protective associations for pancreatic cancer with higher total vitamin D intake (28) and predicted vitamin D status score, calculated from six determinants of 25(OH)D (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure activity; ref. 10). The greatest limitation of these studies is that vitamin D status was not directly measured. In contrast, a nested case-control study conducted in the Alpha-Tocopherol, Beta-Carotene (ATBC) Study population of male Finnish smokers found that higher vitamin D status, as determined by prediagnostic 25(OH)D measured in cases and controls, was associated with a significant close to 3-fold increased risk for pancreatic cancer and with a significant positive trend (29). The risk was stronger among men who had their blood collected during the winter months (29). This finding was unexpected and needs replication. In addition, the results may not be generalizable to nonsmokers, women, or populations residing at geographic latitudes lower than Finland with higher vitamin D status (29).

Given the conflicting results from the recent epidemiologic studies examining vitamin D and pancreatic cancer, we conducted a nested case-control study in the Prostate, Lung, Ovarian, and Colorectal Cancer Screening Trial (PLCO) cohort of men and women to test whether prediagnostic serum 25(OH)D concentrations were prospectively associated with risk of

incident pancreatic cancer. The PLCO study is a large, multicenter randomized trial that includes participants residing in regions at varying latitudes throughout the United States.

Materials and Methods

Study design and population

The PLCO cohort has been previously described in detail (30). Briefly, PLCO is a large, randomized multicenter trial in the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC) that is testing the effectiveness of early detection procedures for prostate, lung, colorectal, and ovarian cancer. Randomization of 152,810 men and women aged 55 to 74 y began in November 1993 and was completed in July 2001. Subjects with a personal history of one of the four PLCO cancers or those currently undergoing treatment for any cancer, except nonmelanoma of the skin, as well as subjects who had been screened for prostate or colorectal cancer during the prior 3 y were excluded from the trial. Subjects randomized to the intervention arm underwent periodic cancer screening tests, including chest X-ray, flexible sigmoidoscopy, prostate-specific antigen, and digital rectal exams (men) and cancer antigen 125 and transvaginal ultrasound (women). Participants in the control arm followed their usual medical care practices. The study was approved by the institutional review boards of the 10 screening centers as well as the U.S. National Cancer Institute. All participants provided informed consent.

Ascertainment of case and control selection

Vital status of cohort participants and pancreatic cancer cases was identified by self-report in the annual mail-in survey, state cancer registries, death certificates, physician referrals, and reports from next of kin for deceased individuals. All medical and pathologic records related to pancreatic cancer diagnosis and supporting documentation were obtained and abstracted by trained medical record specialists for cancer confirmation. For these analyses, we included incident primary adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, 3rd edition code C250–C259). Our case definition excluded endocrine pancreatic tumors (histology type, 8150, 8151, 8153, 8155, 8240) because the etiology of these cancers is thought to be different from exocrine pancreas. One hundred eighty-four incident cases of pancreatic adenocarcinomas occurred between 1994 and 2006 (follow-up to 11.7 y; median, 5.4 y). One hundred sixty-six pancreatic cancer cases (90.2%) were confirmed through medical review. Analyses that excluded the nonconfirmed cancers did not noticeably differ from those based on all cases; therefore, we included all ascertained cases in our analysis to increase the statistical power.

Controls were selected from all PLCO study participants with serum samples and who were alive at the time the case was diagnosed. Two controls were matched to each case by age (±5 y), race, sex, and calendar date of blood draw in 2-mo blocks (to control for seasonal variation in the analysis).

Biomarkers

Nonfasting blood samples were collected using a 10 mL red top blood tube at study year T0 from the intervention arm participants and processed within 2 h of collection, either on site or at a designated processing laboratory into fractions, and stored at −70°C. Aliquoted frozen samples were sent to Heartland Assays (Ames, IA) and analyzed using a RIA method for 25(OH)D status (31), which includes vitamin D_2 and D_3 from plant and animal foods, as well as that synthesized endogenously. Case and control specimens were handled in the same standard manner, and the laboratory was blinded to case-control status. Matched serum case and control samples were analyzed consecutively as triplets within batches and blinded

replicate "phantom" samples from two pooled samples were placed in triplicate toward the beginning and end of each batch and comprised 10% of each batch. Using a nested components of variance analysis, with logarithmically transformed quality control measurements across all batches (32), the estimated overall (intrabatch and interbatch) coefficient of variation percent of the 25(OH)D assay was 4.7%.

Assessment of diet, vitamin/mineral supplements, and baseline characteristics

At the initial screening exam, study subjects completed a self-administered baseline questionnaire that included medical history, family history of cancer, reproductive history, hormone and oral contraceptive use, tobacco use, use of selected drugs, height, weight, physical activity, and exposure to other risk factors. Dietary intake was assessed using a food frequency questionnaire, which used a grid format to determine the frequency of 137 food items over the past 12 mo, 77 of which inquired about usual portion size.[5] Supplemental vitamin and mineral use was assessed for 14 types of supplements by asking number of pills and whether the supplement was taken currently or 2 or 5 y ago for each supplement. Supplemental vitamin D use and dose was derived from the multivitamin (e.g., one-a-day and therapeutic or high-dose type—100% Recommended Dietary Allowance) and vitamin D supplement (including in combination with calcium) questions.

Statistical analysis

We compared the distribution of selected characteristics of the cases and controls using the Wilcoxon rank sum test for the continuous variables and χ^2 tests for categorical variables (Table 1). Means and proportions of baseline characteristics among the controls across 25(OH)D quintiles were calculated to help identify potential confounders (Table 2). Variables examined in analyses and/or as potential confounders in risk models were age; smoking status (never, former, current) and history (number of cigarettes smoked per day, years smoked, pack-years, smoking cessation); education; height, weight, body mass index (BMI); history of diabetes, gallbladder disease, dietary nutrients from foods (energy, carbohydrate, fat, saturated fat, ω-3 fatty acids, saturated fat, calcium, vitamin D, folate), multivitamin use, supplements (folic acid, vitamin D, and calcium), and total (folate, vitamin D, calcium, and vitamin A quantified in retinol equivalents); vitamin D–containing foods (fish, milk, eggs, and margarine), red meat, and alcohol intake; physical activity; season; and UVB residential region at study entry. BMI was categorized to be consistent with the WHO obesity classifications as <25 (normal), 25 to <30 (overweight), and >30 kg/m^2 (obese; ref. 33).

Dietary nutrients and foods highly correlated with energy were energy adjusted using the residual method described by Willett and Stampfer (34). Cutaneous synthesis of pre-vitamin D_3 is affected by exposure to UV light and thus varies by season and geographic residency. Therefore, both season and estimated annual UVB residential region exposure variables were created. Blood collected in March to August (n = 214 controls) had average 25(OH)D concentrations >65 nmol/L each month and were categorized as reflecting the sunny or summer/spring season, whereas blood collected in September to February (n = 154 controls) had average concentrations <65 nmol/L each month and were categorized as reflecting the darker or fall/winter season. The UVB residential regions were based on annual Robertson-Berger (R-B) units in states in which PLCO screening centers are located: low sun (R-B ≤ 105: Detroit, MI; Minneapolis, MN; Marshfield, WI), moderate sun (R-B = 113–134: Pittsburgh, PA; St. Louis, MO; Denver CO; Washington, DC; Salt Lake City, UT), and high sun (R-B ≥ 154: Birmingham, AL; Honolulu, HI; ref. 35). R-B meters are estimates for UVB radiation exposure and are based on surface level readings from meters that were

[5] http://www.cancer.gov/prevention/plco/DQX.pdf

placed at ground level at various National Weather Service stations (35). The meters were calibrated to an action spectrum that parallels that which causes human skin erythema or damage and provide readings that weights the UVB wavelengths by their relative erythema response (35). R-B units consider latitude, altitude, and cloud cover (35).

Conditional logistic regression was used to calculate odds ratios (OR) for pancreatic cancer with subjects in the lowest quintile as the referent. Multivariable models were developed by individually adding covariates to disease and the risk factor and changed the point estimate of risk >10%. BMI was included in the models because it is considered a putative risk factor for pancreatic cancer. Recent multivitamin use or total retinol equivalents for vitamin A intake were not significantly associated with pancreatic cancer and did not confound the 25(OH)D/pancreatic cancer association. The final multivariable models included BMI (median trend of WHO categories) and smoking (never, former quit >15 y ago, former quit <15 y ago, current). We also conducted a lag analysis that excluded the cases that occurred during the first 2 and 5 y of follow-up to evaluate the potential influence of preclinical disease on the association between vitamin D concentrations and pancreatic cancer.

Effect modification of 25(OH)D status on pancreatic cancer risk by season, residential regions (low or moderate/high estimated UVB annual exposure), smoking status (never, former, current or never, ever), sex, physical activity, and retinol equivalents of total vitamin A intake (median split of controls and continuous) was evaluated with cross-product terms of vitamin D status quantile trend with the modification variables in multivariable models and stratified analyses. For analyses stratified by season, quintiles for vitamin D status were examined based on (*a*) the distribution of all the controls, (*b*) the distribution of controls within each season strata, and (*c*) merging subjects in the season-specific vitamin D quintile categories together with dummy variables. For evaluation of effect modification by smoking and residential region (factors not matched), we calculated ORs for the joint effects of 25(OH)D concentrations with smoking and residential region, respectively. As very few subjects were current smokers, the smoking interaction was performed using the median split of 25(OH)D concentrations in the controls.

All statistical analyses were performed using Statistical Analytic Systems software and statistical tests were two tailed. Because cases and controls were matched and we used conditional logistic regression, all risk estimates should be interpreted as adjusted for the matching factors (age, race, sex, and date of blood draw).

Results

Cases and controls were similar with respect to most baseline characteristics shown in Table 1. Compared with the controls, cases more often reported being a current smoker ($P < 0.0002$). Cases and controls did not significantly differ by 25(OH)D concentrations and the proportion with vitamin D inadequacy (<40 nmol/L) or deficiency (<25 nmol/L; ref. 7). The range of 25(OH)D concentrations in cases was 13.2 to 135.5 nmol/L and in controls was 16.2 to 126.0 nmol/L.

Table 2 shows the means and proportions of selected baseline characteristics among the controls according to quintile of 25(OH)D concentrations. Higher vitamin D status was directly related to blood that was collected during the sunny season, residing in regions with high annual UBV exposure, white ethnicity, former smoker status, exercising >4 hours per week, high milk consumption, high vitamin D or calcium intake based on food and/or supplements, and high supplemental and total folate intake (P trend < 0.05). In contrast, Black or Hispanic ethnicity exercising <1 hour per week, higher BMI, and higher red meat intake was related to lower 25(OH)D status (P trend < 0.05).

Higher concentrations of 25(OH)D were not associated with pancreatic cancer [highest compared with lowest quintile; OR, 1.45; 95% confidence interval (95% CI), 0.66–3.15; *P* trend = 0.49; Table 3) overall. The adjusted ORs for each respective quartile compared with the first after the exclusion of the cases that occurred during the first 2 years (*n* = 153 cases in analysis) were 0.78, 0.98, and 1.47 (95% CI, 0.70–2.99; *P* trend = 0.30) and 5 years (*n* = 105 cases in analysis) were 0.52, 1.27, and 2.21 (95% CI, 0.92–5.30; *P* trend = 0.06). The association was not significantly modified by season of blood collection (*P* interaction > 0.14); however, among subjects who had their blood drawn during the fall and winter months, the highest quintile of 25(OH)D tended to be positively associated with pancreatic cancer (compared with the lowest quintile; OR, 3.91; 95% CI, 1.19–12.85; *P* trend = 0.10, based on the distribution of all controls; OR, 2.89; 95% CI, 0.83–10.10; *P* trend = 0.15, based on distribution of within fall/winter strata controls).

Estimated residential annual solar UVB exposure significantly modified the 25(OH)D status/pancreatic cancer association (*P* interaction = 0.015; Table 4). In the joint effects models, among subjects with low estimated annual UBV residential exposure, higher compared with lower 25(OH)D concentrations were positively associated with pancreatic cancer (compared with first quintile, the ORs for each respective quintile were 2.52, 2.33, and 4.03; 95% CI, 1.38–11.79), whereas among subjects with moderate to high residential UBV exposure, 25(OH)D concentrations were not associated with pancreatic cancer.

There was no significant interaction of 25(OH)D status and pancreatic cancer by smoker status (*P* interaction = 0.25), sex (*P* interaction = 0.27), physical activity (*P* interaction = 0.66), or total vitamin A intake (*P* interaction > 0.93; data not shown).

Discussion

We did not observe a reduced risk between prediagnostic vitamin D status, as assessed by 25(OH)D concentrations, and pancreatic cancer risk in this nested case-control study conducted in an American population of men and women. Overall, the highest quintile of vitamin D status was associated with a nonsignificant 45% increased pancreatic cancer risk compared with lower vitamin D status. The positive association seemed somewhat stronger and U shaped with exclusion of cases that occurred during the first 5 years of follow-up. The associations tended to be stronger among participants who had their blood collected during the fall and winter months compared with those collected in the spring and summer months. We observed a significant interaction of the association between 25(OH)D and pancreatic cancer by estimated annual residential exposure to solar UVB light (*P* interaction <0.015) such that significant positive associations were observed with increasing 25(OH)D concentrations among those living in areas of low annual solar UVB exposure, whereas no gradient of risk was observed among those living in regions with moderate to high annual solar UBV exposure. None of the associations showed significant trends across quantiles.

In the nested case-control study conducted in the ATBC population of male Finnish smokers, higher prediagnostic serum 25(OH)D concentrations were associated with a close to 3-fold risk of pancreatic cancer in men with concentrations >65.5 nmol/L compared with those with concentrations <32.0 nmol/L (OR, 2.92; 95% CI, 1.56–5.48; *P* trend = 0.001) and risks were stronger among men who had their blood drawn in the winter season (29). Although positive associations were observed for pancreatic cancer in the present PLCO study, they were not as strong as that observed in the ATBC study. Notable differences between the ATBC and the PLCO populations include gender, smoking history, and geographic location. We did not observe significant interactions by gender or smoking status in the present study; however, we have limited power to observe interactions by smoking because few subjects are current smokers (35 cases and 25 controls). The associations that

we observe are therefore primarily in nonsmokers. Overall, men in the ATBC study had considerably lower vitamin D status compared with those in the PLCO study, which is likely explained by Finland's northern latitude (60°) with less solar UVB photon exposure compared with the locations of the PLCO screening centers (21° in Hawaii to 44° in Minnesota). The median concentration for 25(OH)D was 46.3 nmol/L and 65.15 nmol/L for ATBC and PLCO controls, respectively, with 40% and 13%, correspondingly in the range of inadequacy (<40 nmol/L; refs. 7,29).

Although higher compared with lower 25(OH)D concentrations have shown fairly consistent protective associations for colorectal adenoma and cancer (36–38), most epidemiologic research has not shown clear associations between vitamin D status and other cancers (36–39). In addition to the ATBC pancreatic cancer study (29), several well-conducted studies in varying populations have reported subjects with lower measured 25(OH)D concentrations or in the range of vitamin D deficiency (<25 nmol/L) relative to higher concentrations being associated with a reduced risk for prostate cancer (40–42) and esophageal squamous cell cancer (43) and dysplasia (44). The subjects in some of these studies had relatively low average vitamin D status (29,40,43,44). Given the similarity of results in these studies, it is possible that a mechanism related to low vitamin D status, such as its connection with growth factors (22,23,45), might influence the promotion of tumor growth (29). Mechanisms that may explain these associations are highly speculative because there is a lack of understanding of the molecular mechanism by which $1,25(OH)_2D$ and the VDR regulate the expression of genes involved in carcinogenesis.

The positive association in the present PLCO study with increasing 25(OH)D concentrations among those having blood collected in the fall and winter months and among subjects living in residential regions at northern latitudes with low estimated annual solar UVB light exposure (i.e., Michigan, Minnesota, and Wisconsin with R-B units ≤105) is similar to the previous ATBC results (29). Stratifying by season and geographic residence are methods to address misclassification due to seasonal variation and within-person variability from sun exposure in warmer climates. Vitamin D status is predominantly determined by solar UVB exposure and known to display seasonal variability (7). Other studies have also reported more pronounced cancer associations among subjects who donated blood during the fall/winter months than the spring/summer months (29,46). Individuals with high vitamin D concentrations during the sunny months may have either high or low vitamin D concentrations during the winter months, whereas those with high 25(OH) vitamin D during the winter months may have consistently higher vitamin D status throughout the year, regardless of season (46). The misclassification of exposure during the sunny months could also explain the stronger associations among subjects who provided blood in the darker months. Kimlin and colleagues determined "vitamin D UV" radiation across varying latitude, throughout the year, within the United States using measurements from the U.S. Environmental Protection Agency Brewer Spectrophotometer network (47,48). Within the United States, vitamin D UV is relatively high at lower latitudes with warmer climates compared with higher latitudes and does not vary by season (47,48). Therefore, the geophysical data support that subjects residing at low latitudes with sunny warm climates have vitamin D UV exposure that could sustain efficient vitamin D synthesis with incidental sun exposure throughout the year. The latter could contribute to greater within-person variability for ambulatory individuals. This could account for the lack of association that we observe among participants residing at lower latitudes with greater estimated annual UVB exposure.

The strength of our study is that it is prospective with vitamin D status being assessed up to 11 years before cancer diagnosis, thereby reducing the influence of reverse causality. The PLCO cohort on average does not have extended follow-up (up to 11 years; median, 5.4

years) and the pancreatic cancer risks we observed may become stronger with extended follow-up as evident in the lagged analysis. Our study has internal validity as both cases and controls are derived from the same cohort. The measurement of serum 25(OH)D concentrations reflects internal dose and status, which encompasses cutaneous production of the vitamin and is considered superior to vitamin D intake alone or predictors of vitamin D status. A single measurement of 25(OH)D in adulthood may not reflect long-term vitamin D status. In a steady-state context, it represents the past several weeks to several months of exposure (49) and associations between one measure of 25(OH)D and cancer have been reported by others (37,46). Tominimize misclassification of vitamin D status due to seasonal variation, we matched the controls to the cases by month of blood collection. High vitamin D dietary sources (i.e., vitamin D intake, milk, and vitamin D supplements) and variables related to endogenous vitamin D synthesis (i.e., season, residency at southern latitude, physical activity, and race/ethnicity) were associated with vitamin D status in the expected manner (10), which lends external validity to our results. Residual confounding by cigarette smoking is possible, however, not likely because few subjects are current smokers and current smoking tended to be associated with lower rather than higher vitamin D status. In addition, former smoking was not significantly associated with pancreatic cancer in our study (former compared with never smoker OR, 1.08; 95% CI, 0.64–1.78). Men and women, as well as never, former, and current smokers, were included in this study, making our results generalizable to the American population. Finally, we cannot exclude the possibility that a correlate to serum vitamin D status that is unknown and not controlled could explain the association we observe.

In conclusion, we did not confirm the strong positive association between 25(OH)D and pancreatic cancer observed in the earlier study in male Finnish smokers. The increased risks among participants who had their blood drawn during the winter months and living in regions with estimated low UVB exposure are similar to the previous study; however, the result should be interpreted with caution. Neither study results support the hypothesis that higher vitamin D status plays a protective role in pancreatic cancer carcinogenesis. More epidemiologic research is needed, particularly large prospective studies that relate vitamin D status to pancreatic cancer in populations with a wide range of 25(OH)D concentrations and can better evaluate interactions by residential UVB solar exposure and smoking status. There are also many research gaps in the understanding of the role of vitamin D in carcinogenesis, particularly related to benefits and possibly harm with greater vitamin D exposure (36–38). Therefore, caution is warranted before public health recommendations related to cancer prevention can be established about increasing vitamin D levels in healthy individuals as well as cancer survivors.

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Table 1

Selected baseline characteristics of case and cohort control subjects (median and interdecile range or number and proportion)

Characteristics	Cases (*n* = 184)	Controls (*n* = 368)	*P**
Age (y)	66 (59.0–72.0)	66 (58.0–72.0)	0.83
Sex, male, *n* (%)	120 (65.2)	240 (65.2)	1.00
Serum 25(OH)D (nmol/L)	64.3 (32.12–94.81)	65.15 (35.78–89.92)	0.76
Vitamin D inadequacy (<40 nmol/L), *n* (%)	30 (16.3)	47 (12.8)	0.26
Vitamin D deficiency (<25 nmol/L), *n* (%)	5 (2.7)	14 (3.8)	0.51
Residential sun exposure at study entry,† *n* (%)			
Low sun	91 (49.5)	167 (45.4)	0.61
Moderate sun	78 (42.4)	172 (46.7)	
High sun	15 (8.1)	29 (7.9)	
Race, *n* (%)			
White	166 (90.2)	332 (90.2)	1.00
Black	6 (3.3)	12 (3.3)	
Hispanic	3 (1.6)	6 (1.6)	
Asian	9 (4.9)	18 (4.9)	
Cigarette smoking history, *n* (%)			
Never	72 (39.1)	171 (46.5)	<0.0001
Former	77 (41.9)	172 (46.7)	
Current	35 (19.0)	25 (6.8)	
Cigarette smoking history, *n* (%)			
Never	72 (39.1)	171 (46.5)	0.0002
Former quit >15 y	47 (25.5)	110 (29.9)	
Former quit <15 y	30 (16.3)	62 (16.9)	
Current	35 (19.0)	25 (6.8)	
Height (cm)			
Male	177.8 (167.6–185.5)	177.8 (168.9–185.4)	0.73
Female	162.6 (152.4–170.2)	162.6 (152.4–170.2)	0.78
BMI (kg/m^2)	26.7 (22.3–32.7)	26.3 (22.0–33.0)	0.17
WHO cut points, *n* (%)			
<25.0	56 (30.4)	131 (35.9)	0.28
>25.0 and <30	83 (45.1)	166 (44.8)	
≥30	45 (24.5)	71 (19.3)	
Medical history, *n* (%)			
Diabetes mellitus	22 (12.4)	36 (9.8)	0.43
Gallbladder disease	30 (16.3)	43 (11.7)	0.11
Family history of pancreatic cancer, *n* (%)	6 (3.28)	8 (2.19)	0.44
Education, *n* (%)			
Less than high school	14 (7.6)	39 (10.6)	0.53
High school graduate	48 (26.1)	83 (22.6)	

Characteristics	Cases (*n* = 184)	Controls (*n* = 368)	*P**
Post–high school, vocational training	20 (10.9)	41 (11.1)	
Some college	37 (20.1)	67 (18.2)	
College graduate	37 (20.1)	64 (17.4)	
Post–college graduate	28 (15.2)	74 (20.1)	
NSAID use, yes, *n* (%)‡	102 (55.4)	219 (59.5)	0.36
Dietary intake per day§			
Vitamin D–rich foods			
Ω-3 fatty fish (g)	0.11 (0.04–0.37)	0.12 (0.04–034)	0.81
Eggs (g)	9.3 (1.2–24.6)	10.0 (1.78–27.81)	0.16
Milk (g)	269.4 (11.9–654.5)	263.6 (4.1–649.0)	0.48
Red meat (g)	74.8 (32.0–128.7)	74.7 (23.4–134.0)	0.50
Alcohol (g)	1.54 (0.0–39.1)	1.05 (0.0–33.7)	0.24
Nutrients			
Energy (kcal)	1,842 (1,174–3,021)	1,987 (1,186–3,298)	0.14
Total fat (g)	69.9 (54.7–88.3)	70.0 (55.7–85.6)	0.91
Saturated fat (g)	23.5 (15.8–31.4)	23.7 (17.4–30.5)	0.74
Carbohydrate (g)	275.3 (221.3–343.1)	280.0 (227.9–333.0)	0.22
Total vitamin A (RE)‖	1,734 (770–3,472)	1,658 (863–4,045)	0.51
Folate from diet	453.0 (334.8–641.7)	443.1 (329.3–617.9)	0.65
Total folate	651.9 (361.8–1,161.0)	603.8 (368.9–1,006.1)	0.23
Vitamin D			
Food (μg)	5.6 (2.9–8.7)	5.3 (2.8–8.9)	0.66
Supplemental (μg)	0 (0–10)	0 (0–10)	0.65
Total vitamin D (μg)	10.5 (3.1–23.1)	9.2 (3.6–23.4)	0.99
Calcium			
Food (mg)	937 (656–1,425)	967 (638–1,363)	0.87
Supplemental (mg)	0 (0–412)	0 (0–500)	0.71
Total (mg)	1,091 (710–1,942)	1,133 (732–1,776)	0.76
Vigorous physical activity, hours per week,¶ *n* (%)			
None or <1 h	66 (37.7)	110 (31.3)	
1–3 h	72 (41.1)	144 (41.6)	
>4 h	37 (21.1)	92 (26.6)	0.27

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; RE, retinol equivalents.

*P values for categorical variables based on χ^2 or Fisher's exact test and P values for continuous variables based on Wilcoxon rank sum test.

†Residential regions based on ranges of UV radiation levels obtained from annual R-B meters in states in which screening centers are located: low sun (R-B ≤ 105, Detroit, MI; Minneapolis, MN; Marshfield, WI), moderate sun (R-B = 113–134, Pittsburgh, PA; St. Louis, MO; Denver CO; Washington, DC; Salt Lake City, UT), and high sun (R-B ≥ 154, Birmingham, AL; Honolulu, HI; ref. 39).

‡Aspirin or ibuprofen use during the past year.

§All foods and nutrients energy adjusted except supplements and alcohol and based on *n* = 175 cases and 348 controls.

‖Total vitamin A includes vitamin A from foods and supplements in retinol equivalents.

[¶] Vigorous activity variables based on $n = 175$ cases and $n = 346$ controls.

Table 2

Selected characteristics of control subjects (means or proportions) by quintile of serum 25(OH)D concentration

Characteristics	Serum 25(OH)D, nmol/L* (quintiles)				
	Q1	Q2	Q3	Q4	Q5
	<45.9	>45.9 and <60.3	>60.3 and <69.6	>69.6 and <83.5	>83.5
Age (y)	65.7	65.2	64.5	65.8	64.6
Serum 25(OH) vitamin D (nmol/L)	34.4	52.8	64.8	75.1	93.0
Season of blood draw, sunny† (%)	31	51	64	60	85
Residency at study entry‡					
Low sun (%)	47	50	43	42	45
Moderate sun (%)	49	49	45	53	38
High sun (%)	4	1	12	5	16
Sex, male (%)	58.1	66	60	78	63
Race (%)					
White	77	96	90	97	90
Black	15	1	0.00	0.00	0.00
Hispanic	4	1	3	0.00	0.00
Asian	4	1	7	3	10
Smoker status					
Never (%)	50	49	53	39	41
Former smoker (%)	39.2	44.6	41.1	54	55
Current smoker (%)	11	7	6	7	4
Height (cm)					
Male	177.5	176.5	177.0	180.6	176.5
Female	161.5	161.0	162.8	165.4	163.3
BMI (kg/m^2)	28.9	27.3	27.2	26.1	25.4
Medical history					
Diabetes mellitus (%)	14	10	10	8	9
Gallbladder disease (%)	17	13	6	14	11
Family history of pancreatic cancer (%)	0	1.4	4.1	2.7	2.8

Characteristics	Serum 25(OH)D, nmol/L* (quintiles)				
	Q1	Q2	Q3	Q4	Q5
	<45.9	>45.9 and <60.3	>60.3 and <69.6	>69.6 and <83.5	>83.5
Education (%)					
Less than high school	9.5	8.1	9.6	10.8	15.1
High school graduate	24.3	21.6	17.8	25.7	23.3
Post–high school, vocational training	16.2	12.2	8.2	9.5	9.6
Some college	21.6	18.9	16.4	16.2	17.8
College graduate	16.2	10.8	26.0	14.9	19.2
Post–college graduate	12.2	28.4	21.9	23.0	15.1
Recent NSAID use (%)§	58.1	54.1	57.5	64.9	63.0
Dietary intake per day//					
Vitamin D–rich foods					
Ω-3 fatty fish (g)	0.16	0.15	0.16	0.21	0.16
Eggs (g)	13.3	13.8	12.0	15.4	15.2
Milk (g)	220.7	268.8	302.6	379.2	328.7
Red meat (g)	100.9	78.6	75.3	75.6	73.7
Alcohol (g)	12.1	9.7	10.9	12.1	11.5
Nutrients					
Energy (kcal)	2,096	2,214	2,283	2,177	1,998
Total fat (g)	70.2	72.4	69.1	68.9	70.1
Saturated fat (g)	23.7	24.3	23.7	24.3	23.8
Carbohydrate (g)	275.9	279.9	287.2	283.8	277.7
Vitamin D					
Food (μg)	4.9	5.2	5.5	6.6	5.7
Supplemental (μg)	3.8	5.3	5.7	6.3	9.1
Total (μg)	8.7	10.5	11.2	13.0	14.9
Calcium					
Food (mg)	902	964	1,003	1,054	1,018
Supplemental (mg)	141	206	262	196	322
Total (mg)	1,060	1,172	1,268	1,260	1,351

Characteristics	Serum 25(OH)D, nmol/L* (quintiles)				
	Q1	Q2	Q3	Q4	Q5
	<45.9	>45.9 and <60.3	>60.3 and <69.6	>69.6 and <83.5	>83.5
Total vitamin A (RE)¶	1,809	2,035	2,274	2,323	2,513
Folate					
Foods	457.8	461.4	472.7	466.4	469.9
Total folate	603.4	642.4	666.3	684.3	752.9
Physical activity, hours per week (%)					
None or <1 h	37.8	28.4	30.1	33.8	19.2
1–3 h	40.5	40.5	35.6	36.5	42.5
>4 h	12.2	21.6	30.1	25.7	35.6

*25(OH)D quintiles based on distribution of all controls (*n* = 368).

†Sunny season based on blood drawn during March to August (*n* = 214) versus darker season based on blood drawn during September to February (*n* = 157).

‡Residential regions based on ranges of UV radiation levels obtained from annual R-B meters in states in which screening centers are located: low sun (R-B ≤ 105, Detroit, MI; Minneapolis, MN; Marshfield, WI; *n* = 167), moderate sun (R-B = 113–134, Pittsburgh, PA; St. Louis, MO; Denver, CO; Washington, DC; Salt Lake City, UT; *n* = 172), and high sun (R-B ≥ 154, Birmingham, AL; Honolulu, HI; *n* = 29; ref. 39).

§Aspirin or ibuprofen use during the past year.

//All dietary variables adjusted for energy except supplements and alcohol and based on 348 controls with complete diet data.

¶Total vitamin A includes vitamin A from foods and supplements in retinol equivalents.

Table 3

Age- and multivariable-adjusted ORs and 95% CIs of baseline serum 25(OH)D concentration and pancreatic cancer among 184 cases and 368 matched control subjects

	25(OH)D, nmol/L* (quintiles)					*P* trend
	1	2	3	4	5	
	≤45.9	>45.9 and ≤60.3	>60.3 and ≤69.5	>69.5 and ≤82.3	>82.3	
Case/controls (*n*)	44/74	40/74	27/73	31/74	42/73	
Crude OR (95% CI)†	1.00 (reference)	1.00 (0.50–2.00)	0.74 (0.35–1.54)	0.81 (0.39–1.68)	1.28 (0.61–2.66)	0.70
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	0.97 (0.47–1.98)	0.86 (0.40–1.84)	0.84 (0.39–1.80)	1.45 (0.66–3.15)	0.49
Fall and winter season§						
Case/controls, *n* (77/154)	25/50	15/37	10/26	13/29	14/12	
Crude OR (95% CI)†	1.00 (reference)	1.72 (0.66–4.44)	1.44 (0.46–4.50)	0.99 (0.34–2.86)	3.22 (1.01–10.31)	0.18
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	1.95 (0.72–5.27)	1.82 (0.56–5.96)	1.06 (0.35–3.27)	3.91 (1.19–12.85)	0.10
Spring and summer season§						
Case/controls, *n* (107/214)	19/24	25/37	17/47	18/45	28/61	
Crude OR (95% CI)†	1.00 (reference)	0.49 (0.16–1.45)	0.38 (0.13–1.06)	0.49 (0.17–1.46)	0.58 (0.21–1.59)	0.48
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	0.39 (0.13–1.23)	0.38 (0.13–1.14)	0.44 (0.14–1.35)	0.59 (0.20–1.75)	0.55
Lag analysis for cases >5 y after baseline						
Quartiles*	≤49.3	>49.3 and ≤65.2	>65.2 and ≤78.4	>78.4		
Case/controls, *n* (*n* = 105/212)	28/53	16/56	27/50	34/53		
Crude OR (95% CI) †	1.00 (reference)	0.59 (0.24–1.45)	1.19 (0.53–2.65)	1.84 (0.82–4.16)		0.08
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	0.52 (0.20–1.36)	1.27 (0.55–2.89)	2.21 (0.92–5.30)		0.06
Quintiles fasting vitamin D (D2 and D3), nmol/L, by season‖						
Fall and winter season§,‖	≤39.9	>39.9 and ≤49.8	>49.8 and ≤62.4	>62.4 and ≤73.9	>73.9	
Case/controls, *n* (77/154)	17/31	16/31	9/31	12/31	23/31	
Crude OR (95% CI)†	1.00 (reference)	1.20 (0.39–3.73)	1.36 (0.36–5.17)	0.80 (0.23–2.77)	2.13 (0.65–6.94)	0.29
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	1.68 (0.49–5.74)	1.48 (0.37–5.95)	1.12 (0.31–4.07)	2.89 (0.83–10.10)	0.15
Spring and summer season§,‖	≤51.9	>51.9 and ≤65.2	>65.2 and ≤73.2	>73.2 and ≤86.1	>86.1	

	25(OH)D, nmol/L* (quintiles)					*P* trend
	1	2	3	4	5	
	≤45.9	>45.9 and ≤60.3	>60.3 and ≤69.5	>69.5 and ≤82.3	>82.3	
Case/controls, *n* (107/214)	25/43	25/43	20/43	15/43	22/42	
Crude OR (95% CI)†	1.00 (reference)	0.64 (0.26–1.54)	1.15 (0.49–2.75)	0.64 (0.23–1.80)	1.03 (0.38–2.78)	0.88
Multivariable-adjusted OR (95% CI)‡	1.00 (reference)	0.69 (0.27–1.71)	1.33 (0.54–3.23)	0.63 (0.21–1.90)	1.38 (0.43–3.81)	0.66
Quintiles of fasting vitamin D (D2 and D3) combined quintiles by season (above)//,¶						
Case/controls (*n*)	42/72	41/75	29/75	27/73	45/73	
Crude OR (95% CI)	1.00 (reference)	0.77 (0.39–1.55)	1.17 (0.57–2.41)	0.68 (0.31–1.51)	1.33 (0.64–2.78)	0.57
Multivariable-adjusted OR (95% CI)*	1.00 (reference)	0.89 (0.43–1.82)	1.33 (0.63–2.79)	0.77 (0.33–1.77)	1.66 (0.76–2.66)	0.31

*25(OH)D concentration quintiles and quartiles based on distribution of all controls.

†Crude OR adjusted for matching variables (age, race, sex, and date of blood draw based on 2-mo blocks.

‡Adjusted for BMI (median trend WHO categories) and smoking (never, former quit >15 y ago, former quit <15 y ago, current).

§Sunny season based on blood drawn during March to August versus darker season based on blood drawn during September to February (*P* value for interaction by season is 0.14 in crude models and 0.20 in multivariable models).

//Vitamin D quintiles based on distribution of controls within each season strata.

¶Quintiles based on merging subjects within quintiles of each season strata.

Table 4

ORs and 95% CIs for the joint effect of baseline serum 25(OH)D concentration and pancreatic cancer by residential regions

	25(OH)D, nmol/L* (quartile)				*P* interaction
	1	2	3	4	
	<49.3	>49.3 and <65.2	>65.2 and <78.4	>78.4	
Residential sun exposure, low†					
Case/controls, *n* (91/167)	22/44	22/42	21/43	26/38	
Crude OR‡	1.00 (reference)	2.27 (0.86–5.95)	2.06 (0.77–5.54)	3.28 (1.19–9.02)	0.015
Multivariable-adjusted OR (95% CI)§	1.00 (reference)	2.52 (0.92–6.90)	2.33 (0.83–6.48)	4.03 (1.38–11.79)	0.015
Residential exposure, moderate/high†					
Case/controls, *n* (93/201)	33/48	18/50	18/49	24/54	
Crude OR‡	1.89 (0.80–4.42)	0.71 (0.24–2.08)	0.80 (0.28–2.30)	1.29 (0.50–3.37)	
Multivariable-adjusted OR (95% CI)§	1.97 (0.80–4.82)	0.66 (0.22–2.01)	0.91 (0.31–2.71)	1.45 (0.53–3.96)	

*25(OH)D concentration quartiles based on distribution of all controls.

†Residential regions based on ranges of UV radiation levels obtained from annual R-B meters in states in which screening centers are located: low sun (R-B ≤ 105, Detroit, MI; Minneapolis, MN; Marshfield, WI), moderate/high sun (R-B = 113–134, Pittsburgh, PA; St. Louis, MO; Denver CO; Washington, DC; Salt Lake City, UT and R-B ≥154, Birmingham, AL; Honolulu, HI; ref. 35).

‡Crude OR adjusted for matching variables (age, race, sex, and date of blood draw based on 2-mo blocks).

§Models adjusted for BMI (median trend WHO categories) and smoking (never, former quit >15 y ago, former quit <15 y ago, current).