Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2012 January ; 21(1): 82–91. doi:10.1158/1055-9965.EPI-11-0836.

Plasma 25-Hydroxyvitamin D and Risk of Pancreatic Cancer

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Abstract

Background—Laboratory studies suggest vitamin D may inhibit pancreatic cancer cell growth. However, epidemiologic studies of vitamin D and pancreatic cancer risk have been conflicting.

Methods—To determine whether prediagnostic levels of plasma 25-hydroxyvitamin D (25[OH]D) (IDS Inc. enzymeimuunoassay) were associated with risk of pancreatic cancer, we performed a pooled analysis of nested case-control studies with 451 cases and 1167 controls from five cohorts through 2008. Median follow-up among controls was 14.1 years in HPFS, 18.3 years in NHS, 25.3 years in PHS, 12.2 years in WHI, and 14.4 years in WHS. Logistic regression was used to compare the odds of pancreatic cancer by plasma level of 25(OH)D.

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Conflicts of Interest: None

Results—Mean plasma 25(OH)D was lower in cases *versus* controls (61.3 *vs.* 64.5 nmol/L, *P*=0.005). In logistic regression models, plasma 25(OH)D was inversely associated with odds of pancreatic cancer. Participants in quintiles two through five had multivariable-adjusted odds ratios (OR [95% confidence intervals]) of 0.79 (0.56–1.10), 0.75 (0.53–1.06), 0.68 (0.48–0.97), and 0.67 (0.46–0.97); *P*-trend=0.03), respectively, compared to the bottom quintile. Compared to those with insufficient levels (25[OH]D<50 nmol/L), ORs were 0.75 (0.58–0.98) for subjects with relative insufficiency (25[OH]D 50–<75 nmol/L) and 0.71 (0.52–0.97) for those with sufficient levels (25[OH]D≥75 nmol/L). No increased risk was noted in subjects with 25(OH)D≥100 nmol/L, as suggested in a prior study. In subgroup analyses, ORs for the top versus bottom quartile of 25(OH)D were 0.72 (0.48–1.08) for women, 0.73 (0.40–1.31) for men, and 0.73 (0.51–1.03) for Whites.

Conclusions—Among participants in five large prospective cohorts, higher plasma levels of 25(OH)D were associated with a lower risk for pancreatic cancer.

Impact—Low circulating 25(OH)D may predispose individuals to the development of pancreatic cancer.

Keywords

Pancreatic cancer; Vitamin D; Prospective cohort; Epidemiology

INTRODUCTION

Epidemiologic evidence has suggested that adequate circulating vitamin D is associated with health benefits, leading to proposals to increase vitamin D intake in the general population (1–3). Based principally on studies of bone health, a recent report from the Institute of Medicine recommended dietary intake to achieve circulating 25-hydroxyvitamin D (25[OH]D) of >20 ng/ml (50 nmol/L) (4). Laboratory studies suggest that vitamin D and its analogues may inhibit cancer development and growth, including pancreatic adenocarcinoma (5–7). Despite these data, epidemiologic investigations of vitamin D and incident pancreatic cancer have been inconsistent. Ecological studies of latitude variation and ultraviolet B radiation have suggested a possible inverse relationship between vitamin D and pancreatic cancer risk and mortality (8, 9). Studies of vitamin D intake and predicted vitamin D status have also suggested an association between higher vitamin D and reduced pancreatic cancer risk and mortality (10–12). However, studies evaluating circulating 25(OH)D have been conflicting, with some studies reporting an elevated risk for pancreatic cancer among those with the highest levels of plasma 25(OH)D (13–15).

Given the strong laboratory data and conflicting epidemiologic studies, we prospectively examined the association between plasma 25(OH)D and pancreatic cancer risk in five large cohorts of initially healthy men and women, in which plasma samples were collected prior to cancer diagnosis.

MATERIALS AND METHODS

Study Population

Our study population included pancreatic cancer cases and controls from five large, prospective studies: Health Professionals Follow-Up Study (HPFS), Nurses' Health Study (NHS), Physicians' Health Study (PHS), Women's Health Initiative-Observational Study (WHI), and Women's Health Study (WHS). HPFS was initiated in 1986 when 51,529 U.S. men aged 40–75 years working as dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, or podiatrists responded to a mailed questionnaire. NHS was established in 1976 when 121,700 female registered nurses aged 30–55 years responded to a

mailed questionnaire. The participants in these cohorts have subsequently responded to biennial questionnaires to update exposures and disease diagnoses. PHS is a completed randomized trial initiated in 1982 of aspirin and β-carotene among 22,071 male physicians between 40 and 84 years of age. After completion of the randomized components, study participants were followed as an observational cohort. WHI consists of 93,676 postmenopausal women, aged 50 to 79 years, enrolled between 1994 and 1998. The health of these participants is tracked via annual health forms and clinic visits. WHS is a completed randomized trial initiated in 1992 of low-dose aspirin and vitamin E among 39,876 female professionals 45 years of age or older. The trial was closed in 2004, with all study participants followed as an observational cohort. Further details for these cohorts have been provided previously (HPFS (16), NHS (17), PHS (18), WHI (19), WHS (20)). The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA, and participants provided informed consent.

We included all cases of incident pancreatic adenocarcinoma diagnosed through 2008 with available plasma and no prior history of cancer, except non-melanoma skin cancer. Eligible controls were alive, free of cancer at of the date of the case's diagnosis, and provided a blood sample. We randomly selected 2 or 3 controls for each case, matching on cohort, year of birth, smoking status, fasting status, and month of blood draw. Median follow-up among controls was 14.1 years in HPFS, 18.3 years in NHS, 25.3 years in PHS, 12.2 years in WHI, and 14.4 years in WHS.

Incident cases of pancreatic cancer were identified by self-report or during follow-up of a participant's death. Deaths were ascertained from next-of-kin or the postal service and by searching the National Death Index; this method has been shown to capture >98% of deaths (21). For all cases, medical records were reviewed by study physicians blinded to exposure data. Of the 451 pancreatic cancer cases in the analysis, 448 (99.6%) were confirmed by review of medical records, tumor registry data, or death certificates.

Our pooled analysis of nested case-control studies included 501 cases of pancreatic adenocarcinoma and 1175 matched controls from five prospective cohorts. Two cases and five controls were removed due to failure of the assay. One case (and its two matched controls) and one control were removed due to outlier values for 25(OH)D (>300 nmol/L). Due to concern regarding the possible influence of subclinical malignancy on lifestyle choices and plasma 25(OH)D, we excluded 47 cases diagnosed within 2 years of blood draw. To maximize power, matched controls for these cases were maintained in the dataset, resulting in 451 cases and 1167 controls for analysis.

Assessment of Covariates

Individual characteristics and habits were obtained from baseline questionnaires at study enrollment in PHS, WHI, and WHS and from questionnaires preceding the date of blood draw in HPFS and NHS. In all cohorts, data were available for age at blood draw, sex, race/ethnicity, weight, height, smoking status, history of diabetes, multivitamin use, and region of residence. We used body mass index (BMI) as a measure of total adiposity. For HPFS, NHS, WHI, and WHS, energy-adjusted intakes (22) of vitamin D, calcium and retinol were available from validated food frequency questionnaires (23–25).

In HPFS, NHS, and WHI, alcohol intake was calculated in grams/day. In PHS and WHS, participants were asked number of drinks consumed by pre-specified categories. Since 1 standard drink = 13.7 grams of alcohol, harmonized categories included: rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1+ drinks/day. In HPFS, NHS, WHI, and WHS, physical activity was calculated in metabolic equivalent task-hours/week (MET-hr/week), as previously described and validated.(26, 27) In PHS, participants were asked number of times

per week they exercised vigorously (rarely/never, 1–3/month, 1/week, 2–4/week, 5–6/week, 7/week). Assuming a MET score of 6 for vigorous activity and 60-minutes of exercise per episode, we assigned 6 MET-hours for each episode of activity per week to determine the MET-hr/week for PHS participants.

Plasma Samples

Blood samples were collected from 18,225 men in HPFS from 1993–1995, 32,826 women in NHS from 1989–1990, 14,916 men in PHS from 1982–1984, 93,676 women in WHI-OS from 1994–1998, and 28,345 women in WHS from 1992–1995. All blood samples were continuously stored in well-monitored freezers. Details on blood draw procedures, transportation, and storage of plasma samples in these cohorts have been described previously (HPFS (28), NHS (29), PHS (30), WHI (31), WHS (32)).

Plasma levels of 25(OH)D were assayed in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA), using the Immunodiagnostic Systems (Fountain Hills, AZ) 25-Hydroxyvitamin D enzymeimmunoassay kit, as per manufacturer's instructions. All samples were handled identically in a single batch and laboratory personnel were blinded to case, control, or quality control sample. The mean intra-assay coefficients of variance were ≤9% for blinded, replicate, quality control samples

Statistical Analysis

Quintiles of 25(OH)D were created from control subjects in all five cohorts jointly and in each cohort separately. In our primary analysis, we computed odds ratios to estimate relative risks and 95% confidence intervals using unconditional logistic regression, since the case-control match was broken due to exclusion of cases with short lag time between blood draw and cancer diagnosis. We also performed conditional logistic regression among all subjects and after exclusion of cases and matched controls with blood drawn within 2, 3, and 5 years of pancreatic cancer diagnosis. Furthermore, we evaluated cohort-specific quintiles by meta-analysis in age-adjusted models, using a random effects model (33). Of note, due to small numbers in one cohort (WHS: 29 cases/69 controls), multivariable adjustment led to an unstable logistic regression model, precluding meta-analysis of the multivariable-adjusted data. To evaluate whether one cohort unduly influenced the pooled results, we conducted a sensitivity analysis, whereby risk estimates were assessed after individually excluding each cohort in turn. Tests for trend using two-sided *P*-values were calculated by entering the pooled quintile-specific median values for 25(OH)D as a variable in logistic regression models. Given that 25(OH)D was not normally distributed, we also evaluated a "global" trend test by including log-transformed 25(OH)D as a continuous variable in logistic regression models.

By adding each covariate in turn to age-adjusted models, we investigated possible confounders, including sex, cohort, BMI (World Health Organization categories), smoking status (never, past, current), history of diabetes, multivitamin use, physical activity (continuous, MET-hr/wk), alcohol intake (never/rare, 1–3 drinks/month, 1–6 drinks/week, ≥1 drink/day), and total and dietary intakes of calcium (quartiles), retinol (quartiles), and calories (quartiles). In no instance did addition of the covariate change the point estimate of risk by more than 10%. Given that no strong confounders of the relationship between 25(OH)D and pancreatic cancer risk were found, we investigated three models incorporating covariates, as in previous studies (14, 15, 34). The first model adjusted for age. The second adjusted for covariates thought *a priori* to have the greatest potential for confounding, including age, cohort (which also adjusts for sex), BMI (35), smoking status (36), history of diabetes (37), and multivitamin use (38), plus month of blood draw. The third additionally adjusted for fasting time, physical activity (39), alcohol intake (40), and dietary intakes of

calcium (41), retinol (41), and calories (41). In our analysis of multivariable-adjusted quintiles of plasma 25(OH)D and pancreatic cancer risk, no change was noted in risk estimates between the second and third models, so results from the second model are presented.

Although optimal levels of 25(OH)D have not been definitively determined, plasma 25(OH)D <50 nmol/L has been defined as "insufficiency", 50 to <75 nmol/L as "relative insufficiency", and ≥75 nmol/L as "sufficient" (42, 43). Therefore, we investigated the risk of pancreatic cancer for relatively insufficient and sufficient subjects compared to insufficient subjects, using the above cut-points. We also investigated risk among subjects with 25(OH)D ≥100 nmol/L, given a previous study suggesting increased risk specifically among these subjects (15).

We assessed the association of pancreatic cancer risk with plasma 25(OH)D in specific subgroups using cohort-specific quartiles of 25(OH)D, given fewer subjects within these subgroups. Since plasma levels of 25(OH)D may differ by race/ethnicity and gender, we performed separate analyses in Whites, men, and women. In stratified analyses, we assessed for statistical interaction, by entering the main effect terms and a cross-product term of the 25(OH)D quintile trend and binary stratification variable into the model, evaluating likelihood ratio tests. We assessed heterogeneity in the association between 25(OH)D and pancreatic cancer risk across the cohorts using Cochran's *Q*-statistic (44); the Cochran's *Q*-statistic *P*-value was 0.12 for the comparison of the fifth versus the first quintile of plasma 25(OH)D across the cohorts. All statistical analyses were performed with the SAS 9.1 statistical package (SAS Institute, Cary, North Carolina) and all *P*-values are two-sided.

RESULTS

Baseline characteristics of controls by quintile of 25(OH)D and by cohort are shown in Table 1 and Supplemental Table 1, respectively. Mean 25(OH)D was 64.5 nmol/L in control subjects and 61.3 nmol/L in case subjects (Wilcoxon rank-sum *P*=0.005). The global tests for trend were *P*-trend=0.01 in the age-adjusted logistic regression model and *P*-trend=0.03 in the multivariable-adjusted model, evaluating log-transformed, continuous 25(OH)D. Compared to participants in the bottom quintile of 25(OH)D, those in the second, third, fourth, and fifth quintiles had multivariable-adjusted odds ratios (OR [95% confidence intervals]) of 0.79 (0.56–1.10), 0.75 (0.53–1.06), 0.68 (0.48–0.97), and 0.67 (0.46–0.97), respectively (Table 2).

In both a pooled analysis of the raw data (Table 2) and a meta-analysis of the risk estimates, this inverse association was highly similar utilizing cohort-specific quintiles. In the meta-analysis, the age-adjusted OR for the fifth versus first quintile of plasma 25(OH)D was 0.70 (0.43–1.14; *P*-trend=0.03). Finally, the use of conditional logistic regression also resulted in highly similar inverse associations, even after exclusion of cases with successively greater time between blood draw and pancreatic cancer diagnosis and their matched controls (Table 3).

We next investigated clinically-defined cut-points for 25(OH)D (Table 4) (42, 43). Compared to those with insufficient levels of vitamin D, ORs were 0.75 (0.58–0.98) for those with relative insufficiency and 0.71 (0.52–0.97) for those with sufficient levels. After exclusion of each cohort in turn, ORs for pancreatic cancer were similar comparing those with sufficient levels of 25(OH)D to those with insufficient levels: 0.70 (0.51–0.97) when excluding HPFS, 0.63 (0.45–0.88) when excluding NHS, 0.73 (0.53–1.00) when excluding PHS, 0.77 (0.54–1.11) when excluding WHI, and 0.65 (0.48–0.88) when excluding WHS. Given prior data suggesting a possible elevated risk for pancreatic cancer among subjects

with high 25(OH)D (13, 15), we performed an analysis using cutpoints as defined in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (Table 5) (15). No increased risk for pancreatic cancer was noted among subjects with 25(OH)D levels ≥100 nmol/L.

Similar inverse associations were noted in analyses limited to women, men, and Whites (Table 6). No statistically significant interaction of 25(OH)D and pancreatic cancer risk was seen by other potential predisposing factors for pancreatic cancer, or by month of blood draw, region of residence, or fasting status (Supplemental Table 2; all *P*-interaction≥0.18).

DISCUSSSION

In this pooled analysis of five nested case-control studies, we noted a statistically significant inverse association between prediagnostic plasma 25(OH)D and the subsequent risk of pancreatic cancer. A similar inverse relationship was seen across a wide variety of subgroups, including Whites, women, and men. Furthermore, the inverse association was similar regardless of whether blood was drawn in months with low or high ultraviolet light exposure. Analyses of clinically-defined categories of 25(OH)D demonstrated that those subjects with “sufficient” 25(OH)D had an approximate 30% lower risk for pancreatic cancer, compared to those who were vitamin D “insufficient”. No increase in risk for pancreatic cancer was seen among subjects with 25(OH)D ≥100 nmol/L.

Laboratory studies have demonstrated that pancreatic cancer cells express 25(OH)D-1α-hydroxylase (5) which metabolizes 25(OH)D to the active form of 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). These cells also express vitamin D receptors (VDR) (6), which translocate to the nucleus and bind vitamin D response elements to regulate gene expression, upon engagement by $1,25(OH)_2D$. Thus, VDR-target genes may be regulated locally at the site of a developing cancer, with important implications for cellular proliferation, apoptosis, and angiogenesis (45). Lending support to a role for vitamin D in tumorigenesis, vitamin D and its analogues can slow proliferation of pancreatic cancer cells both in cell culture and in xenograft mouse models (5, 6). Clinical studies are underway to exploit these effects of vitamin D and its analogues in patients with pancreatic cancer (46, 47).

Several epidemiologic approaches have investigated vitamin D and the risk of pancreatic cancer. Ecological studies have suggested an increased risk of pancreatic cancer with greater distance from the equator and lesser exposure to ultraviolet B radiation, both within countries and worldwide (8, 9). A study of vitamin D intake demonstrated a reduced risk for pancreatic cancer in subjects with greater total and dietary vitamin D (10). Two studies have examined the risk of pancreatic cancer in relation to predicted vitamin D status, as calculated using a validated predictive model for plasma level of 25(OH)D (11, 12). This model integrated five independent predictors of plasma 25(OH)D, including race/ethnicity, geographic region, vitamin D intake, body-mass index, and physical activity. In the larger of the two studies (12), the top quintile of predicted 25(OH)D was associated with a relative risk of 0.66 (95% CI, 0.46–0.96), compared with the bottom quintile.

In contrast to the above work, two initial studies examining serum 25(OH)D have generated inconsistent results (13, 14). A nested case-control study of male, Finnish smokers from Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study reported a statistically significant elevated risk of pancreatic cancer among subjects in quintiles 3 and 5 of plasma 25(OH)D, compared to quintile 1 (13). In contrast, a nested analysis of men and women within the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Screening trial demonstrated no statistically significant difference in risk of pancreatic cancer by quintile of plasma 25(OH)D (14). Nevertheless, these studies were relatively small in size (200 cases in ATBC and 184 cases in PLCO).

A pooled analysis has also been performed of 952 pancreatic cancer cases, including subjects previously examined from ATBC and PLCO and cases and controls added from several other prospective cohorts in U.S. and China (15). In contrast to the two previous studies, clinically-defined cut-points were used for 25(OH)D (<25, 25–<37.5, 37.5–<50, 50–<75, 75–<100, ≥100 nmol/L), rather than quintiles, and the referent group consisted of subjects with 25(OH)D levels of 50 to <75 nmol/L. As a result of the post-hoc pooled approach of this study, 25(OH)D was measured in multiple batches and in two separate laboratories. This pooled analysis found no association between circulating 25(OH)D and pancreatic cancer risk. However, in the small subset of subjects with 25(OH)D levels ≥100 nmol/L (39 cases and 30 controls), an increase in the risk of pancreatic cancer was observed (OR, 2.12; 95% CI, 1.23–3.64), when compared to those subjects with 25(OH)D levels between 50 and <75 nmol/L.

In light of these conflicting data, the current study has a number of important strengths. Its prospective design and exclusion of cases diagnosed within 2 years of blood draw greatly reduced the likelihood of bias due to reverse causation. The large number of pancreatic cancer cases and controls from diverse geographic locations across the U.S. allowed for the investigation of a wide spectrum of plasma 25(OH)D values, including subjects with 25(OH)D ≥100 nmol/L. All plasma assays for 25(OH)D were performed in a single batch in a single laboratory, and blinded to any identifiers of case and control status. Furthermore, coefficients of variance were low for repeated measures of quality control samples interspersed within participant samples. Pancreatic cancer cases were rigorously coded, with greater than 99% confirmed by review of medical records, state tumor registries or death certificates. Data on covariates were also rigorously collected from all five cohorts, allowing for robust control of confounding and evaluation of effect modification.

Limitations of the current study include having only a single measure of 25(OH)D. However, we have previously demonstrated a correlation of 0.70 for repeated measures of plasma 25(OH)D within individuals over time (48), suggesting that a single measurement is a reasonable proxy for long-term levels of 25(OH)D. We cannot rule out that our findings may be influenced in part by residual confounding. This may be more likely in an analysis involving multiple cohorts, as not all covariate data are collected identically. However, we evaluated multiple possible confounding covariates and did not observe meaningful changes in our risk estimates. Our sample consisted primarily of White subjects and we did not have adequate power to examine the association of 25(OH)D in non-Whites. Nevertheless, the use of five large cohorts with participants from across the U.S. allows for reasonable generalizability of our results to individuals of European descent. Further studies in non-Whites are warranted.

In this pooled analysis of five nested case-control studies, we observed a statistically significant inverse association between plasma 25(OH)D levels and the subsequent risk of pancreatic cancer. As compared to subjects who were vitamin D insufficient (<50 nmol/L; <20 ng/ml), those with relatively insufficient or sufficient levels (≥50 nmol/L; ≥ 20 ng/ml) experienced an approximate 30% lower risk for pancreatic cancer. In light of the high prevalence of vitamin D insufficiency in the population, further studies should examine whether increasing vitamin D levels impacts the incidence of this highly lethal malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding:

The NHS and HPFS are supported by the National Cancer Institute, National Institutes of Health (Grants No. P01 CA87969, P01 CA55075, P50 CA127003, R01 CA124908). Brian Wolpin, MD, MPH is supported by NCI K07 CA140790, an American Society of Clinical Oncology Career Development Award, and a Howard Hughes Medical Institute Early Career Physician-Scientist Award.

The PHS is supported by grants CA 97193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health (Bethesda, MD).

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators is available (49).

The WHS is supported by grants CA047988, HL043851, and HL080467 from the National Institutes of Health (Bethesda, MD).

Role of the Funding Sources:

The sponsors had no role in the design, data collection, data analysis, interpretation, or writing of the report. The authors had full access to all data in the study and had final responsibility for decision to submit for publication.

The authors would like to thank the subjects of the Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative and Women's Health Study for their participation and steadfast dedication.

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Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2013 January 01.

Table 1

Baseline characteristics of nested control subjects by quintile of plasma 25-hydroxyvitamin D

Characteristic*	Quintiles of Plasma 25(OH)D				
	1	2	3	4	5
Median plasma 25(OH)D, nmol/L	37.3	51.7	62.2	73.9	93.7
Range of plasma 25(OH)D, nmol/L	< 45.6	45.6 – 56.9	56.9 – 66.9	66.9 – 81.1	> 81.1
No. of cases	117	93	87	79	75
No. of controls	233	234	233	233	234
Age, years	63.0 (9.0)	63.4 (8.2)	62.5 (8.1)	62.7 (8.4)	60.8 (8.8)
Female sex, %	81.1	70.9	68.7	64.4	54.7
Race/ethnicity					
White, %	88.0	91.0	93.1	94.4	94.0
Black, %	6.0	3.9	0	0.4	0.9
Other/Missing, %	6.0	5.1	6.9	5.2	5.1
Height, inches	65.4 (3.4)	66.3 (3.6)	66.4 (3.6)	66.4 (3.8)	67.2 (4.2)
Body mass index, kg/m^2	27.8 (5.4)	26.3 (4.8)	25.7 (3.9)	25.2 (3.8)	24.6 (3.8)
Physical activity, MET-hr/week	12.8 (18.1)	15.4 (17.8)	21.7 (32.6)	23.1 (28.1)	24.5 (23.4)
Tobacco use					
Never, %	42.9	42.7	44.6	45.9	39.3
Past, %	37.8	46.2	42.1	42.1	50.0
Current, %	18.4	11.1	12.9	10.7	9.8
Missing, %	0.9	0	0.4	1.3	0.9
History of diabetes mellitus, %	4.7	4.3	2.6	3.9	1.7
Regular multivitamin use, %	25.3	40.2	44.6	45.1	42.3
Total vitamin D intake, IU/day†	289 (239)	416 (284)	424 (274)	430 (242)	446 (292)
Dietary vitamin D intake, IU/day†	176 (107)	221 (145)	230 (134)	230 (119)	232 (120)
Total calcium intake, mg/day†	977 (525)	1107 (500)	1196 (585)	1293 (803)	1192 (547)
Dietary calcium intake, mg/day†	727 (275)	784 (305)	813 (318)	851 (309)	839 (308)
Total retinol intake, IU/day†	2814 (3073)	4440 (4620)	4460 (5260)	4552 (4585)	4370 (4598)
Dietary retinol intake, IU/day†	1526 (982)	1882 (1335)	1995 (1701)	2000 (1595)	1919 (1333)

Characteristic*	Quintiles of Plasma 25(OH)D				
	1	2	3	4	5
Total calories, kcal/day†	1648 (719)	1738 (632)	1719 (527)	1735 (593)	1702 (565)
Alcohol (≥1 drink/day), %	17.6	17.5	20.6	24.9	28.2
Season of blood draw‡					
Winter, %	29.2	23.5	19.7	15.5	9.4
Spring, %	30.9	24.8	19.3	20.1	17.1
Summer, %	15.0	26.5	25.8	29.2	35.5
Fall, %	24.9	25.2	35.2	35.2	38.0
Fasting time, hours	11.2 (4.2)	10.5 (4.6)	10.9 (4.3)	10.0 (4.7)	9.2 (4.8)

*Continuous variables presented as mean (standard deviation)

†Not including PHS participants; data are not available for dietary covariates among PHS participants.

‡Winter: December, January, February; Spring: March, April, May; Summer: June, July, August; Fall: September, October, November

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MET-hr/wk, metabolic equivalent task-hours per week; PHS, Physicians' Health Study

Table 2

Odds ratios (95% confidence intervals) for pancreatic cancer by quintile of plasma 25-hydroxyvitamin D

	Quintiles of Plasma 25(OH)D					*P*-value, trend[†]
	1	2	3	4	5	
Quintiles from all Controls						
Range, nmol/L	< 45.64	45.64 – 56.92	56.93 – 66.94	66.95 – 81.05	> 81.05	
Median, nmol/L	37.7	51.6	61.9	73.9	93.6	
No. of cases/controls	117/233	93/234	87/233	79/233	75/234	
Age-adjusted OR (95% CI)	1.0	0.79 (0.57–1.10)	0.74 (0.53–1.04)	0.68 (0.48–0.95)	0.65 (0.46–0.92)	0.009
Multivariable-adjusted OR (95% CI)[*]	1.0	0.79 (0.56–1.10)	0.75 (0.53–1.06)	0.68 (0.48–0.97)	0.67 (0.46–0.97)	0.03
Cohort-Specific Quintiles[‡]						
Median, nmol/L	37.6	51.2	61.3	73.6	93.6	
No. of cases/controls	114/232	95/234	85/234	79/234	78/233	
Age-adjusted OR (95% CI)	1.0	0.83 (0.60–1.15)	0.74 (0.53–1.03)	0.68 (0.49–0.96)	0.69 (0.49–0.97)	0.02
Multivariable-adjusted OR (95% CI)[*]	1.0	0.82 (0.59–1.15)	0.71 (0.51–1.01)	0.69 (0.48–0.98)	0.70 (0.49–1.01)	0.04

[*] Adjusted for age (continuous), cohort (HPFS, NHS, PHS, WHI, WHS; which also adjusts for sex), body mass index (WHO categories), smoking status (never, past, current), history of diabetes mellitus (yes, no), multivitamin use (yes, no), and month of blood draw (2-month intervals).

[‡] Cohort-specific quintile ranges of plasma 25(OH)D: HPFS: <53, 53–<63.5, 63.5–<72.8, 72.8–<86.6, ≥86.6; NHS: <47, 47–<58.5, 58.5–<67, 67–<80.5, ≥80.5; PHS: <50, 50–<63.1, 63.1–<75, 75–<89.6, ≥89.6; WHI: <40.4, 40.4–<51.9, 51.9–<61.7, 61.7–<75.2, ≥75.2; WHS: <39, 39–<50, 50–<65, 65–<77, ≥77.

[†] Tests for trend calculated by entering quintile-specific median values for 25(OH)D as a single variable in logistic regression models.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; WHI, Women's Health Initiative; WHO, World Health Organization; WHS, Women's Health Study

Table 3

Odds ratios (95% confidence intervals) for pancreatic cancer by quintile of plasma 25-hydroxyvitamin D and time between plasma collection and diagnosis

Time between Plasma Collection and Cancer Diagnosis	No. of Cases	Quintiles of Plasma 25(OH)D					*P*-value, trend[†]
		1	2	3	4	5	
≥ 0 years							
Age-adjusted OR (95% CI) [*]	498	1.0	0.92 (0.66–1.28)	0.78 (0.55–1.10)	0.74 (0.52–1.04)	0.72 (0.50–1.03)	0.04
Multivariable-adjusted OR (95% CI)[≠]		1.0	0.90 (0.64–1.25)	0.77 (0.54–1.09)	0.72 (0.51–1.02)	0.73 (0.50–1.05)	0.05
≥ 2 years							
Age-adjusted OR (95% CI) [*]	451	1.0	0.82 (0.58–1.16)	0.74 (0.52–1.06)	0.69 (0.48–0.98)	0.67 (0.46–0.97)	0.02
Multivariable-adjusted OR (95% CI) [≠]		1.0	0.80 (0.57–1.14)	0.74 (0.51–1.06)	0.68 (0.47–0.98)	0.67 (0.46–0.99)	0.03
≥ 3 years							
Age-adjusted OR (95% CI) [*]	417	1.0	0.84 (0.59–1.22)	0.79 (0.54–1.14)	0.70 (0.49–1.02)	0.69 (0.47–1.02)	0.04
Multivariable-adjusted OR (95% CI) [≠]		1.0	0.83 (0.57–1.20)	0.78 (0.54–1.14)	0.70 (0.48–1.02)	0.70 (0.47–1.05)	0.06
≥ 5 years							
Age-adjusted OR (95% CI) [*]	331	1.0	0.85 (0.56–1.29)	0.63 (0.42–0.97)	0.58 (0.38–0.89)	0.65 (0.42–0.99)	0.02
Multivariable-adjusted OR (95% CI) [≠]		1.0	0.83 (0.54–1.26)	0.61 (0.40–0.94)	0.56 (0.37–0.86)	0.63 (0.41–0.99)	0.02

[*] Matched on year of birth, cohort (HPFS, NHS, PHS, WHI, WHS; which also matches for sex), smoking status (never, past, current), fasting status (<8 hours, ≥ 8 hours), month of blood draw, and adjusted for age (continuous).

[≠] Matched on year of birth, cohort (HPFS, NHS, PHS, WHI, WHS; which also matches for sex), smoking status (never, past, current), fasting status (<8 hours, ≥ 8 hours), month of blood draw, and adjusted for age (continuous), body mass index (WHO categories), history of diabetes mellitus (yes, no), and multivitamin use (yes, no).

[†] Tests for trend calculated by entering quintile-specificmedian values for 25(OH)D as a single variable in logistic regression models.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; WHI, Women's Health Initiative; WHO, World Health Organization; WHS, Women's Health Study

Table 4

Odds ratios (95% confidence intervals) for pancreatic cancer by clinically-defined cut-points of plasma 25-hydroxyvitamin D

	Clinically-Defined Cut-Points of Plasma 25(OH)D		
	Insufficient	**Relative Insufficiency**	**Sufficient**
Range			
ng/ml	< 20	20 – <30	≥ 30
nmol/L	< 50	50 – <75	≥ 75
No. of cases/controls	154/317	189/524	108/326
Age-adjusted OR (95% CI)	1.0	0.74 (0.58–0.96)	0.69 (0.52–0.93)
Multivariable-adjusted OR (95% CI)*	1.0	0.75 (0.58–0.98)	0.71 (0.52–0.97)

*Adjusted for age (continuous), cohort (HPFS, NHS, PHS, WHI, WHS; which also adjusts for sex), body mass index (WHO categories), smoking status (never, past, current), history of diabetes mellitus (yes, no), multivitamin use (yes, no), and month of blood draw (2-month intervals).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; WHI, Women's Health Initiative; WHO, World Health Organization; WHS, Women's Health Study

Table 5

Odds ratios (95% confidence intervals) for pancreatic cancer by cut-points of plasma 25-hydroxyvitamin D and referent group defined by the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

	Plasma 25(OH)D, nmol/L					
	Insufficient			Relative Insufficiency	Sufficient	
	< 25	25 – <37.5	37.5 – <50	50 – <75	75 – <100	≥ 100
No. of cases/controls	8/21	44/98	102/198	189/524	81/247	27/79
Age-adjusted OR (95% CI)	1.05 (0.46–2.41)	1.25 (0.84–1.85)	1.42 (1.07–1.91)	1.0 (referent)	0.92 (0.68–1.25)	0.96 (0.60–1.53)
Multivariable-adjusted OR (95% CI)*	0.97 (0.41–2.29)	1.23 (0.82–1.86)	1.41 (1.05–1.90)	1.0 (referent)	0.93 (0.69–1.27)	1.01 (0.63–1.62)

*Adjusted for age (continuous), cohort (HPFS, NHS, PHS, WHI, WHS; which also adjusts for sex), body mass index (WHO categories), smoking status (never, past, current), history of diabetes mellitus (yes, no), multivitamin use (yes, no), and month of blood draw (2-month intervals).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; WHI, Women's Health Initiative; WHO, World Health Organization; WHS, Women's Health Study

Table 6

Odds ratios (95% confidence intervals) for pancreatic cancer in study subpopulations by quartile of plasma 25-hydroxyvitamin D

Characteristic	Quartiles of Plasma 25(OH)D‡				*P*-value, trend∫
	1	2	3	4	
All					
Median	39.6	55.4	68.3	89.3	
No. of cases/controls	133/290	114/292	112/292	92/293	
Age-adjusted OR (95% CI)	1.0	0.86 (0.63–1.15)	0.84 (0.62–1.13)	0.69 (0.51–0.94)	0.02
Multivariable-adjusted OR (95% CI)*	1.0	0.85 (0.62–1.15)	0.83 (0.61–1.13)	0.70 (0.51–0.98)	0.04
Whites					
Median	39.9	55.6	68.2	89.3	
No. of cases/controls	114/258	102/267	99/273	87/277	
Age-adjusted OR (95% CI)	1.0	0.87 (0.63–1.20)	0.82 (0.60–1.13)	0.72 (0.52–0.99)	0.04
Multivariable-adjusted OR (95% CI)*	1.0	0.87 (0.62–1.20)	0.81 (0.58–1.13)	0.73 (0.51–1.03)	0.07
Women†					
Median	37.2	52.8	65.2	85.3	
No. of cases/controls	91/197	79/198	78/199	63/199	
Age-adjusted OR (95% CI)	1.0	0.87 (0.60–1.24)	0.84 (0.59–1.21)	0.69 (0.47–1.00)	0.06
Multivariable-adjusted OR (95% CI)*	1.0	0.86 (0.59–1.25)	0.85 (0.58–1.25)	0.72 (0.48–1.08)	0.12
Men†					
Median	45.2	60.8	75.0	96.0	
No. of cases/controls	42/93	35/94	34/93	29/94	
Age-adjusted OR (95% CI)	1.0	0.84 (0.49–1.43)	0.82 (0.48–1.41)	0.69 (0.40–1.21)	0.21
Multivariable-adjusted OR (95% CI)*	1.0	0.83 (0.48–1.44)	0.84 (0.48–1.48)	0.73 (0.40–1.31)	0.32

*Adjusted for age (continuous), cohort (HPFS, NHS, PHS, WHI, WHS; which also adjusts for sex), body mass index (WHO categories), smoking status (never, past, current), history of diabetes mellitus (yes, no), multivitamin use (yes, no), and month of blood draw (2-month intervals).

†P-value for interaction by sex = 0.95.

‡Cohort-specific quartile ranges of plasma 25(OH)D: HPFS: <55.8, 55.8–<66.9, 66.9–<83.4, ≥83.4; NHS: <50.4, 50.4–<62.3, 62.3–<77.3, ≥77.3; PHS: <53.1, 53.1–<67.8, 67.8–<85.9, ≥85.9; WHI: <43.9, 43.9–<57.2, 57.2–<71.2, ≥71.2; WHS: <43.5, 43.5–<56.6, 56.6–<74.2, ≥74.2.

∫Tests for trend calculated by entering quartile-specific median values for 25(OH)D as a single variable in logistic regression models.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; WHI, Women's Health Initiative; WHO, World Health Organization; WHS, Women's Health Study