Vitamin D Intake and the Risk for Pancreatic Cancer in Two Cohort Studies

Halcyon G. Skinner,[1] Dominique S. Michaud,[2] Edward Giovannucci,[2,3,4] Walter C. Willett,[2,3,4] Graham A. Colditz,[2,3,4] and Charles S. Fuchs[4,5]

[1]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; Departments of [2]Epidemiology and [3]Nutrition, Harvard School of Public Health, [4]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School; and [5]Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Abstract

Vitamin D and its analogues exhibit potent antitumor effects in many tissues, including the pancreas. Normal and malignant pancreatic tissues were recently shown to express high levels of vitamin D 1-α-hydroxylase, which converts circulating 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D. We examined associations between dietary intake of vitamin D, calcium, and retinol and subsequent risk for pancreatic cancer. We conducted prospective studies in cohorts of 46,771 men ages 40 to 75 years as of 1986 (the Health Professionals Follow-up Study), and 75,427 women ages 38 to 65 years as of 1984 (the Nurses' Health Study), documenting incident pancreatic cancer through the year 2000. Diet was ascertained by semiquantitative food-frequency questionnaire. We identified 365 incident cases of pancreatic cancer over 16 years of follow-up. Compared with participants in the lowest category of total vitamin D intake (<150 IU/d), pooled multivariate relative risks for pancreatic cancer were 0.78 [95% confidence interval (95% CI), 0.59-1.01] for 150 to 299 IU/d, 0.57 (95% CI, 0.40-0.83) for 300 to 449 IU/d, 0.56 (95% CI, 0.36-0.87) for 450 to 599 IU/d, and 0.59 (95% CI, 0.40-0.88) for ≥600 IU/d (P_{trend} = 0.01). These associations may be stronger in men than women. After adjusting for vitamin D intake, calcium and retinol intakes were not associated with pancreatic cancer risk. In two U.S. cohorts, higher intakes of vitamin D were associated with lower risks for pancreatic cancer. Our results point to a potential role for vitamin D in the pathogenesis and prevention of pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1688–95)

Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. More than 32,000 new cases of pancreatic cancer and a similar number of deaths are estimated for 2006 (1). In the absence of effective screening, identifying modifiable risk factors for pancreatic cancer is essential for developing preventive strategies. Nonetheless, other than cigarette smoking, few environmental factors are linked to pancreatic cancer risk. Moreover, information relating diet to pancreatic cancer risk is limited, and no dietary factor has been consistently linked to this malignancy.

Ecologic studies suggest that areas with greater sunlight exposure have lower incidence and mortality rates for colon, breast, and prostate cancer, leading investigators to posit a role for vitamin D in cancer prevention by virtue of the greater potential for vitamin D creation in skin by UV irradiation in areas of greater sunlight (2-8). Laboratory studies show 1,25 dihydroxyvitamin D_3 (calcitriol) receptor expression in pancreatic cancer cell lines; others report that calcitriol and analogues inhibit pancreatic cancer cell proliferation, induce differentiation, and promote apoptosis (9-11). However, investigation of the influence of vitamin D intake on the risk for pancreatic cancer is limited to a single prospective study conducted in Finland among male smokers (12).

Although the capacity of skin to produce vitamin D when exposed to solar UV light (UVB) is large, an individual's total UVB exposure may depend on several factors, including latitude, season of the year (13), local atmosphere (14), manner of dress, and time spent outdoors (15). Moreover, the endogenous capacity for cutaneous production of vitamin D diminishes with age and is inhibited by the presence of melanin (15, 16). Therefore, when cutaneous production of vitamin D is limited or absent, the intake of vitamin D in the diet or through supplements is critical for avoiding vitamin D deficiency (17, 18). Naturally occurring dietary sources of vitamin D include eggs, liver, and fatty fish, but the dominant sources of dietary vitamin D in the United States are fortified dairy products and breakfast cereal. Although many individuals take supplemental vitamin D, most multivitamins also contain retinol, an antagonist of actions of vitamin D on mineral homeostasis and bone function, possibly acting through competition for the retinoid X receptor (19).

We hypothesized that higher intakes of vitamin D from food or supplements might lead to a reduced risk for pancreatic cancer. We therefore examined the association of intakes of vitamin D, calcium, and retinol with risk for pancreatic cancer in two large prospective cohort studies. In both cohorts, diet was measured before pancreatic cancer detection, thus avoiding the potential biases that might occur when obtaining such information from pancreatic cancer patients or their relatives.

Materials and Methods

Study Populations. Two ongoing cohort studies provided data for our analyses: the Nurses' Health Study (NHS), and the Health Professionals Follow-up Study (HPFS). The NHS was initiated in 1976 when 121,701 U.S. female registered nurses ages 30 to 55 years responded to a mailed questionnaire. The HPFS began in 1986 when 51,529 U.S. male health professionals ages 40 to 75 years responded to a mailed questionnaire. Detailed information on individual characteristics and behaviors was obtained from questionnaires at baseline and

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Requests for reprints: Halcyon G. Skinner, Department of Preventive Medicine, 680 North Lake Shore Drive, Suite 1102, Chicago, IL 60611. Phone: 312-503-4798; Fax: 312-908-9588. E-mail: hskinner@northwestern.edu.

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biennially thereafter. Response rates for the biennial questionnaires are 90% for the NHS and 93% for the HPFS. Dietary information was first assessed in the NHS in 1980 (20, 21). For consistency with the HPFS cohort when pooling relative risks, these analyses use the more detailed 1984 food-frequency questionnaire in the NHS as the baseline dietary measure because it is comparable with the dietary assessment obtained in 1986 in the HPFS. After excluding prior cancers, except nonmelanoma skin cancer (4,407 in the NHS; 1,885 in the HPFS), and missing dietary information (1,923 in the NHS; 1,278 in the HPFS), 75,427 NHS women were eligible for analysis in 1984, and 46,771 HPFS men were eligible for analysis in 1986.

Dietary Assessment. Baseline diet was assessed in 1984 in the NHS and 1986 in the HPFS using a 131-item semiquantitative food-frequency questionnaire, described in detail elsewhere (21, 22). Participants were presented with a list of foods, each with a commonly used portion or serving size, and asked how often, on average, they had consumed the specified amount of each food in nine categories of frequency. The questionnaire included information on the brand of multivitamin typically used as well as the brand and type of breakfast cereal used. Participants currently using multivitamins were asked to state how many years they had been taking supplements. Nutrient intakes were computed as the product of consumption frequency for each unit of every food and the nutrient content of the portion. Values for nutrient contents in foods were obtained from the Harvard University Food Composition Database, derived from U.S. Department of Agriculture sources (23). All nutrient values were adjusted for total energy intake by the residuals method (24). All analyses presented use baseline diet as the exposure of interest. Analyses repeated using diet information updated every 4 years (recent) indicated that baseline (distant) diet is temporally suitable for pancreatic cancer.

The validity of the nutrient consumption measured by the food-frequency questionnaires was assessed by comparison to 1-week diet records. In a sample of 150 Boston area women, nutrient compositions derived from the 1984 questionnaire were compared with those from the mean of four 1-week diet records administered in 1980. The Pearson correlation coefficient for energy-adjusted calcium intake was $r = 0.56$ (25). Likewise, a subsample of 127 Boston area HPFS cohort participants completed two detailed 1-week diet records. The Pearson correlation coefficients comparing nutrient compositions from questionnaires to diet records were $r = 0.53$ for total energy-adjusted calcium and 0.68 for total energy-adjusted retinol (25, 26). Finally, in a subsample of 57 men and 82 women, plasma 25-hydroxy vitamin D levels (measured in late winter or early spring) were compared with the total energy-adjusted vitamin D intake computed from food-frequency questionnaires. The (age, sex, energy) adjusted mean concentrations of plasma vitamin D for increasing quartiles of reported vitamin D intake were 63, 79, 76, and 93 nmol/L ($P < 0.001$) with an adjusted Pearson product-moment correlation of 0.35 ($P < 0.01$; ref. 27).

Smoking History and Other Risk Factors. Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires in both cohorts. Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. Height and weight were assessed at baseline and weight was updated in all subsequent questionnaires. In 1986, the questionnaires mailed to the two cohorts included a section assessing physical activity. The reliability and validity of physical activity assessment in these two cohorts was previously reported (28, 29).

Pancreatic Cancer Case and Death Ascertainment. Participants in both cohorts were asked to report specific medical conditions, including cancers diagnosed in the 2-year period before each questionnaire. Whenever a participant (or next of kin for decedents) reported a diagnosis of pancreatic cancer, we requested permission to obtain related medical records including pathology reports. If permission to obtain records was denied, we attempted to confirm self-reported cancer with an additional letter or telephone call to the participant. If the primary cause of death listed on a death certificate was an unreported pancreatic cancer, we contacted a family member (subject to state regulations) to request permission to retrieve medical records or confirm the diagnosis. Most deaths in these cohorts were reported by family members or by the postal service in response to follow-up questionnaires. Additionally, we conducted searches of the National Death Index for nonrespondents, yielding a sensitivity of 98% for identifying decedents (30). We obtained pathology reports confirming diagnoses of pancreatic cancer for >90% of cases. To ensure complete information, we recontacted hospitals if details about cytohistology of pancreatic tumors were missing from the medical record. For remaining cases, we obtained confirmation of self-reported cancer from a secondary source (e.g., death certificate, physician, or family member). All associations were initially examined both including and excluding cases with missing records. Because no material differences were observed between these two types of cases, we included those cases without medical records in the final analyses. Following exclusion of participants with prior cancers or missing dietary information, 178 incident pancreatic cancer cases were diagnosed between 1984 and 2000 among women (NHS) and 187 cases were diagnosed between 1986 and 2000 among men (HPFS).

Statistical Methods. We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up, whichever came first. Incidence rates of pancreatic cancer were computed by dividing the number of incident cases by the number of person-years in each category of exposure. We computed the relative risk (RR) for each upper exposure category by dividing the incidence rate in that category by the rate in the lowest category.

RRs adjusted for potential confounders were estimated using Cox proportional hazards regression (31). SAS/STAT PROC PHREG software was used for proportional hazards regression analysis (SAS Institute, Inc., Cary, NC) and the Anderson-Gill data structure was used to adjust for time-varying covariates (32). A new data record is created for every questionnaire cycle in which a participant was at risk, with covariates set to values reported when the questionnaire was returned. To control for confounding by age and calendar time, and two-way interactions between these time scales, we stratified analyses jointly by age in 1-year categories at start of follow-up and calendar year of the current questionnaire cycle.

Because the distributions of nutrient intakes differ between the two cohorts, and to provide comparability of the primary exposure variables when pooling the cohorts, and based on previous analyses in these cohorts, we divided total vitamin D intake into categories of even 150 IU intervals. Likewise, vitamin D from foods alone, a narrower range of intake, was divided into 100 IU intervals. Height was categorized into quintiles. Cigarette smoking status was categorized as current, former, or never smokers and updated biennially, and we additionally investigated the main associations adjusted by categories of the number of cigarettes smoked per day among current smokers (0, 1-14, 15-34 and 35+ cigarettes/d). We controlled for the presence or absence of a history of diabetes in multivariable models, updating biennially (33, 34). Based on previous analyses in these cohorts (35), participants were categorized into five groups of baseline body mass index using

whole number cutpoints, including widely used definitions of overweight and obese (33, 36). Body mass index was not updated in the analysis because pancreatic cancer is frequently associated with profound weight loss and previous findings in these cohorts showed the strongest associations for baseline body mass index (35). Detailed information on physical activity was first assessed in detail in 1986 in both cohorts. Based on previous analyses in these cohorts, total vigorous and nonvigorous activity was divided into categories of metabolic equivalent tasks (35).

We assessed confounding by physical activity, glycemic load, and glycemic index but excluded them from the final multivariable models because they were not confounders in these analyses. We present multivariate models adjusted for age and the covariates previously identified to have the strongest associations with pancreatic cancer in these cohorts: body mass index, height, cigarette smoking, and diabetes. Because solar UV light exposure is strongly influenced by latitude, we controlled for region of residence in categories based on the state of residence: north (Alaska, Washington, Oregon, Montana, Idaho, North Dakota, South Dakota, Minnesota, Iowa, Wisconsin, Illinois, Michigan, Indiana, Ohio, Pennsylvania, New York, New Jersey, Connecticut, Rhode Island, Massachusetts, Vermont, New Hampshire, and Maine) and south (California, Nevada, Utah, Arizona, Wyoming, Colorado, New Mexico, Nebraska, Kansas, Oklahoma, Texas, Missouri, Arkansas, Louisiana, Mississippi, Kentucky, Tennessee, Alabama, Florida, Georgia, South Carolina, North Carolina, West Virginia, Virginia, Maryland, Delaware, and Hawaii), divided approximately by a latitude of 39° north. Finally, we included multivitamin supplement use in our models, and additionally investigated the intakes of calcium and retinol as potential confounders in the relation between vitamin D intake and pancreatic cancer.

Statistical interaction was assessed by Wald's tests of cross-product terms, and likelihood ratio tests comparing full models, including interaction terms with reduced models without interaction terms. Tests for linear trend were done using the median value of the independent variable for each category as a continuous variable. We pooled results from the two cohorts using a random-effects model for the log of the RRs (37). A test for heterogeneity using the Q-statistic was done for each reported pooled relative hazard (37). The proportionality of hazards was tested by likelihood ratio tests comparing models saturated with age-by-variable interactions to models without interaction terms. The models presented all satisfy the proportionality of hazards assumption. All statistical procedures were done using SAS version 8.2 (SAS Institute). All P values are based on two-sided tests. The Human Research Committee at the Brigham and Women's Hospital approved the NHS, and the Harvard School of Public Health Human Subjects Committee approved the HPFS.

Results

For each cohort, baseline characteristics according to categories of total vitamin D intake are presented in Table 1. In both

Table 1. Age-standardized characteristics of men in the HPFS in 1986 and women in the NHS in 1984 by total daily energy-adjusted vitamin D intake

Variable	Total daily vitamin D intake (IU)				
	<150	150-299	300-449	450-599	≥600
HPFS (1986)					
No. men	10,783	15,321	7,528	5,062	8,077
Age (y)	52	54	54	55	56
Daily vitamin D (IU)	100	214	368	521	893
Residence in northern state	47%	49%	51%	50%	48%
Body mass index (kg/m^2)	25	25	25	25	25
Height (m)	1.8	1.8	1.8	1.8	1.8
Multivitamin supplement use	11%	22%	43%	79%	95%
Physical activity (METs/wk)	19	21	21	22	24
Smoking history					
Current	12%	9%	9%	9%	8%
Former	45%	41%	39%	41%	42%
Never	40%	46%	48%	46%	46%
Diabetic	3%	3%	3%	3%	3%
Total Daily calcium intake (mg)	623	807	1,035	1,032	1,223
Daily calcium intake from foods (mg)	585	761	955	897	931
Total daily retinol intake (IU)	2,307	3,116	4,562	7,290	13,890
Daily retinol intake from foods (IU)	1,969	2,574	2,865	2,626	2,793
NHS (1984)					
No. women	22,494	24,566	10,922	8,104	9,341
Age (y)	49	50	51	51	52
Daily vitamin D (IU)	95	212	368	522	829
Residence in northern state	74%	75%	74%	71%	69%
Body mass index (kg/m^2)	24	24	24	24	24
Height (m)	1.6	1.6	1.6	1.6	1.6
Multivitamin supplement use	8%	17%	56%	88%	94%
Physical activity (METs/wk)	12	14	15	16	17
Smoking history					
Current	30%	22%	22%	21%	20%
Former	30%	31%	32%	34%	36%
Never	40%	46%	46%	45%	44%
Diabetic	1%	1%	1%	1%	1%
Parity (No. full-term pregnancies)	3	3	3	3	3
Total daily calcium intake (mg)	649	838	1,028	1,035	1,245
Daily calcium intake from foods (mg)	553	727	846	761	860
Total daily retinol intake (IU)	1,963	2,805	4,759	7,446	11,919
Daily retinol intake from foods (IU)	1,696	2,300	2,480	2,300	2,656

Abbreviation: MET, metabolic equivalent task.

Table 2. Total daily vitamin D intake at baseline and the risk for pancreatic cancer in the HPFS and NHS cohorts

	Total daily vitamin D intake (IU)					P_{trend}
	<150	150-299	300-449	450-599	≥600	
HPFS (1986-2000)						
No. cases	49	65	23	14	36	
Person-years	142,237	200,615	98,274	65,814	104,629	
Age-adjusted RR (95% CI)	1.00	0.80 (0.55-1.16)	0.57 (0.35-0.93)	0.48 (0.26-0.87)	0.72 (0.47-1.11)	0.09
Multivariate RR (95% CI)*	1.00	0.83 (0.57-1.20)	0.58 (0.35-0.96)	0.49 (0.27-0.90)	0.75 (0.48-1.16)	0.12
Multivariate + multivitamin RR (95% CI) †	1.00	0.77 (0.53-1.12)	0.49 (0.29-0.82)	0.35 (0.18-0.67)	0.49 (0.29-0.82)	0.01
NHS (1984-2000)						
No. cases	55	53	22	22	26	
Person-years	347,219	379,125	167,748	124,542	143,359	
Age-adjusted RR (95% CI)	1.00	0.78 (0.53-1.14)	0.71 (0.43-1.16)	0.91 (0.56-1.50)	0.86 (0.54-1.38)	0.73
Multivariate RR (95% CI)*	1.00	0.80 (0.54-1.16)	0.74 (0.45-1.21)	0.98 (0.59-1.60)	0.90 (0.56-1.44)	0.90
Multivariate + multivitamin RR (95% CI) †	1.00	0.78 (0.53-1.14)	0.68 (0.40-1.15)	0.84 (0.46-1.53)	0.76 (0.42-1.38)	0.47
Pooled RRs						
No. cases	104	118	45	36	62	
Person-years	489,456	579,740	266,022	190,356	247,988	
Age-adjusted RR (95% CI)	1.00	0.79 (0.61-1.03)	0.63 (0.45-0.90)	0.70 (0.48-1.03)	0.78 (0.57-1.08)	0.14
Multivariate RR (95% CI)*	1.00	0.81 (0.62-1.06)	0.65 (0.46-0.93)	0.74 (0.50-1.08)	0.81 (0.59-1.12)	0.22
Multivariate + multivitamin RR (95% CI) †	1.00	0.78 (0.59-1.01)	0.57 (0.40-0.83)	0.56 (0.36-0.87)	0.59 (0.40-0.88)	0.01

NOTE: All RRs are adjusted for age (1-year intervals), time period (2-year intervals), and total energy intake (kcal).
*Multivariate RRs additionally adjusted for cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cutpoints: 23.0, 25.0, 27.0, 30.0), height (quintiles), region of residence (south, north), and parity (among women).
† Multivariate + multivitamin RRs are additionally adjusted for the use of multivitamin supplements.

cohorts, participants in higher categories of vitamin D intake tended to be older, less likely to smoke cigarettes, and more physically active. Intakes of calcium and retinol were positively associated with the intake of vitamin D. These nutrients are commonly found in multivitamin supplements and vitamin D–fortified foods. We observed that 95% of men and 94% of women in the highest categories of vitamin D intake were multivitamin supplement users.

We examined the influence of total energy-adjusted intake of vitamin D on the risk for pancreatic cancer (Table 2). Statistical adjustment for a variety of potential confounders did not materially alter the associations between vitamin D intake and the risk for pancreatic cancer compared with adjusting for age alone. Additional adjustment for the intake of multivitamin supplements strengthened an inverse relationship between vitamin D intake and the risk for pancreatic cancer. Among men in the HPFS, the multivariate adjusted RR comparing those consuming 600 IU/d or more of vitamin D to <150 IU/d was 0.49 [95% confidence interval (CI), 0.29-0.82]. Among women in the NHS, the RR comparing similar extreme categories was 0.76 (95% CI, 0.42-1.38). Before pooling the data from these two cohorts, we assessed heterogeneity of the RRs between studies by the Q-statistic. P values of heterogeneity for increasing categories of vitamin D intake were 0.99, 0.87, 0.66, and 0.83. Thereafter, we pooled RRs from the two cohorts and observed a significant inverse relation between total daily energy-adjusted vitamin D intake and the risk for pancreatic cancer. Compared with participants consuming <150 IU/d of vitamin D, those who consumed 600 IU/d or more had a multivariate RR for pancreatic cancer of 0.59 (95% CI, 0.40-0.88; P_{trend} = 0.01).

To further control for potential confounding by multivitamin supplement use, we excluded multivitamin supplement users and analyzed the association between pancreatic cancer risk and the intake of vitamin D from food sources alone (including fortified foods; Table 3). We observed 199 cases among the subset of participants who did not report multivitamin supplement use at baseline. Although statistical power was diminished in this sample of participants, we

Table 3. Daily vitamin D intake from food sources alone and the risk of pancreatic cancer in the HPFS and NHS cohorts

	Daily vitamin D intake from foods alone (IU)				P_{trend}
	<100	100-199	200-299	≥300	
HPFS (1986-2000)					
No. cases	17	37	20	18	
Person-years	55,731	132,961	86,859	70,250	
Age-adjusted RR (95% CI)	1.00	0.78 (0.44-1.39)	0.56 (0.29-1.08)	0.58 (0.30-1.13)	0.09
Multivariate RR* (95% CI)	1.00	0.79 (0.44-1.40)	0.57 (0.30-1.09)	0.58 (0.29-1.13)	0.08
NHS (1984-2000)					
No. cases	24	45	26	12	
Person-years	171,338	308,937	164,567	80,280	
Age-adjusted RR (95% CI)	1.00	0.93 (0.57-1.53)	0.92 (0.53-1.60)	0.80 (0.40-1.60)	0.54
Multivariate RR* (95% CI)	1.00	0.94 (0.57-1.55)	0.91 (0.52-1.59)	0.80 (0.40-1.60)	0.52
Pooled RRs					
No. cases	41	82	46	30	
Person-years	227,069	441,898	251,426	150,530	
Age-adjusted RR (95% CI)	1.00	0.87 (0.59-1.26)	0.74 (0.49-1.14)	0.67 (0.42-1.09)	0.10
Multivariate RR* (95% CI)	1.00	0.87 (0.60-1.27)	0.74 (0.49-1.14)	0.67 (0.41-1.09)	0.09

NOTE: Analysis of nutrients from food sources excludes participants who reported the use of multivitamin supplements and those for whom information about multivitamin supplement use was missing. All RRs were adjusted for age (1-year intervals), time period (2-year intervals), and total energy intake (kcal).
*Multivariate RRs additionally adjusted for cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cutpoints: 23.0, 25.0, 27.0, 30.0), height (quintiles), region of residence (south, north), and parity (among women).

Table 4. Total daily calcium intake and calcium intake from foods sources at baseline and the risk of pancreatic cancer in the HPFS and NHS cohorts

	Total daily calcium intake (mg)			P_{trend}
	<500	500-999	≥1,000	
HPFS (1986-2000)				
No. cases	17	119	51	
Person-years	59,963	372,213	179,381	
Age-adjusted RR (95% CI)	1.00	1.09 (0.66-1.81)	0.87 (0.51-1.52)	0.26
Multivariate RR* (95% CI)	1.00	1.10 (0.66-1.84)	0.85 (0.49-1.49)	0.19
Multivariate + vitamin D RR† (95% CI)	1.00	1.28 (0.76-2.18)	1.23 (0.67-2.25)	0.86
NHS (1984-2000)				
No. cases	24	109	45	
Person-years	156,300	665,099	340,595	
Age-adjusted RR (95% CI)	1.00	1.00 (0.64-1.56)	0.68 (0.42-1.12)	0.03
Multivariate RR* (95% CI)	1.00	1.01 (0.65-1.58)	0.69 (0.42-1.15)	0.04
Multivariate + vitamin D RR† (95% CI)	1.00	1.09 (0.69-1.73)	0.75 (0.43-1.30)	0.09
Pooled RRs				
No. cases	41	228	96	
Person-years	216,263	1,037,312	519,976	
Age-adjusted RR (95% CI)	1.00	1.04 (0.74-1.45)	0.76 (0.53-1.10)	0.02
Multivariate RR* (95% CI)	1.00	1.05 (0.75-1.47)	0.76 (0.52-1.11)	0.02
Multivariate + vitamin D RR† (95% CI)	1.00	1.17 (0.83-1.66)	0.94 (0.62-1.41)	0.29

	Daily calcium intake from foods (mg)			P_{trend}
	<500	500-999	≥1,000	
HPFS (1986-2000)				
No. cases	10	69	13	
Person-years	44,353	235,211	66,238	
Age-adjusted RR (95% CI)	1.00	1.24 (0.64-2.40)	0.81 (0.35-1.84)	0.31
Multivariate RR* (95% CI)	1.00	1.26 (0.65-2.46)	0.80 (0.35-1.83)	0.29
Multivariate + vitamin D RR† (95% CI)	1.00	1.57 (0.77-3.17)	1.10 (0.41-2.97)	0.89
NHS (1984-2000)				
No. cases	28	67	12	
Person-years	143,240	488,683	81,526	
Age-adjusted RR (95% CI)	1.00	0.67 (0.43-1.05)	0.65 (0.33-1.28)	0.22
Multivariate RR* (95% CI)	1.00	0.68 (0.44-1.06)	0.64 (0.33-1.27)	0.20
Multivariate + vitamin D RR† (95% CI)	1.00	0.66 (0.40-1.07)	0.64 (0.27-1.52)	0.26
Pooled RRs				
No. cases	38	136	25	
Person-years	187,593	723,894	147,764	
Age-adjusted RR (95% CI)	1.00	0.81 (0.56-1.17)	0.71 (0.42-1.20)	0.11
Multivariate RR* (95% CI)	1.00	0.82 (0.57-1.19)	0.70 (0.41-1.19)	0.10
Multivariate + vitamin D RR† (95% CI)	1.00	0.87 (0.58-1.30)	0.81 (0.42-1.56)	0.39

NOTE: Analysis of nutrients from food sources excludes participants who reported the use of multivitamin supplements and those for whom information about multivitamin supplement use was missing. All RRs are adjusted for age (1-year intervals), time period (2-year intervals) and total energy intake (kcal).
*Multivariate RRs additionally adjusted for cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cutpoints: 23.0, 25.0, 27.0, 30.0), height (quintiles), region of residence (south, north), use of multivitamin supplements (for total calcium intake analyses), and parity (among women).
†Multivariate + vitamin D RRs are additionally adjusted for categories of total vitamin D intake or vitamin D intake from foods as appropriate.

observed a similar inverse relation between vitamin D from food sources only and the risk for pancreatic cancer. Compared with those who consumed <100 IU/d of vitamin D from foods, men in the HPFS who reported 300 or more IU/d had a multivariate RR of 0.58 (95% CI, 0.29-1.13), whereas women in the NHS who reported similar consumption has RR of 0.80 (95% CI, 0.40-1.60). When we pooled both cohorts, consumption of ≥300 IU/d of vitamin D from foods was associated with a RR of 0.67 (95% CI, 0.41-1.09; P_{trend} = 0.09).

As indicated in Table 1, intake of vitamin D was strongly correlated with the intakes of calcium and retinol. Pearson's correlations between total calcium and vitamin D intake were 0.48 and 0.46, in men and women, respectively, and correlations between total retinol and vitamin D intake were 0.74 and 0.71 for men and women, respectively. We analyzed associations between the intake of calcium and the risk for pancreatic cancer (Table 4). We observed an inverse relation between total calcium intake and the risk for pancreatic cancer in both cohorts, but this seemed to be stronger among women. In both cohorts, however, the association of total dietary calcium was markedly attenuated after adjusting for total vitamin D intake. Similarly, in the pooled analysis, there was no significant association between either total calcium intake or calcium from food sources and the risk for pancreatic cancer after adjusting for total vitamin D intake (P_{trend} = 0.29 and 0.39, respectively). In contrast, we continued to observe a significant inverse relation between total vitamin D consumption and pancreatic cancer risk after adjusting for total calcium intake (multivariate RR, 0.63; 95% CI, 0.41-0.96, comparing ≥600 to <150 IU/d of vitamin D; Fig. 1).

We examined the association between retinol intake and the risk for pancreatic cancer (Table 5). Among men (HPFS), we found an inverse relation between retinol intake and pancreatic cancer that was strongly attenuated after adjusting for total vitamin D intake. In contrast, among women (NHS), neither total retinol nor retinol from food alone was associated with pancreatic cancer risk. After adjusting for total vitamin D intake, the pooled multivariate RR comparing the highest (≥8,000 IU/d) to lowest (<2,000 IU/d) categories of total retinol intake was 0.90 (95% CI, 0.58-1.38; P_{trend} = 0.43). In contrast, an inverse association between total vitamin D consumption and pancreatic cancer risk persisted after adjusting for retinol intake from both food and supplements (multivariate RR, 0.58; 95% CI, 0.36-0.92, comparing ≥600 to <150 IU/d of vitamin D).

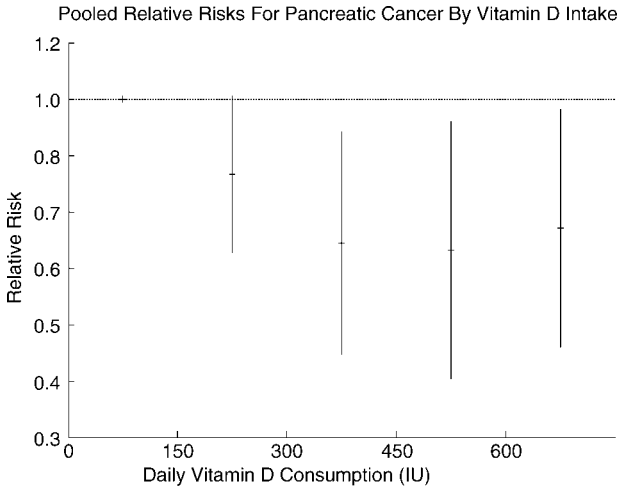

Figure 1. The RRs for pancreatic cancer by categories of baseline total daily vitamin D intake adjusted for calcium intake. RRs are pooled from two U.S. cohort studies, the NHS (1984 baseline) and the HPFS (1986 baseline), and include incident pancreatic cancers through the year 2000. RRs are adjusted for age (1-year intervals), time period (2-year intervals), total energy intake (kcal), cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cutpoints: 23.0, 25.0, 27.0, 30.0), height (quintiles), region of residence (south, north), use of multivitamin supplements, parity (among women), and total daily consumption of calcium.

We further analyzed the relation between vitamin D intake and pancreatic cancer risk by stratifying RRs by cigarette smoking, body mass index, and region of residence (south versus north). We found that the association between total vitamin D intake and the risk for pancreatic cancer did not differ significantly across strata of these factors (P for interactions: 0.14 for smoking; 0.69 for latitude; 0.95 for body mass index). Although not statistically significant, because our power to examine some interactions was limited, we cannot exclude the possibility of an interaction with cigarette smoking. We additionally restricted our analyses to examine the relation between vitamin D intake and pancreatic cancer risk among ''never smokers.'' Compared with those who consumed <150 IU of vitamin D per day, the multivariate-adjusted relative hazards for pancreatic cancer in increasing categories of energy-adjusted total vitamin D intake were 0.74, 0.47, 0.33, and 0.46 (95% CI, 0.26-0.78) among men in the HPFS and 0.75, 0.65, 0.80, 0.73 (95% CI, 0.40-1.32) among women in the NHS.

We examined individual food items that contribute significant vitamin D to the diets of these two cohorts. Skim milk contributed ~19% of the dietary vitamin D in both cohorts, whereas dark fish (salmon, mackerel, sardines, etc.) provided 14% of the total vitamin D in men and ~8% in women. We observed modest, although nonsignificant, inverse associations between consumption of these foods, alone and in combination, and the risk for pancreatic cancer. Among both cohorts combined, compared with participants who never consumed skim milk, those who drank more than one 8-oz serving of skim milk per day had a multivariate RR for pancreatic cancer of 0.83 (95% CI, 0.63-1.10). Likewise, compared with those who reported never eating dark fish, those who consumed a 3 to 5 oz serving of dark fish more than once per week had a RR for pancreatic cancer of 0.78 (95% CI, 0.55-1.11). Other dietary vitamin D contributing foods were not significantly associated with the risk for pancreatic cancer. For example, RRs for cold cereal and eggs were 0.95 and 0.87, comparing those in the highest category of intake to those who reported never consuming these foods.

Discussion

In this analysis of two large prospective cohort studies, we observed a reduced risk for pancreatic cancer with higher intake of vitamin D. Participants consuming 600 IU/d or more of vitamin D experienced a 41% lower risk for pancreatic cancer when compared with those consuming <150 IU/d.

Few studies have examined the association between vitamin D and pancreatic cancer in humans. In a case-control study exploring the intake of several nutrients in relation to pancreatic cancer, nested in a cohort of male Finnish smokers, no association was observed between vitamin D intake and pancreatic cancer (12). In particular, the median reported intake of vitamin D for both cases and controls was 4.9 μg/d (l96 IU/d), about half of the U.S. defined adequate intake for vitamin D intake (400 IU or 10 μg for those ages 50-70 years). Direct comparison with our results is complicated by the ubiquitous cigarette smoking in the Finnish men, the relatively limited range of reported intake (interquartile range 3.5-6.4 μg/d), and the difference in variables selected for adjustments. Finally, an international ecological study identified an association between latitude and pancreatic cancer incidence rates (38, 39), but no results using individual-level exposure to UVB have been published.

Experimental evidence suggests that vitamin D could reduce the risk for pancreatic cancer through regulation of cellular proliferation and differentiation (9, 10, 40). Normal and malignant pancreatic tissues express high levels of vitamin D 1-α-hydroxylase, which converts circulating 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D (40). Laboratory studies point to potent antiproliferative and differentiating effects of an analogue of $1,25(OH)_2D_3$ with reduced calcemic activity, EB1089, on pancreatic cancer cell lines (10, 11, 41) and in xenografted tumor cells (41).

Our study benefits from its prospective design, the availability of detailed data on many potential confounders, a high follow-up response rate, and the incorporation of data from two completely separate, large cohorts. The prospective design precludes recall bias and the need for next-of-kin respondents to assess exposure, a particular concern when studying a rapidly fatal illness. The high follow-up response rates make it unlikely that cases of pancreatic cancer among participants went undetected. Moreover, although both cohorts are large and provide considerable power for statistical analyses, pancreatic cancer is a relatively rare malignancy, and exposure categories may contain sparse numbers of cases when stratified to assess interactions.

A potential limitation of our study is that dietary intake of vitamin D may not reflect internal vitamin D status because it does not account for the cutaneous production of vitamin D. Moreover, misclassification of vitamin D intake by the semiquantitative food-frequency questionnaire is a potential concern. However, any such errors in the measurement of nutrient intake are likely to be nondifferential by disease status, and would therefore have attenuated rather than exaggerated a true association. In a validation study of dietary assessment by the semiquantitative food-frequency questionnaire compared with biochemical indicators of micronutrient status, we observed a 50% higher concentration of plasma 25-hydroxyvitamin D when comparing the highest to lowest quartiles of intake (27). Moreover, based on two substudies in this cohort, one a nested case-control study of prostate cancer and another study to examine racial differences and reproducibility over time. Among 393 men who provided a blood sample in the winter or spring months when vitamin D tends to be lowest, the prevalence of vitamin D deficiency (<37.5 nmol/L) decreased with increasing vitamin D intake (<150 IU/d, 50% deficient; 150-299 IU/d, 21%; 300-449 IU/d, 15%; and >450 IU/d, 14%). Therefore, among men with relatively low vitamin D intakes, the

prevalence of vitamin D deficiency is high in the winter and spring months. Thus, although intake alone at current levels may not yield very high levels of vitamin D in circulation, it is an important factor in preventing vitamin D deficiency in winter months, as shown in other studies (16-18, 42). Finally, because we do not have detailed information about sun exposure for participants in either cohort, we used state of residence divided by geographic latitude as a limited proxy for potential solar UVB exposure.

We cannot exclude the possibility that vitamin D may be acting as a surrogate for some other, as yet unknown, factor that is associated with the risk for pancreatic cancer. However, in our multivariable analyses, we controlled for factors previously associated with pancreatic cancer, as well as other potential confounders, including multivitamin supplement use and calcium and retinol intake. Adjusting for multivitamin supplement use strengthened the association between total vitamin D intake and the risk for pancreatic cancer, particularly at the highest levels of intake. We have previously reported a modest positive association between multivitamin supplement use and the risk of pancreatic cancer (43), and this raised the possibility that some factor in multivitamin supplements other than vitamin D, potentially retinol, antagonizes a protective effect of vitamin D, or plays an independent role in increasing the risk for pancreatic cancer. Moreover, when excluding multivitamin supplement users, we continued to observe an inverse relation between vitamin D from food sources and the risk for pancreatic cancer. The observed inverse associations between vitamin D intake and pancreatic cancer risk were nominally stronger in the cohort of men than in the cohort of women, possibly related to the higher proportion of cigarette smokers and higher concentration of residence at northern latitudes among women in the Nurses Health Study. Finally, stratifying our analyses by a number of factors, including region of residence, cigarette smoking status, and body mass index to assess potential effect modification, yielded no significant interactions.

In summary, we observed that a higher intake of vitamin D was associated with a decreased risk for pancreatic cancer in two large U.S. cohorts. To our knowledge, this is the first epidemiologic report of an association between vitamin D intake

Table 5. Total daily retinol intake and retinol intake from foods sources at baseline and the risk of pancreatic cancer in the HPFS and NHS cohorts

	Total daily retinol intake (IU)				P_{trend}
	<2,000	2,000-3,999	4,000-7,999	≥8,000	
HPFS (1986-2000)					
No. cases	58	57	36	36	
Person-years	201,264	158,920	128,379	122,415	
Age-adjusted RR (95% CI)	1.00	1.11 (0.77-1.60)	0.83 (0.55-1.26)	0.82 (0.54-1.24)	0.18
Multivariate RR* (95% CI)	1.00	1.03 (0.71-1.50)	0.64 (0.40-1.02)	0.59 (0.36-0.96)	0.02
Multivariate + vitamin D RR† (95% CI)	1.00	1.24 (0.84-1.83)	0.87 (0.53-1.42)	0.76 (0.42-1.37)	0.21
NHS (1984-2000)					
No. cases	63	37	48	30	
Person-years	472,115	228,733	294,519	166,627	
Age-adjusted RR (95% CI)	1.00	1.11 (0.74-1.66)	1.04 (0.71-1.51)	1.08 (0.70-1.67)	0.78
Multivariate RR* (95% CI)	1.00	1.09 (0.73-1.65)	0.98 (0.64-1.51)	1.01 (0.59-1.73)	0.99
Multivariate + vitamin D RR† (95% CI)	1.00	1.17 (0.77-1.77)	1.07 (0.68-1.69)	1.09 (0.58-2.03)	0.79
Pooled RRs					
No. cases	121	94	84	66	
Person-years	673,379	387,653	422,898	289,042	
Age-adjusted RR (95% CI)	1.00	1.11 (0.84-1.45)	0.94 (0.71-1.24)	0.93 (0.69-1.26)	0.41
Multivariate RR* (95% CI)	1.00	1.06 (0.80-1.40)	0.81 (0.59-1.11)	0.75 (0.52-1.08)	0.07
Multivariate + vitamin D RR† (95% CI)	1.00	1.20 (0.91-1.60)	0.97 (0.69-1.36)	0.90 (0.58-1.38)	0.43

	Daily retinol intake from foods (IU)			P_{trend}
	<2,000	2,000-3,999	≥4,000	
HPFS (1986-2000)				
No. cases	46	38	8	
Person-years	176,586	117,671	51,312	
Age-adjusted RR (95% CI)	1.00	1.06 (0.69-1.62)	0.51 (0.24-1.07)	0.09
Multivariate RR* (95% CI)	1.00	1.05 (0.68-1.61)	0.49 (0.23-1.04)	0.08
Multivariate + vitamin D RR† (95% CI)	1.00	1.22 (0.77-1.94)	0.56 (0.26-1.20)	0.16
NHS (1984-2000)				
No. cases	57	32	18	
Person-years	444,845	174,066	106,211	
Age-adjusted RR (95% CI)	1.00	1.26 (0.82-1.95)	1.07 (0.63-1.83)	0.57
Multivariate RR* (95% CI)	1.00	1.23 (0.80-1.91)	1.00 (0.59-1.70)	0.77
Multivariate + vitamin D RR† (95% CI)	1.00	1.27 (0.82-1.98)	1.05 (0.61-1.81)	0.64
Pooled RRs				
No. cases	103	70	26	
Person-years	621,431	291,737	157,523	
Age-adjusted RR (95% CI)	1.00	1.15 (0.85-1.57)	0.83 (0.54-1.29)	0.51
Multivariate RR* (95% CI)	1.00	1.14 (0.84-1.54)	0.79 (0.51-1.22)	0.36
Multivariate + vitamin D RR† (95% CI)	1.00	1.25 (0.91-1.72)	0.85 (0.54-1.32)	0.58

NOTE: Analysis of nutrients from food sources excludes participants who reported the use of multivitamin supplements and those for whom information about multivitamin supplement use was missing. All RRs are adjusted for age (1-year intervals), time period (2-year intervals), and total energy intake (kcal).
*Multivariate RRs additionally adjusted for cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cutpoints: 23.0, 25.0, 27.0, 30.0), height (quintiles), region of residence (south, north), use of multivitamin supplements, and parity (among women).
† Multivariate + vitamin D RRs are additionally adjusted for categories of total vitamin D intake or vitamin D intake from foods as appropriate.

and the risk for pancreatic cancer. In concert with laboratory demonstrations of antitumor effects of vitamin D, our results point to a potential role for the vitamin D pathway in the prevention and pathogenesis of pancreatic cancer. Considering the paucity of epidemiologic data on this malignancy, additional study of vitamin D and pancreatic cancer is warranted.

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Vitamin D Intake and the Risk for Pancreatic Cancer in Two Cohort Studies

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