

Vitamin D and Pancreatic Cancer

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Sun exposure has been associated with lower death rates for pancreatic cancer in ecological studies. Skin exposure to solar ultraviolet B radiation induces cutaneous production of precursors to 25-hydroxy (OH) vitamin D (D) and is considered the primary contributor to vitamin D status in most populations. Pancreatic islet and duct cells express 25-(OH) D₃-1 α -hydroxylase that generates the biologically active 1,25-dihydroxy(OH)₂ D form. Thus, 25(OH)D concentrations could affect pancreatic function and possibly pancreatic cancer etiology. Serum 25-(OH)D is the major circulating vitamin D metabolite and is considered the best indicator of vitamin D status as determined by the sun and diet. Although recent prospective epidemiologic studies of higher predicted vitamin D status score and vitamin D intake and pancreatic cancer risk suggest protective associations, a nested case-control study showed a significant 3-fold increased risk for pancreatic cancer with higher vitamin D status. Limitations of these studies include the former do not measure vitamin D status on pancreatic cancer cases and the later was conducted in a male smoker population. More research is needed, particularly examination of pre-diagnostic vitamin D status and risk of pancreatic cancer, prior to conclusions for vitamin D's potential role in the etiology of this highly fatal cancer. *Ann Epidemiol* 2009;19:89–95. © 2008 Elsevier Inc. All rights reserved.

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PANCREATIC CANCER EPIDEMIOLOGY

Pancreatic cancer is estimated to be the tenth and ninth most frequent incident cancer, but the fourth most-common cause of cancer mortality for men and women, respectively in the United States (1). There is no effective screening test for the malignancy; therefore, it is often diagnosed at an advanced stage, which contributes to a dismal 5-year survival rate of 4.3% (2). More than 90% of pancreatic cancers are ductal adenocarcinomas, with islet-cell tumors constituting an additional 5%. The incidence of pancreatic cancer increases with age and is higher in men compared with women. Within the United States, this is a site often noted for its relevance to cancer disparities, with African-American patients experiencing incidence rates 30–40% greater than their white counterparts (1). Internationally, rates of pancreatic cancer vary by 10- to 15-fold (2), with the highest rates in Northern and Eastern Europe and lowest rates in Hong Kong (3). Of the few risk factors that have been identified, cigarette smoking and diabetes mellitus (2) are the most consistent. Chronic pancreatitis also predisposes to the disease (4). An association with obesity has been reported in the majority of studies (5, 6), but the effect of most nutritional factors is unclear.

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SOURCES FOR VITAMIN D STATUS

For most people, more than 90% of their vitamin D status comes from exposure to sunlight (7). Exposure of the skin to solar ultraviolet B light (280–320 nm) induces cutaneous production of precursors to vitamin D. In addition to vitamin D synthesized endogenously from sunlight, dietary sources of vitamin D include cholecalciferol (D₃) that occurs naturally in some animal foods (i.e., fatty saltwater fish, liver, and egg), ergocalciferol (D₂) from plants, used in pharmaceutical preparations, and fortified foods such as milk and margarine (D₂ and D₃) (7, 8). 25-hydroxy(OH) vitamin D (D) is the major circulating vitamin D metabolite in humans and is also considered the best indicator of vitamin D status as determined by the sun and diet.

ECOLOGIC STUDIES OF LATITUDE AND PANCREATIC CANCER

United States pancreatic cancer rates do not exhibit North-South gradients (9), as do colon and prostate cancers (10). However, greater sun exposure has been associated with lower death rates for pancreatic cancer in ecological studies in Caucasian (11, 12), Japanese (13, 14), and African-American (15) populations. A suggested explanation for these associations is variation in sun exposure by geographic latitude with individuals at lower latitudes have higher vitamin D status and less cancer (11–13, 15). Several risk factors for pancreatic cancer, such as age, obesity, and African-American ethnicity, have also been associated with reduced vitamin D status (16). Although these observations have generated the hypothesis that vitamin D “status” may be

Selected Abbreviations And Acronyms

HPFS = Health Professionals Follow-up Study
NHS = Nurses Health Study
RR = relative risk
95% CI = 95% confidence interval
ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

related to a reduced risk of pancreatic cancer, causation can not be concluded because characteristics are attributed to a group without having exposure (i.e., vitamin D status) or outcome data on individuals in the group.

THE PANCREAS AND EXPERIMENTAL STUDIES OF VITAMIN D

There is experimental evidence for vitamin D having anti-carcinogenic properties, although few studies have examined this with respect to pancreatic cancer. Extra-renal synthesis of hormonally active 1,25 α -dihydroxy(OH)₂ D has been shown to be involved in autocrine and paracrine regulation of cell differentiation, proliferation, and apoptosis, processes involved in carcinogenesis (17). Expression of 25(OH) vitamin D₃-1 α -hydroxylase (18), the enzyme that catalyzes the synthesis of the active 1,25(OH)₂ vitamin D form, has been observed in pancreatic duct cells, and normal and adenocarcinomatous tissue (18–20).

Pancreatic cancer cell line growth is inhibited by 25-(OH)vitamin D₃ (19;20). 1,25 vitamin D analogs inhibit pancreatic cancer cell proliferation, induce differentiation, promote apoptosis in vitro (21–25), and inhibit pancreatic xenograph tumor growth in immunodeficient mice (24, 26). In addition, the pancreatic islet cells possess vitamin D receptors and express 25(OH) vitamin D₃-1 α -hydroxylase, which has lead to the postulation that vitamin D status may be linked to endocrine pancreatic function (27). In vitro evidence supports vitamin D's involvement in the regulation of insulin synthesis, binding, and responsiveness (28–30). Endocrine pancreatic function may be relevant to pancreatic carcinogenesis because diabetes, greater glucose and insulin concentrations, and insulin resistance have been implicated in pancreatic cancer development in both animal (31–38) and epidemiologic studies (39–46). Thus, 25(OH) vitamin D concentrations could plausibly affect pancreatic function and possibly pancreatic cancer etiology.

EPIDEMIOLOGIC STUDIES OF VITAMIN D INTAKE AND PREDICTED 25(OH) VITAMIN D SCORE AND PANCREATIC CANCER

In two prospective analyses conducted in the Health Professionals Follow-up Study (HPFS) and Nurses Health Study (NHS), researchers suggested that vitamin D may be

protective for pancreatic cancer. The first conducted in the HPFS showed that a higher predicted 25(OH) vitamin D status score was associated with lower total cancer incidence and mortality including pancreatic cancer (pancreatic cancer $n = 170$, relative risk [RR] = 0.49, 95% confidence interval [95% CI], 0.28–0.86 for increment of 25nmol/L predicted plasma 25(OH) vitamin D) (47). Predicted vitamin D status score was a constructed variable based on six determinants of 25(OH) vitamin D measured on 1075 men of this cohort (48, 49) using a linear regression model. The individuals that the score variable was calculated from were cases and controls from a nested case control study of prostate cancer and a small sample of African-American, Asian, and white men (48, 49). The strongest predictors were race or darker skin (Caucasian, African-American, and Asian) and leisure activity, followed by dietary intake from foods, body mass index, and geographic residence (South, Midwest/West, and Northeast/Mid-Atlantic) (47). Supplemental vitamin D increased 25(OH) vitamin D the least (47).

The second study was a pooled analysis of the HPFS and NHS that observed an inverse association between total vitamin D intake and pancreatic cancer (Table 1, $n = 365$ cases, diet and supplemental vitamin D, > 600 IU compared with < 150 IU, RR, 0.59, 95% CI, 0.40–0.88, p -trend = 0.01) (50). Greater than 90% of the men and women in the > 600 IU category reported multivitamin use (50). In analyses stratified by cohort, significant inverse total vitamin D associations were evident only in the HPFS ($n = 178$ cases, > 600 IU compared with < 150 IU, RR, 0.49, 95% CI, 0.29–0.82, p -trend = 0.01) and not NHS ($n = 187$ cases, > 600 IU compared with < 150 IU, RR, 0.76, 95% CI, 0.42–1.38, p -trend = 0.47) (50). No associations were observed for vitamin D intake from foods (50).

Although these findings have fostered enthusiasm for vitamin D having a protective potential for pancreatic cancer, the inherent limitations of these studies should be recognized. In the first study, the six determinants of 25(OH) vitamin D status only explain 28% of the variability of vitamin D status and race was not controlled in any model (47). Data on time spent outside, an important determinant for vitamin D status, was not used to create the score. African-American race was one of the most important components of the predicted 25(OH) vitamin D status score (47) but is an established risk factor for pancreatic cancer, associated with a greater than 2-fold increase risk for digestive cancer mortality in the HPFS, and factors other than vitamin D status could explain the race-cancer disparity. Greater than 70% of 25(OH) vitamin D status among the men in this cohort was explained by factors other than those of the predicted 25(OH) vitamin D score, and the study's reported association for pancreatic cancer may be confounded by race.

TABLE 1. RRs and 95% CIs of baseline total vitamin D intake, vitamin D intake from food sources, and pancreatic cancer in the HPFS and NHS cohorts^a

	Total vitamin D intake (IU per day)					<i>p</i> -trend
	<150	150–299	300–449	450–599	> 600	
HPFS (1986–2000)						
Case, n	49	65	23	14	36	
Person-years	142,237	200,615	98,274	65,814	104,629	
Age-adjusted RR (95% CI) ^b	1.00 (referent)	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) ^c	1.00 (referent)	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) ^d	1.00 (referent)	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)						
Case, n	55	53	22	22	26	
Person-years	347,219	379,125	167,748	124,542	143,359	
Age-adjusted RR (95% CI) ^b	1.00 (referent)	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) ^c	1.00 (referent)	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) ^d	1.00 (referent)	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 RR						
Case, n	104	118	45	36	62	
Person-years	489,456	579,740	266,022	190,356	247,988	
Age-adjusted RR (95% CI) ^b	1.00 (referent)	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) ^c	1.00 (referent)	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) ^d	1.00 (referent)	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
	Vitamin D intake from food alone (IU per day)					
	<100	100–199	200–299	>300		
HPFS (1986–2000)						
Case, n	17	37	20	18		
Person-years	55,731	132,961	86,859	70,250		
Age-adjusted RR (95% CI) ^b	1.00 (referent)	0.78 (0.44–1.39)	0.56 (0.29–1.08)	0.58 (0.30–1.13)		0.09
Multivariate RR (95% CI) ^{c, e}	1.00 (referent)	0.79 (0.44–1.40)	0.57 (0.30–1.09)	0.58 (0.29–1.13)		0.08
NHS (1984–2000)						
Case, n	24	45	26	12		
Person-years	171,338	308,937	164,567	80,280		
Age-adjusted RR (95% CI) ^b	1.00 (referent)	0.93 (0.57–1.53)	0.92 (0.53–1.60)	0.80 (0.40–1.60)		0.54
Multivariate RR (95% CI) ^{c, e}	1.00 (referent)	0.94 (0.57–1.55)	0.91 (0.52–1.59)	0.80 (0.40–1.60)		0.52
Pooled RRs						
Case, n	41	82	46	30		
Person-years	227,069	441,898	251,426	150,530		
Age-adjusted RR (95% CI) ^b	1.00 (referent)	0.87 (0.59–1.26)	0.74 (0.49–1.14)	0.67 (0.42–1.09)		0.10
Multivariate RR (95% CI) ^{c, e}	1.00 (referent)	0.87 (0.60–1.27)	0.74 (0.49–1.14)	0.67 (0.42–1.09)		0.09

^aUsed with permission from Skinner et al. (50).

^bAll RRs are adjusted for age (1-year intervals) and time period (2-year intervals), and total energy.

^cMultivariate RR additionally adjusted for cigarette smoking (current, former, never), history of diabetes (ever, never), body mass index (cut-points: 23.0, 25.0, 27.0, 30.0), height (quintiles), regions of residence (south, north), and parity (among women).

^dMultivariate + multivitamin RRs are additionally adjusted for the use of multivitamin supplements.

^eAnalyses 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.

A limitation of both studies, particularly the second, is that vitamin D intake does not necessary reflect vitamin D status because it excludes cutaneous production of vitamin D.

In addition vitamin D intake from foods is imprecisely estimated from United States food composition databases for vitamin D are inadequate (51). This could contribute to inaccurate or attenuated associations. The protective association between total vitamin D intake and pancreatic cancer was observed only among men who reported taking supplemental vitamin D. Total vitamin D intake was modestly correlated with vitamin D status (Pearson correlation

$r = 0.35$) (50) and supplemental vitamin D was not a strong predictor of vitamin D status (47) in subsets of the HPFS cohort. It is possible that the reported association for total vitamin D intake, particularly related to supplemental vitamin D, could be explained by other vitamins, behaviors or lifestyle factors that are protective for pancreatic cancer and not adequately controlled. Although these studies are both prospective and represent important contributions to our understanding of this question, neither study examined vitamin D status and some caution is warranted in interpreting their results.

EPIDEMIOLOGIC STUDY OF VITAMIN D STATUS AND PANCREATIC CANCER

We recently conducted a nested case-control study in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) cohort of male Finnish smokers to examine whether vitamin D status, as determined by prediagnostic serum 25(OH) vitamin D concentrations, was associated with pancreatic cancer (52). The study included 200 incident exocrine pancreatic cancer cases that occurred between 1985 and 2001 (up to 16.7 years of follow-up) and 400 controls who were alive and free of cancer at the time the case was diagnosed and matched to the cases by age and month of blood draw (52). The later was to minimize misclassification of vitamin D status due to seasonal variation in exposure to sunlight. Contrary to expectations, in multivariable models adjusted for smoking habits, education, occupational activity, and serum retinol, higher as opposed to lower vitamin D concentrations were associated with a nearly three times the risk of pancreatic cancer (Table 2, highest vs. lowest quintile, >65.5 vs. <32.0 nmol/L: odds ratio, 2.92, 95% CI, 1.56–5.48, *p*-trend = 0.001) (52). The association was strong among men who had their blood drawn in the winter season and the significant positive association remained after exclusion of cases diagnosed early during follow-up (52). Season of blood draw, dietary vitamin D from foods (fish and margarine) and supplements, greater leisure activity, serum retinol, and primary school education or less were positive predictors of 25(OH) vitamin D status among controls in the study (52), similar to the predictors in the HPFS (47).

The findings from the ATBC study may not be generalizable to populations that include nonsmokers or populations

that are vitamin D adequate (52). Residual confounding by cigarette smoking dose was unlikely in our study since the smoking exposures were not confounders, the positive association between vitamin D and pancreatic cancer was not modified by cigarette smoking dose (*p*-interaction = 0.36), and analyses restricted to men who reported exactly 20 cigarettes daily (*n* = 53 cases, and 133 controls) yielded similar positive results (fifth quintile, odds ratio, 2.92) (52). Vitamin D status could also be correlated to unmeasured exposures that may increase pancreatic cancer risk. In particular, organochlorine compounds have been associated with pancreatic cancer (53, 54) and are potential contaminants of vitamin D-rich fish consumed in the Finnish diet (55). Although fish intake was a predictor of vitamin D status in our study, controlling for fish did not attenuate the vitamin D/pancreatic cancer association (fifth vs. first quintile vitamin D, HR, 3.62, 95% CI, 1.88–6.97, *p*-trend = 0.0002) (52). In addition, total or processed fish, nitrite, and nitrate (potential pancreatic carcinogens in fish) (56) intake were not associated with pancreatic cancer in our cohort (57).

The ATBC population had lower vitamin D status compared with North American populations (58); however, they had a status similar to other Nordic populations (59), which likely reflects Finland's northern latitude with less solar ultraviolet B photon exposure and less cutaneous vitamin D synthesis (52). Approximately 40% of the controls in our study were in the range of inadequacy (8). Therefore, the association between vitamin D and pancreatic cancer could differ in populations with more adequate or high status.

Our results, along with results of other studies (60), suggest a seasonal effect, with cancer associations being more

TABLE 2. ORs and 95% CIs of baseline fasting 25 (OH) vitamin D (D2 and D3) status and pancreatic cancer risk, among 200 cases and 400 matched control subjects from the ATBC Study^{a,b}

	Quintiles fasting vitamin D (D2 and D3), nmol/L ³					<i>p</i> -trend
	1, <32	2, >32 and <41.1	3, >41.1 and <51.1	4, >51.1 and <65.5	5, >65.5	
Case/controls, <i>n</i>	27/80	34/80	47/80	35/81	57/79	
Crude OR (95% CI)	1.00 (referent)	1.28 (0.71–2.31)	1.91 (1.06–3.42)	1.34 (0.74–2.41)	2.43 (1.34–4.38)	0.006
Multivariable adjusted OR (95% CI) ^c	1.00 (referent)	1.30 (0.70–2.40)	2.12 (1.15–3.90)	1.50 (0.81–2.76)	2.92 (1.56–5.48)	0.001
Winter season ^{c,d}						
Case/controls, <i>n</i>	22/59	24/55	24/47	23/44	25/24	
Crude OR (95% CI)	1.00 (referent)	1.12 (0.56–2.22)	1.45 (0.71–2.94)	1.41 (0.71–2.81)	2.46 (1.15–5.30)	0.02
Multivariable adjusted OR (95% CI) ^c	1.00 (referent)	1.19 (0.59–2.46)	1.95 (0.92–4.14)	1.84 (0.88–3.84)	3.37 (1.47–7.77)	0.003
Spring, summer, and fall season ^{d,e}						
Case/controls, <i>n</i>	5/21	10/25	23/33	12/37	32/55	
Crude OR (95% CI)	1.00 (referent)	1.99 (0.59–6.69)	3.30 (1.06–10.27)	1.38 (0.42–4.49)	2.86 (0.98–8.33)	0.15
Multivariable adjusted OR (95% CI) ^c	1.00 (referent)	1.47 (0.43–5.78)	2.18 (0.66–7.18)	0.93 (0.27–3.24)	2.13 (0.68–6.60)	0.29

^aFrom Stolzenberg-Solomon et al. (52).

^bAll odds ratios should be considered adjusted for the matching factors age and month of blood draw.

^cAdjusted for years smoked, number of cigarettes smoked per day, reporting to have quit smoking > 3 consecutive visits (>1 year) during the trial (1985–1993), occupational physical activity, education, and serum retinol.

^dVitamin D quintiles based on distribution of all controls.

^eSeason, sunny season based on blood drawn during May, June, August, September, October, and November (*n* = 118 cases) vs. darker season based on blood drawn during December, January, February, March, and April (*n* = 82).

pronounced in participants who donated blood during the winter months than during the sunnier months. A single measurement of 25(OH) vitamin D may not reflect long-term vitamin D status; however in a steady state context, it represents the past several weeks to several months of exposure, and is known to display seasonal variability (61). Subjects 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 greater vitamin D status throughout the year, regardless of season (60). In other words, subjects who have high vitamin D concentrations in summer may more likely be misclassified as having high concentrations during other seasons. Although speculative, this could possibly explain the stronger associations among subjects who provided blood in the winter.

The nested case-control study in ATBC cohort, however, does have a number of epidemiologic design strengths. It is a prospective study with vitamin D status being assessed up to 16 years before cancer diagnosis, thereby reducing the influence of reverse causality. The measurement of serum 25(OH) vitamin D concentrations reflects internal dose and status which encompasses cutaneous production of the vitamin and is considered superior to vitamin D intake alone or exogenous predictors of vitamin D status. Technicians of an experienced lab measured serum vitamin D₂ and D₃ on our study samples using a radioimmunoassay (RIA, DiaSorin, Inc., Stillwater, MN) (52) and our blinded quality control have similar reliability to others reported in the literature (62, 63). The direction of our results is similar to that observed for digestive cancers (including pancreatic cancer), other than colorectal cancer in a recent prospective study conducted in the Third National Health and Nutrition Examination Examination Survey (64). In addition, in an earlier nested case-control study conducted in the ATBC cohort, 25(OH) vitamin D was inversely associated with colorectal cancer, particularly distal colorectal cancer (65), a direction similar to that of other studies (66). These observations lend external validity to association studies of 25(OH) vitamin D in the ATBC cohort.

CONCLUSIONS

The results from epidemiologic studies, including ecologic, predicted 25(OH) vitamin D status score, vitamin D intake, and biochemical measured vitamin D status, are conflicting and the respective limitations of each study should be considered. As the effect of vitamin D on molecular mechanisms underlying pancreatic carcinogenesis are not well understood, in addition to examination of potential anticarcinogenic effects of high vitamin D and vitamin D analogs,

alternative and biologically plausible mechanisms related to how lower vitamin D levels might influence tumor growth should also be considered and investigated in basic research studies. At present no conclusions can be made regarding vitamin D's potential role(s) in the etiology of pancreatic cancer. More epidemiologic research is needed, particularly prospective studies that relate pre-diagnostic vitamin D status to pancreatic cancer in cohorts that include women and non-smokers.

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