

Serum Vitamin D and Risk of Bladder Cancer

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Abstract

Vitamin D may protect against several cancers, but data about the association between circulating vitamin D and bladder cancer are limited. Within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a randomized controlled trial conducted to determine the effects of α -tocopherol and β -carotene supplements on cancer incidence in male smokers, 250 bladder cancer cases were randomly sampled by month of blood collection. Controls were matched 1:1 to cases on age at randomization and date of blood collection. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of bladder cancer by a priori categories of baseline serum 25-hydroxyvitamin D [25(OH)D; i.e., <25, 25 to <37.5, 37.5 to <50, \geq 50 nmol/L] and by season-specific quartiles. After multivariable adjustment, we found that lower 25(OH)D was associated with a statistically significantly increased risk of bladder cancer (versus \geq 50 nmol/L; <25 nmol/L: OR, 1.73; 95% CI, 1.03–2.91; 25 to <37.5 nmol/L: OR, 1.81; 95% CI, 1.05–3.14; 37.5 to <50 nmol/L: OR, 1.76; 95% CI, 1.02–3.02; P trend = 0.04). Similarly, increased risks for the lowest vitamin D category were observed when season-specific quartiles were used (Q1 versus Q4: OR, 1.63; 95% CI, 0.96–2.75; P trend = 0.03). In this prospective study of male smokers, lower serum 25(OH)D was associated with an increased risk of bladder cancer. Future studies should examine the association in other populations, especially nonsmokers and women. *Cancer Res*; 70(22); 9218–23. ©2010 AACR.

Introduction

Urinary bladder cancer is an important health concern in developed countries, particularly for men, among whom incidence is three to five times greater than in women (1, 2). In the United States, bladder cancer is the fourth most common cancer diagnosed among men, and the eighth leading cause of cancer death (3). Cigarette smoking, occupational exposure to certain chemical carcinogens, and, in the Middle East, infection with *Schistosoma hematobium* are known risk factors for bladder cancer (1, 2), although they do not fully explain its etiology. Dietary factors, including intake of fruits and vegetables, red meat, and micronutrients such as vitamins A, C, and E, are hypothesized to influence bladder cancer risk, but evidence remains inconclusive (1).

Vitamin D is one nutritional factor that is thought to protect against cancer at many sites (4, 5). The primary circulating

form of vitamin D is 25-hydroxyvitamin D [25(OH)D], which is considered the best indicator of an individual's vitamin D status (5). 25(OH)D is converted to its active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D], by 1- α -hydroxylase (5, 6). 1,25(OH)₂D has been shown to promote cell differentiation and decrease proliferation, invasion, angiogenesis, and metastasis (4, 5). Because most cells in the body express 1- α -hydroxylase, it is reasonable to hypothesize that 1,25(OH)₂D is available locally and may prevent cancer in multiple organs (4, 5), with evidence being supportive for colorectal cancer and suggestive for breast cancer (5). On the other hand, recent results from the Cohort Consortium Vitamin D Pooling Project of rarer cancers, which examined the association between serum vitamin D and risk of pancreatic, ovarian, upper gastrointestinal, endometrial, and renal cancers, and lymphoma, suggest that vitamin D has little influence on the occurrence of cancer at these sites (7–12). Few studies have examined the association between vitamin D and bladder cancer, however.

One laboratory study showed vitamin D inhibition of bladder cancer cell proliferation and bladder tumorigenesis in rats (13). To our knowledge, no studies have examined the association between serum vitamin D and risk of bladder cancer, although two studies of vitamin D intake found no association (14) and an inverse association (only among individuals \geq 63 years old; ref. 15). Self-reported dietary intake of vitamin D is a less accurate measure of vitamin D status than are serum or tissue 25(OH)D concentrations, however. One study reported bladder cancer risk to be higher among persons with alleles of the vitamin D receptor

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doi: 10.1158/0008-5472.CAN-10-0985

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rs10735810 polymorphism ("FokI") that are known to decrease the activity of the receptor (16).

We analyzed nested case-control data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a large primary cancer prevention trial of α -tocopherol and β -carotene supplementation, to examine whether circulating concentration of 25(OH)D was prospectively associated with risk of bladder cancer.

Materials and Methods

The ATBC Study was a randomized, double-blind, placebo-controlled, primary prevention trial conducted to determine the effects of supplementation with α -tocopherol and β -carotene on cancer incidence (17). Caucasian male smokers ($n = 29,133$) from southwestern Finland were recruited between 1985 and 1988. Men were between 50 and 69 years old at baseline and smoked at least five cigarettes per day as part of the enrollment criteria. Men were ineligible if they had previously had cancer or another serious illness at enrollment, or if they reported current use of supplements containing vitamin E (>20 mg), vitamin A ($>20,000$ IU), or β -carotene (>6 mg). Men who were enrolled in the trial were assigned to one of four groups based on a 2×2 factorial design: (a) α -tocopherol (DL- α -tocopheryl acetate, 50 mg/d), (b) β -carotene (20 mg/d), (c) both supplements, or (d) placebo. Trial participants were supplemented for 5 to 8 years, until death, or until the trial ended on April 30, 1993. Although the intervention trial ended, follow-up is ongoing through the Finnish Cancer Registry and the Register of Causes of Death and, for this analysis, is complete through April 20, 2005. The ATBC Study was approved by institutional review boards at both the U.S. National Cancer Institute and the Finnish National Public Health Institute, and written informed consent was obtained from all participants. At enrollment, participants completed questionnaires about general risk factors, smoking, and medical history, as well as a food frequency questionnaire. Participants also underwent physical examination by registered nurses to measure their height and weight, and to collect an overnight fasting blood sample.

Bladder cancer cases were identified by linkage with the Finnish Cancer Registry, which provides $\sim 100\%$ complete incident cancer ascertainment in Finland (18). Medical records for the cases diagnosed before September 2001 were reviewed by one or two study oncologists to confirm diagnosis and staging, with subsequent cases reviewed by a study physician. Two hundred fifty of the 558 total bladder cancer cases in the ATBC Study were randomly sampled by month of blood collection such that 25 cases were included from each month, with 25 cases total from June to August because there were few clinic visits during the summer months (and none in July). Controls were sampled without replacement from ATBC Study participants who were alive and cancer-free at the time the case was diagnosed and were matched 1:1 with cases on age at randomization (± 1 year) and date of blood collection (± 30 days). Bladder cancer cases were not eligible to be controls.

Fasting serum samples collected at baseline were stored at -70°C . 25(OH)D was measured by Heartland Assays, Inc. using the DiaSorin Liaison 25(OH)D TOTAL assay (19). Each batch of samples contained four or six blinded quality control (QC) samples from our study and from standard reference materials provided by the National Institute of Standards and Technology (NIST) at both level 1 (prepared from "normal" human serum and not altered, ~ 60 nmol/L) and level 2 (prepared by diluting level 1, ~ 35 nmol/L; ref. 20). Interbatch and intrabatch coefficients of variation were as follows: 12.7% and 9.3%, respectively, for NIST level 1; 13.6% and 11.0%, respectively, for NIST level 2; 12.3% and 10.5%, respectively, for the ATBC cohort QC samples. Further details of the laboratory and QC methods are discussed elsewhere (21).

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of bladder cancer by a priori categories of baseline 25(OH)D (<25 , 25 to <37.5 , 37.5 to <50 , 50 to <75 , ≥ 75 nmol/L). The association for the 50 to <75 and ≥ 75 nmol/L groups was similar, so we collapsed these categories. To capture whether the association differed at very low 25(OH)D levels, we split the <25 category into <15 and 15 to <25 , but the association was similar. Thus, we present our results for baseline serum 25(OH)D by the previously defined four-level a priori categories. These cut points were chosen using clinical definitions for vitamin D deficiency and sufficiency (6, 22, 23). Further, because these cut points are commonly used in research studies (7–12, 24), categorizing serum 25(OH)D in this way enables comparison of our findings with those from other studies. We chose ≥ 50 nmol/L as the referent category because it contains the mean 25(OH)D level of the U.S. population as determined in the 2000 to 2004 National Health and Nutrition Examination Survey (25). We evaluated the trend across categories by modeling the median of each category as a continuous variable and evaluating its statistical significance using the Wald test. Because bladder cancer is a rare disease, the OR is a good approximation of the relative risk, and we use these terms interchangeably. All models were conditioned on the matching factors (age and date of blood collection).

The following factors that are hypothesized or known to be associated with either bladder cancer or vitamin D were assessed as potential confounding variables: height, weight, body mass index (BMI), urban residence, attained education, skin behavior in the sun, trips to the south, cigarettes per day, years smoked, family history of bladder cancer, physical activity, marital status, high-risk occupation (chemical dye manufacture), intake of dairy, total fluid, dietary calcium, supplemental vitamin D, supplemental calcium, serum total cholesterol, α -tocopherol, β -carotene, and retinol. Although family history of bladder cancer and high-risk occupation seemed to be associated with the outcome, there were too few individuals in these groups (family history, $n = 6$; high-risk occupation, $n = 8$) to adjust for them in the multivariable model. Each of the remaining variables was entered into the age-adjusted model to evaluate whether the point estimates for 25(OH)D categories changed by at least 10%, and none did so. Thus, our final model

Table 1. Selected baseline characteristics [medians (interquartile range) or number (percent)] for case and control subjects, ATBC Study

Characteristic	Controls (n = 250)	Cases (n = 250)
Age (y)	59 (56-63)	59 (55-63)
Height (cm)	173 (168-176)	174 (169-178)
Weight (kg)	76.5 (70.1-85.2)	76.5 (70.0-86.0)
BMI (kg/m ²)	25.8 (23.5-28.4)	25.5 (23.3-27.8)
Cigarettes per day	20 (15-25)	20 (15-25)
Years of smoking	38 (32-43)	40 (35-44)
Occupational physical activity		
Not working	125 (50.0)	113 (45.2)
Very light/light	72 (28.8)	85 (34.0)
Moderate/heavy	53 (21.2)	52 (20.8)
Physically active		
No	205 (82.0)	203 (81.2)
Yes	45 (18.0)	47 (18.8)
Urban residence	146 (58.4)	161 (64.4)
Married	218 (87.2)	215 (86.0)
>Elementary school education	46 (18.4)	59 (23.6)
Family history of bladder cancer	2 (0.9)	4 (2.3)
Skin behavior in the sun*		
Burns easily	76 (32.0)	69 (35.0)
Burns slightly	70 (29.0)	48 (24.0)
Will not burn	93 (39.0)	80 (41.0)
Total energy intake (kcal/d)	2,650 (2,241-3,068)	2,597 (2,144-3,022)
Dietary vitamin D (IU/d)	4.8 (3.5-6.9)	4.6 (3.0-6.5)
Dietary calcium (mg/d)	1,313 (1,034-1,737)	1,326 (1,017-1,645)
Dairy (g/d)	777 (553-1,002)	740 (507-1,001)
Poultry (g/d)	15.7 (8.2-27.4)	13.9 (8.5-21.3)
Ethanol (g/d)	8.5 (1.8-23.0)	7.6 (1.3-22.7)
Total beverages (g/d)	1,972 (1,659-2,421)	1,915 (1,657-2,304)
Supplemental vitamin D use		
Yes	14 (5.6)	13 (5.8)
Supplemental calcium use		
Yes	22 (8.8)	23 (9.2)
Serum cholesterol (mmol/L)	6.1 (5.5-6.9)	6.3 (5.5-7.0)
Serum α -tocopherol (mg/L)	11.4 (10.2-13.8)	11.6 (9.8-14.3)
Serum β -carotene (μ g/L)	180 (118-284)	185 (127-285)
Serum retinol (μ g/L)	564 (498-667)	579 (494-666)

*Among the 197 cases and 239 controls that completed the study follow-up form.

is conditioned on the matching factors (age and date of blood collection) without adjustment for further covariates. We also present our main results further adjusted for cigarettes per day and years smoked because smoking is such a strong, well-established risk factor for bladder cancer.

Because 25(OH)D levels are known to vary by season, we used two approaches to address its influence. First, as mentioned previously, blood was collected throughout the year (except in July) and cases and controls were matched on date of blood draw. Second, we examined the bladder cancer association by categorizing men according to season of blood draw-specific quartiles of 25(OH)D based on the control

distribution of each season (sunnier season: June to October; darker season: November to May). Analyses were conducted stratifying by age at diagnosis (<60, \geq 60 years), cigarettes smoked per day (<20, \geq 20), α -tocopherol and β -carotene intervention arms, season (sunnier season, darker season), physical activity (yes = at least light or moderate occupational activity or moderate leisure time activity), time between blood collection and case diagnosis (<10, \geq 10 years), and less than median versus \geq median of BMI, serum total cholesterol, and dietary intake of vitamin D and calcium. Stratified analyses were conducted using unconditional logistic regression adjusting for the matching factors. The main model results

Table 2. ORs and 95% CIs of baseline serum 25(OH)D and bladder cancer risk, ATBC Study

	Serum 25(OH)D (nmol/L)				P
	<25	25 to <37.5	37.5 to <50	≥50	
No. cases/no. controls	83/73	61/52	54/46	52/79	
OR (95% CI)*	1.85 (1.11–3.08)	1.87 (1.09–3.20)	1.81 (1.06–3.08)	1.0 (reference)	0.02
OR (95% CI)†	1.73 (1.03–2.91)	1.81 (1.05–3.14)	1.76 (1.02–3.02)	1.0 (reference)	0.04
	Season-specific quartiles‡ of serum 25(OH)D				P
	Q1	Q2	Q3	Q4	
No. cases/no. controls	79/63	72/63	54/64	45/60	
OR (95% CI)*	1.69 (1.01–2.83)	1.51 (0.91–2.51)	1.10 (0.66–1.83)	1.0 (reference)	0.02
OR (95% CI)†	1.63 (0.96–2.75)	1.48 (0.88–2.48)	1.15 (0.68–1.93)	1.0 (reference)	0.03

*Conditioned on age and date of baseline blood draw.

†Conditioned on age and date of baseline blood draw and adjusted for number of cigarettes per day and years of smoking.

‡Winter quartile cut points (in nmol/L) = Q1: <19, Q2: 19 to <29, Q3: 29 to <44, Q4: ≥44; summer quartile cut points (in nmol/L) = Q1: <29, Q2: 29 to <43, Q3: 43 to <57, Q4: ≥57.

were unchanged when this approach was used instead of conditional logistic regression, making biased estimates unlikely. Statistical interaction was assessed using the likelihood ratio test.

Results

Characteristics of cases and controls were essentially similar with the exception of heavier smoking and somewhat lower consumption of poultry among cases (Table 1).

Lower serum 25(OH)D was associated with a statistically significantly increased risk of bladder cancer (Table 2). Men

in each of the three categories of 25(OH)D below 50 nmol/L were at nearly twice the risk compared with men with 25(OH)D ≥50 nmol/L (<50 versus ≥50 nmol/L: OR, 1.84; 95% CI, 1.20–2.84; $P = 0.005$). The results were somewhat attenuated with adjustment for smoking (Table 2). We observed similar results when quartiles based on season of blood draw were used (Table 2). For every 1 nmol/L increase in 25(OH)D, the odds of bladder cancer decreased by 2.4% ($P = 0.04$).

There was no statistical evidence for interactions with any of the a priori factors examined (data not shown). There was a suggestion, however, that the vitamin D–bladder cancer association was stronger among men whose blood was drawn

Table 3. ORs and 95% CIs of baseline serum 25(OH)D and bladder cancer risk stratified by selected potential effect modifiers, ATBC Study

Subgroup	Serum 25(OH)D (nmol/L)				P for interaction
	<50		≥50		
	No. cases/no. controls	OR (95% CI)	No. cases/no. controls	OR (95% CI)	
Season of blood collection					
Darker	125/115	1.40 (0.78–2.50)	25/32	1.0 (reference)	0.24
Sunnier	73/56	2.28 (1.27–4.11)	27/47	1.0 (reference)	
Physically active					
No	158/140	1.65 (1.05–2.60)	45/65	1.0 (reference)	0.41
Yes	40/31	2.62 (0.94–7.30)	7/14	1.0 (reference)	
α-Tocopherol supplementation					
No	106/72	2.36 (1.34–4.18)	27/43	1.0 (reference)	0.18
Yes	92/99	1.35 (0.75–2.46)	25/36	1.0 (reference)	
Time from blood collection to case diagnosis					
<10 y	96/89	2.59 (1.38–4.85)	33/40	1.0 (reference)	0.11
≥10 y	102/82	1.33 (0.77–2.30)	19/39	1.0 (reference)	

NOTE: Unconditional models adjusted for matching factors (age and date of baseline blood draw).

in the sunnier months, who were not receiving the trial α -tocopherol supplement, and who were more physically active, and for bladder cancer cases diagnosed within 10 years of blood collection (Table 3). These interactions were not statistically significant, however.

Discussion

We observed that men with lower 25(OH)D serum concentrations were at increased risk of bladder cancer compared with men with higher serum levels. These findings are consistent with previous cell culture, *in vivo*, and genetic evidence suggesting that greater exposure to vitamin D could have a role in protecting against bladder cancer (13, 15, 16). Higher serum 25(OH)D may be associated with greater urinary excretion and concentration of free and conjugated vitamin D metabolites (26, 27). Increased exposure of the bladder mucosa to these metabolites could promote transitional cell differentiation and apoptosis and, thus, reduce epithelial proliferation and neoplasia.

Our results were somewhat attenuated, but more consistent with a dose-risk association, when we classified men based on season-specific vitamin D categories compared with a priori cut points. Which method most accurately accounts for normal seasonal fluctuation in vitamin D levels is not clear. One recent simulation study suggested that use of season-specific categories yielded less biased risk estimates compared with adjustment for season through a covariate term in multivariable models, although the influence of case-control matching on date of blood collection, as was done in the present study, was not evaluated (28). It is important to note, however, that regardless of how vitamin D was categorized in our analysis, men with lower vitamin D levels were at substantially increased risk of bladder cancer, with the OR range of 1.6 to 1.7 for the lowest categories being quite consistent across approaches. Interestingly, although the interaction test was not statistically significant and the observation could be due to chance, the inverse association seemed stronger among men whose blood was obtained during the sunnier months. If substantiated by other studies, this could indicate that lower circulating vitamin D during periods expected to reflect greater solar UVB-related vitamin D biosynthesis is a more sensitive predictor of bladder cancer

risk than are lower levels obtained during the darker, "basal state" months. Our data also indicate that the association between vitamin D status and risk of bladder cancer might be stronger in men whose blood was collected less than 10 years before diagnosis. One interpretation of this finding is that lower vitamin D status may play a greater role later, rather than earlier, in bladder carcinogenesis (i.e., by promoting tumor growth and progression). Although this is speculative and requires examination in other cohorts with long follow-up, it is consistent with experimental findings of cancer cell culture growth inhibition by 1,25(OH)₂D (13).

Our measurement of 25(OH)D in prospectively collected serum in one laboratory and our detailed information on potential confounding factors, including date of blood draw, smoking dose and duration, physical activity, and dietary and supplemental intakes of vitamin D, are important strengths of this study. Although we were able to examine many potential effect modifiers, we had limited statistical power to detect modest differences between strata. It is possible that larger studies could clarify the suggested interactions observed here (i.e., with season of blood draw, physical activity, and vitamin E supplementation).

In this population of male smokers, lower serum 25(OH)D was associated with an increased risk of bladder cancer over a 20-year period. Future studies should examine the association in other populations, especially nonsmokers and women, and evaluate possible effect modification by season of blood draw, physical activity, and intake of other nutrients, including vitamin E.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

USPHS (contract numbers N01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN26120100006C) from the National Cancer Institute, Department of Health and Human Services, and Intramural Research Program of the National Cancer Institute.

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Received 03/29/2010; revised 08/17/2010; accepted 09/07/2010; published OnlineFirst 10/26/2010.

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Cancer Res 2010;70:9218-9223. Published OnlineFirst October 26, 2010.

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