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Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men

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Abstract

Background—Published studies suggesting a relationship between vitamin D and some common cancers sparked interest in the association of vitamin D with head and neck cancers. Prolonged darker months in Finland are associated with lower levels of ultraviolet B radiation, raising concerns about low vitamin D levels.

Methods—We used a nested case-control study in the prospective Alpha-Tocopherol Beta Carotene (ATBC) Study of male smokers in Finland, to examine the relationship between serum 25(OH)D and risk of developing squamous cancers of the head and neck. Using conditional logistic regression we calculated the multivariate adjusted odds ratio (OR) and confidence interval (CI) comparing those with serum 25(OH)D adequate levels of 50–<75 nmol/L to those <25.0.

Results—We identified incident cancers of the oral cavity (n=134), pharynx (n=48), and larynx (n=158). Median serum vitamin D was 31 nmol/L (interquartile range 21–48), which is below the 50 nmol/L cutoff considered adequate for bone and overall health. Comparing those with serum 25(OH)D below 25 nmol/L to those 50–<75 nmol/L as the referent, the OR was 1.35 (95% CI: 0.53, 3.43, p-trend=0.65) for overall head and neck cancers. Stratification by cancer sub-sites of the oral cavity, pharynx and larynx (p-trend= 0.93, 0.78, 0.26 respectively) or by season of blood draw also showed no association.

Conclusions—Our study showed no association between serum 25(OH)D and risk of head and neck cancers.

Impact—This study does not support the hypothesis that greater vitamin D exposure would reduce the risk of developing head and neck squamous cancers.

Keywords

Head and neck/oral cancers; Diet; alcohol; smoking; and other lifestyle risk factors; vitamin D; Cohort; Finland

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Conflicts of interest: none

Introduction

Head and neck cancer is a general term that includes epithelial malignancies that arise in the nasal cavity, paranasal sinuses, oral cavity, pharynx or larynx (1). Head and neck cancer is the sixth most common cancer, with about 650,000 new cancer cases and 350,000 worldwide each year(1). Widely recognized risk factors include tobacco and alcohol, which account for an estimated 75% of head and neck cancers in industrialized regions. Human Papillomavirus (HPV) infection has also been implicated in an increasing fraction of cancers of the head and neck (2, 3).

Ecological studies have suggested that populations with more solar UV radiation exposure, the primary source of vitamin D for most people, have lower rates of some cancers (4). Observational studies preferentially use individual exposure measures and serum 25(OH)D concentration appears to be a reasonably stable assessment of vitamin D status (5). Many studies have used this marker to test the association between vitamin D and cancers of the breast, colon, prostate, and some rarer cancers (4, 6–12). Some studies show an association between higher concentrations of serum vitamin D and a reduced risk of prostate, colon, and breast cancer incidence and/or mortality(4, 6). Higher 25(OH)D, however, has been associated with increased risk of pancreatic(12, 13) and upper gastrointestinal tract cancers(7, 14).

The relationship between vitamin D and head and neck cancers has only minimally been explored. At present there is no published literature on serum vitamin D and incidence of head and neck cancers in humans, and a recent study exploring the relationship between dietary vitamin D, serum 25(OH)D, and head and neck cancer prognosis found no association (15). One prospective study in men using predicted 25(OH)D level based on participant characteristics showed an association between predicted plasma 25(OH)D level and risk of oral and pharyngeal cancers combined (relative risk 0.30; 95% CI: 0.11–0.81), but did not report on the association with larynx cancer (16).

The current prospective study examines the association between serum 25(OH)D concentration and the risk of developing cancer of the oral cavity, pharynx and larynx (a subset of all head and neck cancers) in a nested case-control study within the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study.

Materials and Methods

Study population

Cases and controls were selected from the ATBC Study cohort, a randomized, double-blind, placebo-controlled primary cancer prevention trial. Study design, methods and rationale have been published elsewhere (17). Participants included 29,133 males between the ages of 50–69 from southwestern Finland who smoked 5 or more cigarettes daily. Enrollment occurred between 1985–1988 and participants completed baseline questionnaires on general characteristics, medical history, smoking, dietary and physical activity history. At baseline, staff collected anthropometric measurements and calculated body mass index (BMI) from height and weight. Serum alpha-tocopherol, beta-carotene, and retinol were assessed using high performance liquid chromatography assay (17). The randomization scheme was based on a 2×2 factorial design, assigning participants to alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both alpha-tocopherol and beta-carotene, or a placebo. Follow up for cancer incidence and cause-specific mortality continues through the Finnish Cancer Registry with nearly 100% case ascertainment.(18) All participants provided written informed consent and the institutional review boards of both the National Public Health Institute in Finland and the U.S. National Cancer Institute approved the study.

Case identification and control selection

There were 348 incident cases of head and neck cancer as defined by the International Classification of Diseases 9 codes 140–145 (oral cavity),146–149 (pharnyx) and 161 (larynx) diagnosed between September, 1985 and April, 2005. We excluded non-squamous cell carcinomas and metastatic tumors of non-specific origin (n=8). The final number of cases (n=340) included 134 oral cavity, 48 pharynx and 158 larynx cancer cases. Controls were alive and free of cancer at the time of case diagnosis and were matched to cases (1:1) on age at randomization (+/− 1 year) and date of baseline serum collection (+/− 30 days).

Serum 25-hydroxyvitamin D measurements and exposure metrics

At the pre-randomization visit, fasting serum samples were collected and stored at −70° C. There were no participant visits or blood collection during July, and relatively few in June and August. The samples were measured for 25(OH)D with the DiaSorin Liaison 25(OH)D TOTAL assay platform using a direct, competitive chemiluminescence immunoassay at Heartland Assays, Inc. (Ames, Iowa) in early 2008 (19, 20). Previous research shows that 25(OH)D concentrations are correlated in samples assayed up to 14 years apart (5, 21–24). Methods used for this sample have been described in detail elsewhere (20). In short, matched case/control sets were placed in the same batch, with 4 or 6 quality controls samples from both the ATBC pool and the National Institute of Standards and Technology (NIST) standard reference material #972. For the NIST sample the median interbatch coefficient of variation (CV) for cohort quality control samples was 13.2% (range 4.8%–17.0%), and the intrabatch CV was 9.9% (range 3.8%–16.4%). For the ATBC pool interbatch and intrabatch CVs for duplicate aliquots were 12.3% and 10.5%, respectively.

Serum concentrations for the primary analyses used five *a priori* defined 25(OH)D categories based on cut points thought to have clinical relevance: <25, 25 to <37.5, 37.5–<50, 50–<75 (reference), >75 nmol/L. Previously published studies used these cut points, (20) and the reference level of 50–<75 nmol/L includes the mean for subjects in the US National Health and Nutrition Examination Survey (25). We also constructed two other metrics for exposure that account for seasonal differences in mean serum 25(OH)D because a simulation study indicated that using season-specific cut points reduced the bias associated with different dates of blood draw (26). First, we created season-specific quartile cut points using the distribution of control samples within each season (defined below). Second, we created quartiles of residual-based vitamin D measure which adjusted out the effect of season, using the Local Polynomial Regression Method (SAS Proc LOESS) to regress log transformed 25(OH)D against calendar week of blood collection (27). We also stratified our analyses by season of blood draw to create a “season-adjusted” measure, which is defined as “darker months” (November-April) and “sunnier months” (May-October) based on monthly median 25(OH)D concentrations among controls.

Statistical analysis

Descriptive analyses comparing cases and controls used χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Crude and adjusted conditional logistic regression models were used to estimate of the association between serum vitamin D and head and neck cancers. Trend tests used a scored serum vitamin D level of either 1–4 or 1–5 as appropriate. All reported P-values are two-sided and an alpha error level was set at <0.05. All statistical analysis was carried out using SAS 9.2 (SAS Institute, Inc. Cary, NC).

Serum 25(OH)D had a skewed distribution, which we corrected using log transformation. Variables assessed for confounding included age, pack-years, cigarettes per day, smoking years, alcohol intake, BMI, physical activity (both leisure and occupational), history of hypertension, history of diabetes, dentures, missing teeth, daily calorie intake, fish intake,

serum retinol, serum alpha tocopherol, serum beta carotene, serum cholesterol, high density lipoprotein (HDL), season of blood draw, marital status and vacations to sunny areas. Potential confounders associated with cancers of the oral cavity, pharynx or larynx were added to the univariate model to test whether there was a change of greater than 10% in the 25(OH)D coefficients.

We considered variables that showed a significant relationship with both outcome and exposure at a 0.10 statistical significance level for the final model. Using backward selection, we included all variables and performed stepwise elimination of variables with the highest p-value until all variables included in the model were significant at a 0.05 level. Variables excluded from the model did not change betas by >10%. The final models included adjustment for continuous age, pack-years, body mass index, alcohol intake (categorized as missing, no alcohol, up to one drink (reference), one to three drinks, or greater than three drinks per day), and serum beta-carotene.

The primary analyses treated all head and neck cancers as a single outcome, but we also report models examining cancers of the oral cavity, pharynx and larynx separately. We further explored potential risk modifiers using unconditional logistic regression, based on median split categories for age, BMI, pack-years, alcohol drinks per day, serum alpha-tocopherol, serum beta-carotene, and alpha-tocopherol and beta-carotene intervention groups. To conserve power we maintained serum 25(OH)D concentration as a continuous measure by scaling the change in risk associated with a 15 nmol/L increase in 25(OH)D serum concentration. Because of a large mode in the number of cigarettes consumed daily, in Figure 1 we categorized tobacco as less than 20 cigarettes per day, 20 cigarettes per day, and greater than 20 cigarettes per day. To examine whether there was evidence of reverse causation in cases with serum collected most proximate to the time of blood collection, we also modeled the data excluding cases diagnosed during the first two years of follow-up and also models stratified on median diagnosis date (4/15/1996).

Results

Table 1 presents characteristics of the study population. Compared to controls, cases had statistically significantly lower BMI, serum beta-carotene, and serum alpha-tocopherol. Cases had higher levels of smoking, based on number of cigarettes smoked per day, years of smoking, pack-years of smoking, serum HDL, and alcohol intake compared to controls. A smaller percentage of cases reported physical activity outside of occupation. Cases and controls were similar with respect to other variables. Median serum 25(OH)D concentrations did not differ between cases and controls (Table 1). We found that 25(OH)D had a Pearson correlation coefficient of −0.045 (p=0.408) for cigarettes per day, and −0.100 (p=0.0659) for years of smoking.

Using the pre-defined clinical cut points, serum 25(OH)D was not associated with risk of head and neck cancer either overall, by sub-site, or by season (Table 2). We tested the alternative exposure metrics of season-specific and season-adjusted quartiles (Table 3). Neither construct showed a significant association between serum 25(OH)D and risk of head and neck cancers.

Exclusion of cases diagnosed within two years of blood collection did not alter the relationship between vitamin D and cancer, nor did an analysis stratified by median diagnosis date (data not shown). Models stratified by the median for potentially interacting variables age, BMI, smoking, alcohol intake, serum beta carotene, trial supplementation group or season of blood draw also did not show significant differences for the association between 25(OH)D and head and neck cancers (Figure 1).

Discussion

This study found no relationship between serum 25(OH)D and head and neck cancer among white, male smokers. Testing the association with cancer risk using concentrations of vitamin D based on *a priori*, season-specific, or season-adjusted cut points each suggested a null relationship. The null association remained in strata of many potential risk modifiers. This study is a first attempt to inform reports such as the World Cancer Research Fund's Expert Report on Diet or the International Agency for Research on Cancer's report on Vitamin D and Cancer, since previous data was not available for the association between serum vitamin D and incidence of head and neck cancer.

Animal models,(28) ecologic studies,(29, 30) and an observational epidemiologic study based on predicted vitamin D exposure(16) suggest reduced risk of head and neck cancers for higher vitamin D exposures. Although this study conflicts with the previously published prediction model suggesting a 70% (95% CI: 0.17–0.80) reduction in risk for oral and pharyngeal cancers, the previous publication was based on predicted, and not measured 25(OH)D levels (16). The study was also conducted in a US population, where average serum 25(OH)D is higher, and although most head and neck cancer cases are smokers, the study included a mixture of smokers and non-smokers..

A recent animal study found that treatment with vitamin D_3 delayed carcinogenesis in the hamster buccal pouch model, but exposure to the carcinogen was initiated at the time of vitamin D dosing and the relationship has not been extended to humans (28). An early phase human trial examined whether treatment with 25-hydroxyvitamin D_3 reduces immune inhibitory CD34+ progenitor cell levels and improves immune parameters since head and neck squamous cell carcinoma patients often present with great immune defects. The study found no evidence of clinical benefit, but did report a positive association between vitamin D treatment and reduced numbers of immune suppressive cells (31).

The strengths of this study are multiple. It is the first to date to examine head and neck cancer incidence in relation to serum 25(OH)D. The prospectively collected data minimizes recall bias for behavioral risk factors such as alcohol and tobacco consumption and also minimizes reverse causality in the serum measure. Furthermore, anthropometric and biological measurements were standardized and the vitamin D assays used the newly available standard reference material for quality control. Although the serum 25(OH)D was a single measure and may fluctuate over time, previous studies using a single measure have shown a consistent protective relationship with other cancer sites such as the colon (32). Also, several studies have shown that correlation coefficients between two measures of 25(OH)D in an individual are generally high enough (0.53–0.70) that a single measure conveys meaningful information (5, 21, 33). Study weaknesses include the potential residual confounding of smoking, even after adjustment. However, correlation coefficients between cigarettes smoked per day and years of smoking were modest, suggesting that the effects of smoking length and intensity on serum vitamin D concentrations are quite small. As previous studies report significant differences in cancer incidence by gender, race, and smoking status,(7) our results for Caucasian male smokers may not generalize to others. Furthermore, we lacked information on HPV exposure and cancers related to HPV may show a different association with vitamin D. Finally, our cases and controls had mean vitamin D levels of 31 and 32 respectively, and few individuals in the highest category above or equal to 75 nmol/L. Therefore we cannot comment on the association between high levels of vitamin D and head and neck cancer.

In this study, we observed no overall or site-specific associations between serum 25(OH)D concentrations and risk of head and neck cancer. Future studies including women, non-white

populations, and non-smokers may further shed light on the relationship between head and neck cancer incidence and vitamin D.

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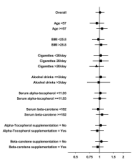

Figure 1.

Table 1

Serum 25(OH)D Concentration and Selected Characteristics in the ATBC Study by Case Status[a]

Characteristic	Cases	Controls	P-value[b]
Number	340	340	*c*
Demographics and Anthropometrics			
Age at randomization (years)	57 (53–61)	57 (53–61)	*c*
Weight (kg)	75 (69–84)	78 (71–87)	0.01
Height (cm)	173 (169–177)	174 (169–177)	0.34
Body mass index (kg/m^2)	25 (23–28)	26 (24–29)	0.01
Urban residence (over 20,000)	208 (61)	201 (59)	0.58
Coastalresidence	178 (52)	159 (47)	0.15
Education (more than elementary)	68 (20)	64 (19)	0.70
Lifestyle Factors			
Number of years of regular smoking	37 (32–43)	36 (31–42)	0.03
Cigarettes per day	20 (17–25)	20 (15–20)	<0.001
Pack years	40 (29–51)	32 (23–44)	<0.001
Alcohol intake (g/day)	16 (5–32)	8.6 (1.7–23)	<0.001
Total Calories	2511(2058–3108)	2647(2184–3091)	0.18
Total Calcium intake (mg/day)	1342 (883–1765)	1310(988–1765)	0.38
Total Vitamin D intake (μg/day)	5.2 (3.5–7.2)	5.0 (3.5–7.2)	0.84
Physical Activity			
Leisure (heavy)	13 (3.8)	26 (7.7)	0.03
Occupational (heavy)	40 (12)	38 (11)	0.86
Vacations to sunny areas	0 (0–4)	0 (0–6)	0.86
Medical History			
History of hypertension	68 (20)	62 (18)	0.56
History of diabetes	11 (3.2)	17 (5.0)	0.25
Serum			
Alpha-Tocopherol (mg/L)	11.2 (9.2–13.4)	11.8 (10.4–13.8)	0.002
Beta-Carotene (ug/L)	145.0 (82.0–225.0)	181.5 (121.0–282.5)	<0.001
Retinol (ug/L)	585.0 (499.0–660.5)	557.0 (491.5–636.0)	0.07
Total cholesterol (mmol/L)	6.21 (5.40–6.98)	6.41 (5.58–7.10)	0.09
HDL (mmol/L)	1.21 (1.01–1.49)	1.15 (0.97–1.40)	0.02
Blood drawn in darker months(Nov-April)	208 (61)	213 (63)	*c*
Serum 25(OH)D (nmol/L)	31(21–47)	32 (21–48)	0.66

[a] Table values are median (interquartile range) for continuous variables and n (column %) for categorical variables.

[b] P-value is for Wilcoxon rank sum test (continuous variables) or χ^2 test (categorical variables).

[c] Matched

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Table 2

Odds Ratios (OR) and 95 % Confidence Intervals(CI) for Serum 25(OH)D Concentration and Risk of Head and Neck Cancers Using *a Priori* Categories Overall, by Sub-site, and by Season in the ATBC Study

	25 (OH) D (nmol/L)									
	<25.0		25.0–<37.5		37.5–<50.0		50.0–<75.0	≥75		P_{trend}
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	
Overall[a]										
Cases/Controls, N	123/119		85/79		59/62		57/68	16/12		
Crude Model	1.24	0.79,1.94	1.27	0.79,2.04	1.14	0.69,1.88	Reference	1.52	0.67, 3.48	0.56
Adjusted Model[b]	0.96	0.58,1.59	1.11	0.65,1.88	1.20	0.69,2.08	Reference	1.35	0.53, 3.43	0.65
Oral Cavity										
Cases/Controls, N	43/50		31/35		29/21		26/24	5/4		
Crude Model	1.33	0.67,2.66	1.27	0.61,2.64	0.81	0.38,1.71	Reference	0.82	0.18,3.84	0.25
Adjusted Model[b]	0.88	0.39,1.98	1.10	0.48,2.51	0.73	0.32,1.66	Reference	0.55	0.09,3.41	0.93
Pharynx										
Cases/Controls, N	16/22		11/12		9/3		11/8	1/3		
Crude Model	2.27	0.63,8.16	1.45	0.37,5.69	0.50	0.11,2.34	Reference	2.18	0.20,23.45	0.26
Adjusted Model[b]	1.07	0.20,5.64	0.86	0.12,6.03	1.34	0.20,9.10	Reference	3.61	0.28,45.93	0.78
Larynx										
Cases/Controls, N	51/60		38/37		35/24		25/31	9/6		
Crude Model	1.01	0.51,2.01	1.33	0.64,2.74	2.06	0.92,4.58	Reference	2.17	0.68,6.98	0.40
Adjusted Model[b]	0.92	0.40,2.13	1.04	0.44,2.48	2.86	1.09,7.53	Reference	2.50	0.61,10.25	0.26
Overall - Darker										
Cases/Controls, N	93/95		51/45		28/28		30/33	4/5		
Crude Model	1.10	0.61–1.96	1.21	0.66,2.24	1.11	0.55,2.23	Reference	0.85	0.22,3.28	0.72
Adjusted Model[b]	0.98	0.51,1.86	1.23	0.62,2.42	1.14	0.53,2.49	Reference	0.69	0.14,3.39	1.00
Overall - Sunnier										
Cases/Controls, N	29/24		33/32		31/34		27/35	12/7		
Crude Model	1.51	0.74,3.11	1.32	0.62,2.81	1.25	0.60,2.59	Reference	2.22	0.74,6.71	0.64

	25 (OH) D (nmol/L)									
	<25.0		25.0–<37.5		37.5–<50.0		50.0–<75.0	≥75		P_{trend}
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	
Adjusted Model[b]	0.94	0.37,2.40	1.07	0.42,2.69	1.15	0.48,2.74	Reference	2.41	0.65,8.90	0.45

[a] Includes cancers of the oral cavity, pharynx and larynx.

[b] Adjusted for age at randomization, pack years, BMI, alcohol intake and serum beta carotene.

Table 3

Odds Ratios (OR) and 95% Confidence Intervals(CI) for Serum 25(OH)D Concentration and Head and Neck Cancers Using Season-Specific or Season-Adjusted Quartilesin the ATBC Study

	Quartiles							
	1		2		3		4	P_{trend}
Overall season-specific[a]								
Cases/Controls, N	93/85		77/85		91/85		79/85	
	OR	95% CI	OR	95% CI	OR	95% CI		
Crude Model	1.14	0.72,1.78	1.06	0.68,1.66	1.12	0.74,1.71	Reference	0.66
Adjusted Model[b]	0.82	0.49,1.38	0.95	0.58,1.57	1.10	0.69,1.76	Reference	0.40
Overall season-adjusted[c]								
Cases/Controls, N	106/85		67/85		90/85		77/85	
	OR	95% CI	OR	95% CI	OR	95% CI		
Crude Model	1.41	0.90, 2.19	0.90	0.57,1.41	1.19	0.77, 1.83	Reference	0.26
Adjusted Model	1.02	0.62, 1.69	0.85	0.52,1.40	1.07	0.66, 1.73	Reference	0.83

[a] Season-specific quartiles cut points were winter Q1: ≤18.176, Q2: >18.176 and ≤26.544, Q3: >26.544 and ≤42.192, Q4: >42.192; summer Q1: ≤30.194, Q2: >30.194 and ≤41.292, Q3: >41.292 and ≤54.443, Q4: >54.443

[b] Adjusted for age at randomization, pack years, BMI, alcohol intake and serum beta carotene.

[c] Season-adjusted loess adjusted quartiles cut points were Q1: ≤3.186, Q2: >3.186 and ≤3.483, Q3: >3.483 and ≤3.845, Q4: >3.845