Research Article

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Plasma 25-Hydroxyvitamin D Levels and the Risk of Colorectal Cancer: The Multiethnic Cohort Study

Christy G. Woolcott[1], Lynne R. Wilkens[1], Abraham M.Y. Nomura[1], Ronald L. Horst[2], Marc T. Goodman[1], Suzanne P. Murphy[1], Brian E. Henderson[3], Laurence N. Kolonel[1], and Loïc Le Marchand[1]

Abstract

Vitamin D is obtained from the diet and synthesized in skin exposed to sunlight. Vitamin D status, assessed by circulating 25-hydroxyvitamin D [25(OH)D], has been associated with a reduced risk of colorectal cancer in previous studies. To complement existing evidence, we conducted a case-control study nested within the Multiethnic Cohort including men and women of Japanese, Latino, African-American, White, and Native Hawaiian ancestry. Using a direct competitive chemiluminescence immunoassay, 25(OH)D level was determined in plasma drawn before diagnosis from 229 cases and 434 controls matched to cases by area (Hawaii, Los Angeles), sex, ethnicity, birth year, blood draw date and time, and hours fasting. Odds ratios (OR) were estimated with conditional logistic regression. An inverse trend was observed (OR per doubling of 25(OH)D, 0.68; 95% confidence interval, 0.51-0.92; $P = 0.01$), but when examined in categories, relative to the first quintile (<16.8 ng/mL), the ORs in all other quintiles were quite similarly reduced between 37% and 46%. The association was not significantly heterogeneous among the four largest ethnic groups ($P_{heterogeneity} = 0.46$). In summary, this study provides evidence of an association between vitamin D status and reduced risk of colorectal cancer in an ethnically diverse population. *Cancer Epidemiol Biomarkers Prev; 19(1); 130–4. ©2010 AACR.*

Introduction

Vitamin D is obtained from oily fish, eggs, fortified foods such as milk, and supplements, but it is also synthesized in skin exposed to light in the 280 to 315 nm UVB range (1). Vitamin D could reduce cancer risk by promoting differentiation and apoptosis and suppressing cell proliferation and angiogenesis (2). Observational epidemiologic studies of sunlight exposure and diet suggest that vitamin D may reduce the risk of colorectal cancer (1, 3-5). Circulating concentrations of 25-hydroxyvitamin D [25(OH)D] are thought to be the best marker of vitamin D status because all sources are captured and a recent meta-analysis of nine studies estimated that 10 ng/mL higher 25(OH)D is associated with a 15% lower risk of colorectal cancer (1). The previous studies examining colorectal cancer incidence were conducted in primarily White or Asian populations.

We examined the association between plasma 25(OH)D and colorectal cancer risk in an ethnically diverse cohort with Japanese, Latino, African-American, White, and Native Hawaiian participants. A previous analysis in this cohort suggested that dietary intake of vitamin D reduced the incidence of colorectal cancer (6). However, because the cohort was conducted in areas with high sun exposure and because dietary vitamin D was strongly correlated with calcium intake, another suspected protective factor (4), we were interested in examining the association with 25(OH)D level. We expected that our participants would have an unusually large range in vitamin D status due to having a wide range of skin pigmentation and living at lower latitudes.

Materials and Methods

We conducted a case-control study nested within the biorepository subcohort of the Multiethnic Cohort (7, 8). The baseline cohort comprised over 215,000 people between the ages of 45 and 75 y who returned a questionnaire by mail between 1993 and 1996. The biorepository subcohort ($n = 67,594$) included White, Hawaiian, and Japanese American participants in Hawaii and African-American, Japanese American, and Latino participants in Los Angeles who agreed to donate a biospecimen, largely between 2001 and 2006. Fasting blood was drawn in heparinized tubes, processed, and separated; the 0.5 mL aliquots of plasma for this study were stored in the vapor phase of liquid nitrogen (–150°C). The Multiethnic Cohort and this study were approved by the Institutional Review Boards of the University of Southern California and the University of Hawaii. All participants provided informed consent at time of blood collection.

Cases were diagnosed with primary colorectal cancer after contributing a biospecimen but before the end of

Authors' Affiliations: [1]Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii; [2]Heartland Assays, Inc., Ames, Iowa; and [3]Keck School of Medicine, University of Southern California, Los Angeles, California

Corresponding Author: Christy Woolcott, Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813. Phone: 808-586-7491; Fax: 808-586-2984. E-mail: cwoolcott@crch.hawaii.edu

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2006. Diagnoses were identified by linkage with population-based cancer Surveillance, Epidemiology, and End Results Program registries in Hawaii, Los Angeles County, and the California State Cancer Registry. Deaths were identified by linkage with the state vital statistics databases and the National Death Index. Two controls per case were randomly selected from a pool of subcohort members alive and not diagnosed with colorectal cancer at the age of the diagnosis of the case, and matched to the case by area (Hawaii, Los Angeles), sex, race/ethnicity, birth year (±1 y), date (±6 mo) and time of blood draw (± 2 h), and hours fasting before blood draw (8 to <10 h, ≥10 h).

The concentration of 25(OH)D was determined at Heartland Assays using a direct, competitive chemiluminescence immunoassay using the DiaSorin LIAISON platform2 (DiaSorin; ref. 9). The antibody used is co-specific for 25(OH)D_3 and 25(OH)D_2. The samples from each matched case-control set were analyzed together within laboratory batches in random order. Laboratory

Table 1. Characteristics of the cases and controls, and association of these characteristics with plasma levels of 25(OH)D among controls

Characteristic	Cases	Controls	Association with 25(OH)D in controls	
	n (%)	*n* (%)	Mean*± SEM	*P*
Sex†				
Male	146 (63.8)	278 (64.1)	26.6 ± 0.6	
Female	83 (36.2)	156 (35.9)	23.4 ± 0.8	<0.01
Ethnicity†				
Japanese American	89 (38.9)	171 (39.4)	27.0 ± 0.7	
Latino	46 (20.1)	88 (20.3)	20.7 ± 0.9	
African-American	45 (19.7)	81 (18.7)	16.8 ± 1.0	
White	39 (17.0)	74 (17.1)	30.8 ± 1.0	
Native Hawaiian	10 (4.4)	20 (4.6)	29.6 ± 1.9	<0.01
Study area†				
Hawaii	127 (55.5)	245 (56.5)	28.6 ± 0.6	
Los Angeles	102 (44.5)	189 (43.5)	19.5 ± 0.7	<0.01
First-degree family history of colorectal cancer				
No	200 (87.3)	394 (90.8)	25.2 ± 0.5	
Yes	29 (12.7)	40 (9.2)	22.1 ± 1.4	0.03
Season of blood draw				
December to June	127 (55.5)	243 (56.0)	23.4 ± 0.6	
July to November	102 (44.5)	191 (44.0)	27.1 ± 0.7	<0.01
	Mean ± SD	**Mean ± SD**	**Correlation‡**	***P***
Age at blood draw, y	69.3 ± 8.0	69.2 ± 7.9	0.02	0.74
Time between blood draw and case diagnosis, y†	1.7 ± 1.4	1.7 ± 1.4	–0.02	0.62
BMI, kg/m^2	26.7 ± 5.0	25.8 ± 4.2	–0.08	0.09
Physical activity, MET-h/d§	6.3 ± 7.7	6.2 ± 7.1	0.07	0.13
Energy intake, kcal/d	2,242 ± 975	2,185 ± 1,031	–0.10	0.03
Processed red meat intake, g/1,000 kcal/d	8.0 ± 6.1	7.8 ± 6.6	–0.01	0.82
Calcium intake, mg/1,000 kcal/d	430.0 ± 229.2	479.8 ± 283.3	0.11	0.02
Vitamin D intake, IU/1,000 kcal/d	151.6 ± 167.9	165.5 ± 204.7	0.09	0.06
Plasma 25(OH)D, ng/mL	23.2 ± 10.1	25.0 ± 9.9	—	—

Abbreviation: MET-h, metabolic equivalent hours.

*Among controls, mean 25(OH)D (ng/mL) by level of the characteristic, adjusted for sex and ethnicity as appropriate (except for area). *P* value from analysis of covariance. To convert to nmol/L, multiply these values by 2.5.

†Matching variables.

‡Among controls, partial correlation between 25(OH)D and the characteristic, adjusted for sex and ethnicity.

§Summary statistics based on slightly fewer than 229 cases and 434 controls due to missing values.

Table 2. ORs and 95% CIs for the association of plasma levels of 25(OH)D with the risk of colorectal cancer

25(OH)D	Cases	Controls	OR* (95% CI)	OR† (95% CI)
<16.8 ng/mL	67	87	1.00 (Reference)	1.00 (Reference)
16.8 to <22.2	42	86	0.61 (0.37-1.02)	0.63 (0.37-1.08)
22.2 to <26.3	38	88	0.52 (0.31-0.89)	0.54 (0.32-0.93)
26.3 to <32.8	43	87	0.58 (0.34-0.99)	0.62 (0.36-1.07)
≥32.8	39	86	0.53 (0.30-0.93)	0.60 (0.33-1.07)
Per doubling			0.65 (0.48-0.86)	0.68 (0.51-0.92)
			P_{trend}‡ = 0.003	P_{trend}‡ = 0.01

*Controlled for age, sex, race/ethnicity, study area, date and time of blood draw, and hours fasting through case-control matching and adjusted using conditional logistic regression.
†Further adjusted for family history of colon cancer, BMI, and intake of processed red meat.
‡Trend tests based on the significance of the continuous variable, the logarithm (base 2) of 25(OH)D.

personnel were blind to case status. Based on 27 quality control samples, the intrabatch coefficient of variation was 6.7% and the intraclass correlation coefficient was 0.83. Based on 24 quality control samples, the interbatch coefficient of variation was 5.0% and the intraclass correlation coefficient was 0.82.

The baseline questionnaire, completed between 1993 and 1996, assessed ethnicity/race, weight and height, smoking, physical activity, and diet (7). Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Volume of physical activity was calculated as metabolic equivalents spent in moderate activity, strenuous sports, and vigorous work (10). Diet over the past year was assessed with a food frequency questionnaire from which food nutrient intake was calculated using a food composition table maintained at the Cancer Research Center of Hawaii (7). Total nutrient intake was the sum from both food and supplement sources.

Of the 234 cases who had a fasting plasma sample available, 1 had a missing 25(OH)D result and 3 had missing covariate information. Of the 460 controls matched to the remaining cases, 6 did not have a sample available, 1 had a missing 25(OH)D result, and 19 had missing information about diet or BMI. One additional case was not included because both matched controls had been excluded. Thus, 205 cases with 2 matched controls and 24 cases with 1 matched control were included in the analyses (229 cases, 434 controls).

The odds ratios (OR) for the association between plasma 25(OH)D and colorectal cancer risk were estimated using conditional logistic regression. Using season-specific quintiles (11) affected our results minimally so our results use quintiles based on the overall distribution in controls. Included in the models were the matching factors, as well as age at blood draw and hours fasting as continuous variables to control for any residual differences. We evaluated as potential confounders first-degree family history of colorectal cancer, BMI, physical activity, pack-years of smoking, years of education, alcohol intake, ever use of nonsteroidal anti-inflammatory drugs for >2 y, processed red meat intake, fruit and vegetable intake, and season (December to June, July to November). Family history, BMI, and intake of processed red meat were retained as confounders because only these factors changed at least one of the ORs associated with 25(OH)D more than 3% when added to the models. Trend tests were calculated by using the logarithm (base 2) of 25(OH)D levels. A square term of log-transformed 25(OH)D levels was added to the model to investigate nonlinearity. Supplementary analyses included the investigation of associations by subsite (colon, ICD-O2 C18.0-C18.9; rectum, ICD-O2 C19.9 and 20.9) and ethnicity. P values to test for the significance of effect modification were derived from Wald tests of the interaction terms. The analyses were done using SAS version 9.1 (SAS Institute). All statistical tests were two sided with a 0.05 level of significance.

Results

Characteristics of the participants are shown in Table 1. The mean age at blood draw was 69 years and the mean time between blood draw and case diagnosis was 1.7 years. The mean ± SD plasma 25(OH)D concentration was 23.2 ± 10.1 ng/mL in cases and 25.0 ± 9.9 ng/mL in controls. Mean 25(OH)D concentration was higher in Hawaii than Los Angeles ($P < 0.01$), but confounding this association is that Whites, Japanese Americans, and Native Hawaiians, almost all of whom lived in Hawaii, had higher 25(OH)D levels than African-Americans and Latinos, who lived in Los Angeles ($P < 0.01$).

In analyses controlling only for the matching factors (Table 2), colorectal cancer risk was significantly reduced among participants with plasma 25(OH)D concentrations

in the three highest quintiles (≥22.2 ng/mL) relative to the lowest quintile (<16.8 ng/mL). In analyses controlling for additional confounders, the risk estimates were slightly attenuated but only the OR for the third quintile remained statistically significant. An inverse trend was observed [OR per doubling of 25(OH)D, 0.68; 95% confidence intervals (95% CI), 0.51-0.92; $P = 0.01$]. Although the results for 25(OH)D quintiles suggest a nonmonotonic, slightly U-shaped relationship, adding a square term of log-transformed 25(OH)D levels did not significantly improve the prediction of colorectal cancer risk. The risk estimates were slightly attenuated when calcium was added to the model but the trend remained (OR per doubling of 25(OH)D, 0.71; 95% CI, 0.53-0.95; $P_{trend} = 0.02$), suggesting that calcium intake and plasma vitamin D are independently related to colorectal cancer risk.

Plasma 25(OH)D was associated with a significant reduction in risk of rectal cancer ($n = 43$ cases, $n = 83$ controls) but not of colon cancer ($n = 170$ cases, $n = 319$ controls; OR per doubling of 25(OH)D, 0.40; 95% CI, 0.19-0.85 versus 0.79; 95% CI, 0.56-1.10). No interaction between ethnicity and 25(OH)D on colorectal cancer risk was observed, even when subjects of Native Hawaiian ancestry ($n = 10$ cases) were excluded ($P_{heterogeneity} = 0.46$; Fig. 1). The inverse trend was only significant in Japanese Americans ($P_{trend} = 0.03$), the largest group, in whom a nonmonotonic pattern of risk was observed when 25(OH)D was examined in quartiles [1.00, 0.68 (0.33-1.40), 0.52 (0.24-1.14), and 0.83 (0.39-1.79)]. The OR for Whites was <1.0 but was less precise, reflecting the smaller sample size.

Discussion

In this study, colorectal cancer risk was inversely associated with plasma 25(OH)D concentration. No significant effect modification was observed by ethnic/racial group but the association seemed to be stronger for rectal cancer than colon cancer. An important strength of this study was the use of 25(OH)D measured in plasma collected before diagnosis. This is because circulating 25(OH)D not only reflects vitamin D status in populations with high sunlight exposure better than estimates of dietary intake, but also because it has been shown to be the limiting factor in the synthesis of the active vitamin D form, $1,25(OH)_2D$, in colonic cells (12).

Before further commenting on the implications of this study, its limitations should be considered. The mean time between blood draw and diagnosis was short (1.7 years) and 25(OH)D levels further in the past may be more relevant to colorectal cancer risk. The level of 25(OH)D was measured only once. A single measurement, however, may represent concentrations over a period of years since a high correlation (0.70) has been reported between samples taken 3 to 4 years apart (13). The questionnaire from which dietary intakes and BMI were estimated was completed a median of 8.9 years (interquartile range, 7.6-9.6 years) before the blood draw. Our study was limited in size and statistical power for analyses within some subgroups of potential importance, such as those defined by ethnicity and anatomical subsite. Furthermore, we were unable to separate the effect of ethnicity from geographic area.

The summary risk estimate computed in a recent meta-analysis, 0.85 (95% CI, 0.79-0.91) per increase of 10 ng/mL in 25(OH)D (1), matches almost exactly that computed in this study (without log-transformation, 0.82; 95% CI, 0.67-1.01). All studies within prospective cohorts have observed an inverse association between 25(OH)D and colorectal cancer, although some were not statistically significant (14-24). In contrast, two randomized controlled trials did not find an effect of vitamin D supplementation on the risk of colorectal cancer (19, 25). In one of these trials (19), low compliance and a dose (400 IU/day) that was expected to increase 25(OH)D levels by 4 ng/mL only (26-28) may have resulted in an insufficient difference between the groups for an effect to be detected. In most published studies, a fairly monotonic relationship of colorectal cancer risk across the full range of 25(OH)D levels has been observed (14, 16, 17, 19), with the exception of the Health Professionals Follow-up Study (15), the males in the Japan Public Health Center–Based Prospective Study (20), and the study in Washington County, MD (21, 22). We observed that risk was sharply reduced after the first quintile of plasma 25(OH)D (≥16.8 ng/mL) with no further reduction at higher levels. It has been proposed that 20 to 30 ng/mL is the level below which 25(OH)D is insufficient to help prevent cancer and other chronic outcomes (29); a pooled analysis of existing studies could help to better define the optimal 25(OH)D levels for colorectal cancer risk reduction (1).

This study is the first to examine a multiethnic cohort composed of participants with a range of skin pigmentation living at lower latitudes. It suggests that the inverse association between 25(OH)D levels and colorectal

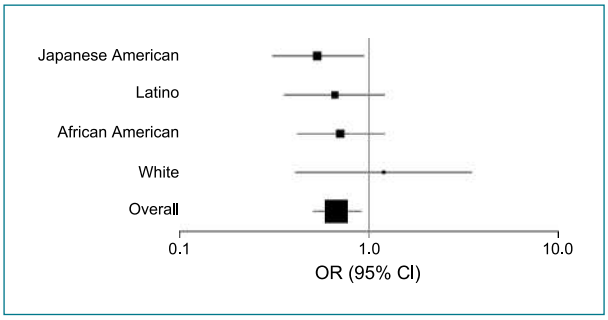

Figure 1. ORs (95% CI) for colorectal cancer associated with a doubling of plasma concentration of 25(OH)D, by race/ethnicity. ORs controlled for age, sex, race/ethnicity, study area, date and time of blood draw, and hours fasting through case-control matching and adjusted for hours fasting, age at blood draw, family history of colon cancer, BMI, and intake of processed red meat using conditional logistic regression.

cancer risk has generalizability beyond the largely Caucasian populations in most previous studies (14-19, 21-24). The ORs from stratified analyses suggested a protective effect in all ethnic groups except Whites but these estimates were imprecise due to the small sample size. In summary, this study provides additional evidence in support of a protective effect of vitamin D status against colorectal cancer.

Disclosure of Potential Conflicts of Interest

R. Horst is the President and Chief Executive Officer of Heartland Assays, Inc.

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