Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies

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Abstract

It remains unknown whether increased risk with low levels of vitamin D is present for colon and/ or rectal cancer. To investigate the association between circulating vitamin D levels and colon and rectal cancer, we examined the associations between plasma levels of 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) and colon and rectal cancer in the Physicians' Health Study and then conducted a meta-analysis of eight prospective studies of circulating levels of 25-hydroxyvitamin D (25(OH)D) and colon and rectal cancers, including the Physicians' Health Study. Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were pooled using a random-effects model. A total of 1822 colon and 868 rectal cancers were included in the meta-analysis. We observed a significant inverse association for colorectal cancer (OR = 0.66; 95% CI = 0.54–0.81), comparing top versus bottom quantiles of circulating 25(OH)D levels. The inverse association was stronger for rectal cancer (OR = 0.50 for top versus bottom quantiles; 95% CI = 0.28–0.88) than colon cancer (OR = 0.77; 95% CI = 0.56–1.07; P for difference between colon and rectal cancer = 0.20). These data suggest an inverse association between circulating 25(OH)D levels and colorectal cancer, with a stronger association for rectal cancer.

Introduction

Vitamin D may decrease cancer risk by improving differentiation and apoptosis and decreasing proliferation, invasiveness, metastatic potential, and angiogenesis (1–4). Ultraviolet radiation is required for conversion of 7-dehydrocholesterol to vitamin D (cholecalciferol) in the skin, which is then hydroxylated to 25-hydroxylvitamin D (25(OH)D) in the liver. This 25(OH)D is converted to 1,25(OH)2D (the most active

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metabolite of vitamin D) by 1-α-hydroxylase (5). Low vitamin D status has been suggested to increase colorectal cancer (6–10). Some previous studies found a stronger inverse association for colon cancer compared to rectal cancer (8–9, 11), but another studies found that the association was particularly strong for rectal cancer (7, 12–14).

To examine whether circulating blood vitamin D levels were inversely associated with colon or rectal cancer separately, we examined the associations of plasma levels of 25(OH)D and 1,25(OH)2D in relation to risk of colon and rectal cancer in the Physicians' Health Study and performed a meta-analysis of eight individual prospective studies (1822 colon and 868 rectal cancers and their matched controls), including the Physicians' Health Study and three recently published studies (9–10, 12) that were not reviewed in a previous meta-analysis, which included four studies (15).

Materials and Methods

Physicians' Health Study

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial of aspirin and β-carotene for the primary prevention of cancer and cardiovascular disease among 22,071 US male physicians aged 40 to 84 enrolled in 1982 (16). Participants were excluded if they had a prior diagnosis of myocardial infarction, stroke, or transient ischemic attack, cancer (except non-melanoma skin cancer), renal or liver disease, peptic ulcer, or gout or used vitamin A or β-carotene supplements.

Blood samples were obtained during 1982 and 1984 (more than 70% of participants provided blood between September and November 1982) before randomization from 14,916 men. Blood collection kits were sent to all participants with instructions to have their blood drawn into the EDTA tubes. These samples were centrifuged, sent to Channing Laboratory, divided into aliquots, and stored at −82°C (later, at −140°C). Information on height, weight, physical activity, alcohol intake, multivitamin use, and smoking habits was collected by self-administered questionnaires at baseline. The frequency of intakes of whole milk, skim/low-fat milk, ice cream, hard cheese, and cold cereal with specified portions was obtained on the 18-week or 12-month questionnaire. Daily dairy calcium consumption was calculated using the U.S. food composition databases (17). This study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Most cases were initially identified by annual follow-up questionnaires and the others were identified through mortality follow-up procedures. Initial reports were confirmed by review of medical records by the end-point committee. Among those who provided baseline blood samples, colorectal cases were ascertained through March 31, 2000, and controls were matched on age (±1 year for younger participants, up to ±5 years for older participants) and smoking status (never, past, current). A total of 229 colorectal cancer cases and 389 controls were included in the present analysis.

Plasma concentrations of 25(OH)D and 1,25(OH)2D were measured by radioimmunosorbent assay in the laboratory of Dr. Bruce Hollis (Medical University of South Carolina, Charleston, South Carolina). The median intraassay coefficient of variation (CV) from blinded quality-control samples was 13.8% for plasma 25(OH)D and 10.3% for plasma 1,25(OH)2D. Cases and their controls were analyzed in the same batch, and laboratory personnel were blinded to case, control, and quality-control status.

Identification and Selection of Studies for a Meta-Analysis of 25(OH)D and Colon and Rectal Cancer

We searched the PubMed database for the period from January 1966 to February 2010 using the terms ((vitamin D [MeSH] and "vitamin D" or "25-hydroxyvitamin D") and ("cohort" or "case-control" or "case-cohort" or "epidemiology") and ("cancer")). The search was restricted to human studies published in English-language articles. We also examined references from these publications to identify further studies. We identified nine studies (7–14, 18) that examined serum or plasma 25(OH)D and colorectal cancer incidence in a prospective design (blood drawn prior to diagnosis of cancer). We contacted authors of three papers (10–12, 18) that did not report results for colon and rectal cancer separately. One study provided the odds ratios (ORs) and 95% confidence intervals (95% CIs) for rectal cancer, but not for colon cancer (10). Another study provided the ORs and 95% CIs for both colon and rectal cancers (12). Two reports from the CLUE cohort reported results for only colon cancer using the same dataset with different time periods (1975–1983 and 1984–1991) (11, 18). As a result, we included in this meta-analysis a total of seven published individual prospective studies of colon cancer (7–9, 11–14, 18) and seven studies of rectal cancer (7–10, 12–14), plus the present data from the Physicians' Health Study.

Statistical Analyses

In the Physicians' Health Study, to estimate ORs and 95% CIs, participants were categorized into quartiles based on plasma vitamin D metabolite levels among the controls. To remove the variation in vitamin D metabolites due to season of blood collection, we regressed plasma 25(OH)D or 1,25(OH)2D on the periodic function $-sin(2\Pi X/12)-cos(2\Pi X/12)$, where X is the month of sample collection (19). The residuals from this model were added to the ethnic-specific plasma 25(OH)D means (Caucasian or non-Caucasian). We used a conditional logistic regression model to account for the matched case-control study design. To test for trend across quartiles, participants were assigned the median value of their quartile level. This variable was entered as a continuous term in the model, the coefficient for which was evaluated by the Wald test. In the multivariate analyses, we adjusted for season of blood collection (winter/spring, summer/autumn), ethnicity (Caucasian, non-Caucasian), fasting status (8, > 8 hours), body mass index (BMI; <23, 23–<25, 25–<27, 27 kg/m^2), dairy calcium intake (146, 146<–340, 340<–580, 580 mg/d), and vigorous exercise (<1, 1–4 times/wk, 5 times/wk). The study was analyzed with the SAS 9.1 statistical package (SAS Institute, Cary, NC).

For the meta-analysis, we used a random effects model developed by DerSimonian and Laird (20). The individual study estimates were weighted by the inverse of their variance. We tested for heterogeneity between studies using the Q statistic (20). To test the null hypothesis that there is no difference between colon and rectal cancers, we use a contrast test (21). Pooled ORs and 95% CIs were calculated with the statistical software STATA 10.1 (StataCorp, College Station, TX). P<0.05 (two sided) was considered statistically significant.

Results

In the Physicians' Health Study, plasma 25(OH)D levels were higher among men who took multivitamins, regularly exercised, and provided blood samples during summer/autumn. Plasma 1,25(OH)2D levels were higher among men who consumed moderate alcohol and provided blood samples during summer/autumn (data not shown). The median follow-up time from baseline to diagnosis of colorectal cancer was 8.9 years. We found no significant association between plasma 25(OH)D and overall colorectal cancer risk (Table 1). When we examined colon cancer and rectal cancer separately, a suggestive inverse association was

observed for rectal cancer with a threshold effect (ORs for each subsequent quartile vs. 1st quartile of plasma 25(OH)D were 0.53, 0.42, 0.45; P for trend = 0.05), but not for colon cancer. We also observed a suggestive inverse trend for 1,25(OH)2D and risk of colorectal cancer but neither the point estimates or the P for trends were statistically significant for overall colorectal or site-specific cancers (Table 1).

We conducted a meta-analysis of the associations between circulating 25(OH)D levels and colorectal cancer in eight prospective studies (Figure 1A). The pooled multivariate OR (95% CI) was 0.66 (0.54–0.81) for colorectal cancer risk comparing the highest quantile with the lowest quantile of circulating 25(OH)D levels. We specifically evaluated the associations separately for colon and rectal cancer in a meta-analysis of the previous studies plus the present data from the Physicians' Health Study (Table 2). We found a stronger inverse association for rectal cancer than colon cancer, although a formal test for difference between colon and rectal cancers was not statistically significant (P for difference = 0.20). The pooled multivariate OR was 0.77 (95% CI = 0.56–1.07; P for heterogeneity between studies = 0.04; Figure 1B) for colon cancer and 0.50 (95% CI = 0.28–0.88; P for heterogeneity between studies = 0.04; Figure 1C) for rectal cancer, comparing the highest quantile with the lowest quantile of circulating 25(OH)D levels. When we pooled the estimates from the three published studies that examined 1,25(OH)2D levels (7, 14, 18) plus the Physicians' Health Study, the pooled multivariate OR (95% CI) comparing the highest quantile with the lowest quantile of circulating 1,25(OH)2D levels was 1.01 (0.59–1.73) for colorectal cancer and 0.88 (0.57–1.35) for colon cancer.

Discussion

In the Physicians' Health Study, we found an inverse trend of circulating blood 25(OH)D levels with rectal cancer risk, which was in line with the results from some of the previous studies that reported a significant inverse association or trend for rectal cancer (7, 12–14). By combining results from the Physicians' Health Study and the previous seven prospective studies, a meta-analysis of eight prospective studies support a stronger inverse association of circulating blood 25(OH)D levels with rectal cancer risk than with colon cancer risk. Statistically non-significant difference warrants more prospective studies of circulating vitamin D levels and colon and rectal cancers and additionally distal and proximal cancers.

Etiologic differences between colon and rectal cancer, such as differences in the associations with life style modifiers, prevalence of specific gene mutations, and expression levels of specific genes, are commonly described (22–24). In a clinical study that examined vitamin D deficiency among 221 colon cancer and 94 rectal cancer patients, severe vitamin D deficiency (defined as 15 ng/mL) was more common among rectal cancer patients than colon cancer patients (25). Several studies reported difference in associations for vitamin D receptor polymorphisms and calcium or vitamin D by tumor sites. The SS genotype of poly(A) mononucleotide repeat and BB genotype of BsmI were associated with a reduced risk of rectal cancer, not with colon cancer in the presence of low calcium and low energy (26). There is evidence that the associations for calcium and vitamin D were stronger for more distal and rectal tumors than proximal colon tumors (26–27). Also, in a study of molecular marker in rectal tumors, the associations of vitamin D intake and vitamin D receptor polymorphism with TP53 mutation status were present in rectal tumors (28). These studies further suggest a possible difference in vitamin D-related mechanisms in the pathogenesis of rectal cancer compared with colon cancer.

The lack of a significant inverse association in the Physicians' Health Study between circulating 25(OH)D levels and colon cancer may be because the association of 25(OH)D is weaker for colon cancer or because most of our blood samples (>70 %) were collected

during summer/autumn, which may not fully capture differences in levels throughout the year. One study that examined the associations across seasons found that an inverse association was limited to those whose blood samples were collected during winter (8). Also, we cannot rule out the possibility of laboratory measurement error or misclassification of one-time baseline measurement of 25(OH)D levels in the Physicians' Health Study because of the possible changes in vitamin D levels influenced by lifestyle factor modification during the follow-up period or the influence of multivitamin intervention arm from the trial, which started in 1997 and is scheduled to end by 2012.

Only three prospective studies examined the association of circulating 1,25(OH)2D levels with risk of colorectal cancer or colon cancer (7, 14, 18), and our meta-analysis, including the Physicians' Health Study, suggests no association. This may be because 1,25(OH)2D is more tightly regulated largely by renal 1-α-hydroxylase activity (29).

Vitamin D may reduce the risk of rectal cancer through regulation of progression and differentiation (1) and inhibition of angiogenesis (3). In animal studies, vitamin D (the vitamin D3 analogue; EB 1089) improved tumor control by radiation treatment, possibly by promoting apoptosis (4). However, because vitamin D status is largely dependent on sun exposure, there was limited evidence of inverse associations between total or dietary vitamin D intake and colorectal cancer (30). In contrast, serum or plasma concentrations of 25(OH)D are regarded as a good biomarker of vitamin D status integrating intake through foods, supplements, and exposure to ultraviolet light.

Each study had only a single measure of plasma vitamin D metabolite levels, which did not allow us to examine changes across time. However, a single measure of vitamin D metabolites has shown to be a useful marker to reflect long-term vitamin D status (31–33). We could not investigate the effects of changes in vitamin D, or in other variables during follow-up because only baseline measures were available. However, a significant trend for rectal cancer may suggest that misclassification might not be too serious to exclude the association we observed. Also, we cannot rule out the possible residual confounding because our study did not allow us to adjust for cumulative information on covariates across follow-up time. However, we found no appreciable change in the associations after adjusting for various measured risk factors, suggesting that residual confounding by risk factors may not explain the association observed in the Physicians' Health Study. Heterogeneity across studies in a meta-analysis may be due to differences in laboratory measurement methods, follow-up periods, seasons of blood draw, exposure to sun light, ethnicity, and prevalence of other interaction factors and unknown/unmeasured confounding factors. Important strengths of our study and meta-analysis include the prospective design in which blood samples were collected before cancer diagnosis.

Taken together, these prospective results support the hypothesis that vitamin D is inversely related to colorectal cancer risk, and that vitamin D is more strongly associated with reduced risk of rectal cancer than colon cancer.

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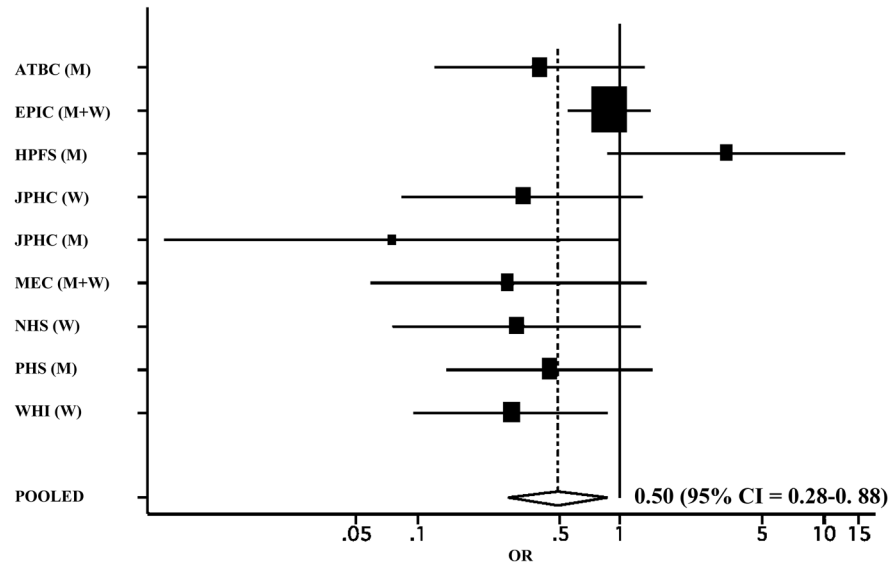A. Study-specific and pooled ORs and 95% CIs of colorectal cancer
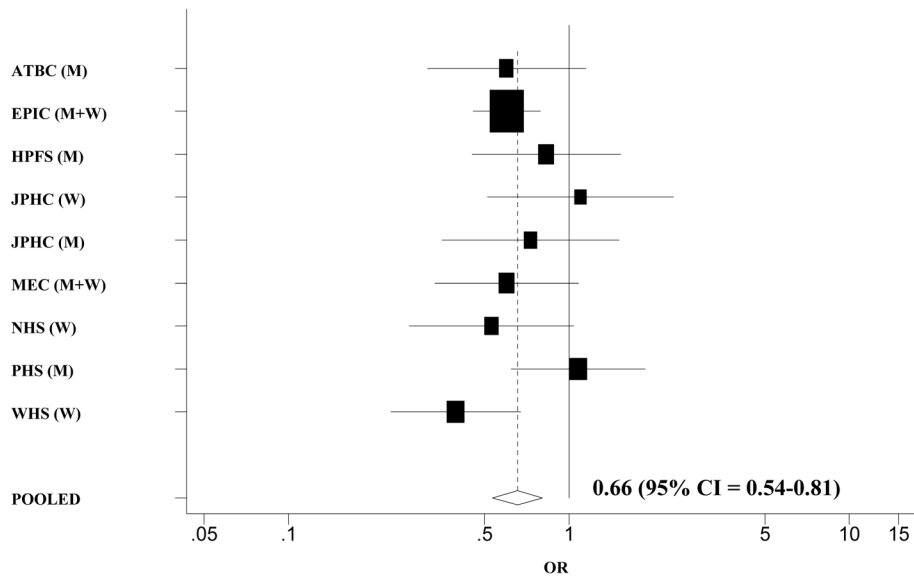
B. Study-specific and pooled ORs and 95% CIs of colon cancer
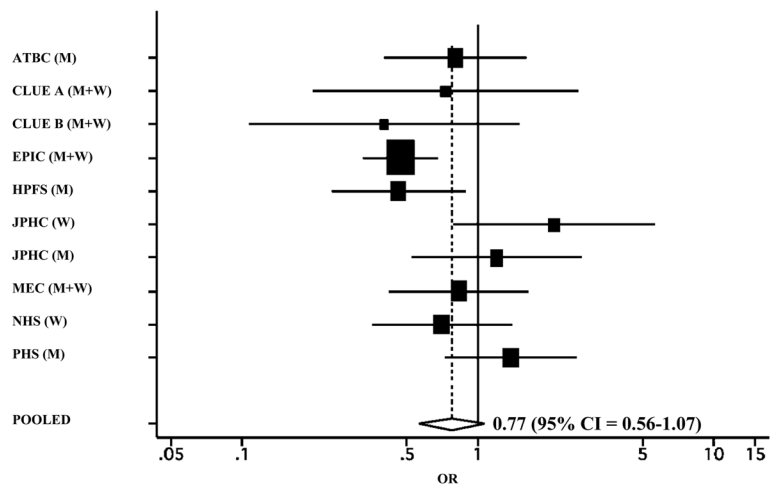
C. Study-specific and pooled ORs and 95% CIs of rectal cancer

Figure 1.
A. Study-specific and pooled ORs and 95% CIs of colorectal cancer comparing the highest with lowest quantiles of blood 25(OH)D levels. B. Study-specific and pooled ORs and 95% CIs of colon cancer comparing the highest with lowest quantiles of blood 25(OH)D levels. C. Study-specific and pooled ORs and 95% CIs of rectal cancer comparing the highest with lowest quantiles of blood 25(OH)D levels. The **black squares** indicate the study-specific odds ratios; the **horizontal lines** represent the 95% CIs. The area of the black squares reflects the study-specific weights (inverse of the variance). The **dashed line** represents the pooled OR and the **diamond** represents the 95% CI for the pooled OR. ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CLUE = from the campaign slogan, "Give us a CLUE to cancer" (A = 1975–1983; B = 1984–1991); EPIC = European Prospective Investigation into Cancer and Nutrition; HPFS = Health Professionals Follow-up Study; JPHC = Japan Public Health Center Study; MEC = multiethnic cohort study; NHS = Nurses' Health Study; PHS = Physicians' Health study; WHI = Women's Health Initiative; M = men; W= women

Table 1

Odds Ratio (OR) and 95% confidence intervals (CIs) of colorectal cancer according to plasma vitamin D metabolites in the Physicians' Health Study

Categories*	Colorectal cancer				Colon cancer		Rectal cancer	
	Cases/controls (N)	Median	Simple matched OR†	Multivariate OR‡	Cases/controls (N)	Multivariate OR‡	Cases/controls (N)	Multivariate OR‡
25(OH)D (ng/mL)								
Quartile1	57/96	15.7	1.00	1.00	36/70	1.00	20/24	1.00
Quartile2	41/97	22.3	0.72 (0.43–1.20)	0.71 (0.42–1.21)	37/72	0.95 (0.52–1.74)	15/26	0.53 (0.18–1.60)
Quartile3	74/99	26.7	1.26 (0.78–2.02)	1.24 (0.76–2.04)	52/74	1.34 (0.75–2.39)	9/28	0.42 (0.13–1.40)
Quartile4	57/97	37.9	1.02 (0.62–1.69)	1.08 (0.62–1.87)	47/71	1.38 (0.73–2.64)	13/24	0.45 (0.14–1.46)
P for trend			0.99	0.67		0.35		0.05
1,25(OH)2D (pg/mL)								
Quartile1	66/93	25.5	1.00	1.00	49/68	1.00	20/24	1.00
Quartile2	60/96	31.2	0.87 (0.54–1.41)	0.91 (0.55–1.50)	40/71	0.83 (0.46–1.49)	13/24	0.57 (0.20–1.60)
Quartile3	53/96	34.7	0.79 (0.49–1.27)	0.84 (0.51–1.38)	47/71	0.96 (0.54–1.68)	10/26	0.43 (0.13–1.39)
Quartile4	45/94	41.1	0.66 (0.39–1.09)	0.70 (0.41–1.18)	33/71	0.64 (0.34–1.19)	12/24	0.75 (0.27–2.09)
P for trend			0.14	0.24		0.22		0.72

*
Among control participants, quartile cutoff points were determined by season (summer/autumn or winter/spring) and batches (two batches).

†
Matched on age (±1 year for younger participants, ±5 years for older participants) and smoking status (never, past, current).

‡
Matched on age (±1 year for younger participants, ±5 years for older participants) and smoking status (never, past, current). Further adjusted for seasons (summer/autumn or winter/spring), fasting status (8, > 8 hours), race (Caucasian or non-Caucasian), vigorous exercise (<1, 1–4 times/wk, 5 times/wk), dairy calcium intake (146, 146<–340, 340<–580, 580 mg/d), and body mass index (<23, 23–<25, 25–<27, 27 kg/m^2).

Table 2

Included prospective studies of circulating levels of 25(OH)D and risk of colon and rectal cancers

Study name*	First author, year (Ref no.)	Country (Sex)†	Age at blood donation in controls (years)	Study dates (Follow-up)	25(OH)D, mean or median	Colon: 25(OH)D levels in the top vs. bottom quantiles	Colon: No. of cases/controls	Colon: OR (95% CI) in the quantiles‡	Rectum: No. of cases/controls	Rectum: 25(OH)D levels in the top vs. bottom quantiles	Rectum: OR (95% CI) in the quantiles‡
CLUE A§	Garland, 1989 (11)	US (M, W)	74.7% in 45–74 year	1975–1983	30.5 in cases and 33.3 ng/mL in controls, mean	42 vs. 19 ng/mL, cutoff	34/67	Q1–Q5; 1.0 (ref), 0.48, 0.25, 0.21, 0.73 (0.20–2.66)	N/A	N/A	N/A
CLUE B§	Braun, 1995 (18)	US (M, W)	55, median	1984–1991	23.6 in cases and 23.2 ng/mL in controls, mean	30.1 vs. 17.2 ng/mL, cutoff	57/114	Q1–Q5; 1.0 (ref), 0.3, 0.5, 0.7, 0.4 (0.1–1.4); P-trend = 0.57	N/A	N/A	N/A
ATBC§	Tangrea, 1997 (14)	Finland (M)	60, median	1985–1993	12.1 in cases and 13.8 ng/mL in controls, mean	19.3 vs. 9.8 ng/mL, cutoff	91/181	Q1–Q4; 1.0 (ref), 0.6, 0.8, 0.8 (0.4–1.6); P-trend = 0.69	55/109	19.2 vs. 9.8 ng/mL, cutoff	Q1–Q4; 1.0 (ref), 0.9, 0.8, 0.4 (0.1–1.1); P-trend = 0.06
NHS∥	Feskanich, 2004 (7)¶	US (W)	60.0, mean	1989–2000	23.6 in cases and 24.3 ng/mL in controls in lab1, 27.0 in cases and 30.3 ng/mL in controls in lab2, mean	28.7 vs. 18.9 ng/mL in lab1, 35.9 vs. 23.6 ng/mL in lab 2, cutoff	149/295	Q1–Q4; 1.0 (ref), 1.03, 0.54, 0.70 (0.35–1.38); P-trend = 0.17	44/88	27.2 vs. 20.5 ng/mL in lab1, 33.5 vs. 26.1 ng/mL in lab 2, cutoff	Q1–Q3; 1.0 (ref), 0.52, 0.31 (0.08–1.31); P-trend = 0.03
HPFS∥	Wu, 2007 (8)	US (M)	66.1, mean	1993–2002	28.7 in cases and 29.4 ng/mL in controls, mean	38.8 vs. 19.3 ng/mL, median	139/276	Q1–Q4; 1.0 (ref), 0.74, 0.29, 0.46 (0.24–0.89); P-trend = 0.005	40/80	37.4 vs. 21.2 ng/mL, median	Q1–Q3; 1.0 (ref), 1.74, 3.32 (0.87–12.69); P-trend = 0.08

Study name *	First author, year (Ref no.)	Country (Sex)[†]	Age at blood donation in controls (years)	Study dates (Follow-up)	25(OH)D, mean or median	Colon			Rectum		
						25(OH)D levels in the top vs. bottom quantiles	No. of cases/controls	OR (95% CI) in the quantiles [‡]	25(OH)D levels in the top vs. bottom quantiles	No. of cases/controls	OR (95% CI) in the quantiles [‡]
WHI[§]	Wactawski-Wende, 2006 (10) **,††	US (W)	50–79, range	1993–2005	N/A	N/A	N/A	N/A	23.4 vs. 12.4 ng/mL, cutoff	68/68	Q1–Q4: 3.40 (1.13–10.21)[‡‡], 1.08, 3.41, 1.00 (ref); P-trend = 0.22
JPHS[‖]	Otani, 2007 (13)	Japan (M)	56.9, mean	1990–2003	27.3 in cases and 27.6 ng/mL in controls, median	35.6 vs. 19.9 ng/mL, median	119/237	Q1–Q4: 1.0 (ref), 0.98, 1.0, 1.2 (0.51–2.7); P-trend = 0.70	35.6 vs. 19.9 ng/mL, median	44/87	Q1–Q4: 1.0 (ref), 0.17, 0.25, 0.075 (0.0057–0.99); P-trend = 0.06
		Japan (W)	56.4, mean	1990–2003	22.5 in cases and 22.3 ng/mL in controls, median	31.4 vs. 16.6 ng/mL, median	106/195	Q1–Q4: 1.0 (ref), 1.7, 2.1, 2.1 (0.78–5.6); P-trend = 0.12	31.4 vs. 16.6 ng/mL, median	54/102	Q1–Q4: 1.0 (ref), 0.26, 0.46, 0.33 (0.084–1.3); P-trend = 0.17
EPIC[‖],[§]	Jenab, 2010 (9)[††]	Europe (M, W)	58.7 for colon, 58.0 for rectum, mean	1992–2003	20.7 in cases and 22.9 ng/mL in controls for colon, 22.0 in cases and 22.0 ng/mL in controls for rectum, geometric mean	39.7 vs. 13.2 ng/mL, median	785/785	Q1–Q5: 1.0 (ref), 0.77, 0.65, 0.66, 0.47 (0.33–0.68); P-trend<0.001	41.7 vs. 12.8 ng/mL, median	463/463	Q1–Q5: 1.0 (ref), 1.29, 1.06, 1.18, 0.89 (0.56–1.43); P-trend=0.647
MEC[‖]	Woolcott, 2010 (12)[§§]	US (M,W)	69.2, mean	2001–2006	23.2 in cases and 25.0 ng/mL in controls, mean	32.8 vs. 16.8 ng/mL, cutoff	170/319	Q1–Q5: 1.0 (ref), 0.82, 0.70, 0.73, 0.83 (0.42–1.63)	32.8 vs. 16.8 ng/mL, cutoff	43/83	Q1–Q5: 1.0 (ref), 0.55, 0.34, 0.28, 0.28 (0.06–1.38)

Study name [*]	First author, year (Ref no.)	Country (Sex)[†]	Age at blood donation in controls (years)	Study dates (Follow-up)	25(OH)D, mean or median	Colon			Rectum		
						No. of cases/controls	25(OH)D levels in the top vs. bottom quantiles	OR (95% CI) in the quantiles [‡]	No. of cases/controls	25(OH)D levels in the top vs. bottom quantiles	OR (95% CI) in the quantiles [‡]
								P-trend = 0.17			P-trend = 0.02
								Q1–Q4			Q1–Q4
PHS[‖]	Lee (present study)	US (M)	56.6, mean	1982–2000	26.6 in cases and 25.6 ng/mL in controls, mean	172/287	36.8 vs. 14.9 ng/mL, median	1.0 (ref), 0.95, 1.34, 1.38 (0.73–2.64)	57/102	39.2 vs. 17.9 ng/mL, median	1.0 (ref), 0.53, 0.42, 0.45 (0.14–1.46)
								P-trend = 0.35			P-trend = 0.05

[*] ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CLUE = from the campaign slogan, "Give us a CLUE to cancer"; EPIC = European Prospective Investigation into Cancer and Nutrition; HPFS = Health Professionals Follow-up Study; JPHC = Japan Public Health Center Study; MEC = Multiethnic Cohort Study; NHS = Nurses' Health Study; PHS = Physicians' Health study; WHI = Women's Health Initiative

[†] M = men; W=women

[‡] Q1–Q5 = quintiles; Q1–Q4 = quartiles; Q1–Q3 = tertiles

[§] Serum specimen was used.

[‖] Plasma specimen was used.

[¶] Estimates of quantile cutoff were obtained from the investigator of the Nurses' Health Study

[**] Estimates for rectal cancer were obtained from the Publications and Presentations committee of the Women's Health Initiative

[††] The conversion factor for 25(OH)D from nmol/L to ng/mL is 0.401

[‡‡] For top vs. bottom quartiles, OR (95% CI) = 0.29 (0.098–0.89)

[§§] Estimates for colon and rectal cancers were obtained from the investigator of the Multiethnic Cohort Study