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Predicted vitamin D status and colorectal cancer incidence in the Black Women's Health Study

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Abstract

Background—Observational studies, mostly among White populations, suggest that low vitamin D levels increase colorectal cancer (CRC) risk. African Americans, who are disproportionately burdened by CRC, often have lower vitamin D levels compared to other populations.

Methods—We assessed predicted vitamin D score in relation to CRC among 49,534 participants in the Black Women's Health Study, a cohort of African American women followed from 1995 to 2017 through biennial questionnaires. We derived predicted vitamin D scores at each questionnaire cycle for all participants using a previously validated prediction model based on actual 25-hydroxyvitamin D values from a subset of participants. We calculated cumulative average predicted vitamin D score at every cycle by averaging scores from cycles up to and including that cycle. Using Cox proportional hazards regression, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for CRC incidence according to predicted score quartiles.

Results—Over follow-up, 488 incident CRC occurred. Compared to women in the highest quartile of predicted vitamin D score, those in the lowest had an estimated 41% (HR=1.41, 95% CI 1.05–1.90) higher CRC risk. Comparable HRs were 1.44 (95% CI 1.02–2.01) for colon and 1.34 (95% CI 0.70–2.56) for rectal cancer.

Conclusion—Low vitamin D status may lead to elevated CRC risk in African American women.

Impact—Our findings, taken together with established evidence that vitamin D levels are generally lower in African Americans than other U.S. groups, suggest that low vitamin D status may contribute to the disproportionately high CRC incidence among African Americans.

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Keywords

Vitamin D status; Colorectal cancer; African American; Women

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in the United States, impacting nearly 150,000 Americans each year.[1] However, studies show that colorectal cancer does not impact all racial/ethnic groups equally. African Americans are disproportionately burdened by colorectal cancer, exhibiting the highest incidence and mortality rates of any other racial/ethnic group.[2] Reasons for these racial disparities have not been fully elucidated. One hypothesis is that low vitamin D levels may contribute to higher rates of colorectal cancer among African Americans.[3,4]

The major function of vitamin D in the human body is the regulation of calcium and phosphorus levels to form and maintain healthy bones.[5,6] However, animal and experimental studies indicate that vitamin D also exhibits anti-cancer properties, including promoting cell differentiation and apoptosis, and reducing inflammation, cell proliferation, angiogenesis, and metastatic potential.[7,8] Consequently, vitamin D has been investigated as a chemopreventive agent in studies of colorectal cancer.[9–14]

To date, most, but not all,[15,16] epidemiologic studies on this topic have observed a 15–60% reduction in colorectal cancer risk with increasing vitamin D status.[17–28] Vitamin D has also been inversely associated with colorectal adenoma,[29,30] recurrent colorectal cancer,[31] and colorectal cancer-specific mortality.[32] Importantly, however, almost all studies of vitamin D and colorectal cancer were conducted among majority White populations. Vitamin D is primarily obtained through photosynthesis in the skin. Upon exposure to ultraviolet (UV) B radiation via sunlight, cutaneous 7-dehydrocholesterol or provitamin D_3 is photosynthesized into previtamin D_3 which is then converted into vitamin D_3, one of two major forms of vitamin D.[5] The extent to which UVB radiation penetrates the skin to ignite the photosynthesis of vitamin D_3 depends on skin color. Darker skin pigmentation blocks out UVB radiation and reduces vitamin D production.[33] Consequently, African Americans have lower vitamin D levels compared to other racial/ethnic groups[34] and are at higher risk of vitamin D deficiency/insufficiency.[35] In three studies of African Americans,[19,20,27] vitamin D levels were not significantly associated with colorectal cancer risk, but the studies included only 41,[20] 45,[19] and 224[27] colorectal cancer cases. A sufficiently powered study is necessary to determine the vitamin D-colorectal cancer association in an African American population.

In the present study, we prospectively analyzed the association between predicted vitamin D status and colorectal cancer risk in a large population of African American women. We utilized a previously derived prediction model for 25-hydroxyvitamin D [25(OH)D],[36] the main circulating form of vitamin D, which reflects both endogenous production and dietary intake.[5] This approach allowed us to assess the association of average long-term vitamin D status with colorectal cancer risk.

METHODS

Study Population

In 1995, 59,000 women enrolled in the Black Women's Health Study (BWHS) by completing a 14-page questionnaire mailed to subscribers of Essence magazine and members of the Black Nurses Association.[37,38] Follow-up questionnaires have been completed every two years since then, with follow-up complete for 85% of person-years. Participants were excluded from this analysis if they reported a cancer diagnosis, except non-melanoma skin cancer, at baseline in 1995 (n=1,439) or were missing data on any factor used to create the predicted vitamin D score (n=8,027). After exclusions, 49,534 participants remained in the analytic sample. The Boston University Institutional Review Board approved the study protocol.

Exposure Ascertainment

Predicted vitamin D score, a proxy measure for average long-term vitamin D status,[39] was the exposure of interest. To calculate predicted vitamin D score, we utilized a prediction model previously derived and validated.[36] In brief, the prediction model was created using 25(OH)D levels measured from plasma samples provided by 2,856 BWHS participants from 2013 to 2015. The median 25(OH)D level was 31 ng/mL. 25% of participants who provided a sample had a 25(OH)D level <21 ng/mL, while 25% had levels ≥40 ng/mL. Participants were cancer-free and had complete data on known or suspected candidate predictors of 25(OH)D, which were measured on the 2013 questionnaire. Candidate predictors included vitamin D supplementation, multivitamin use, body mass index (BMI), intake of foods containing vitamin D, vigorous exercise, walking for exercise, cigarette smoking, alcohol consumption, postmenopausal hormone use, oral contraceptive use, menopausal status, and UVB radiation exposure. Repeated five-fold cross-validation was used to obtain the best fitting model with the optimal set of predictors by dividing the sample of 2,856 participants into five equally sized groups. Four out of five groups were used in the training set, while the remaining group was used as the test set. Multivariable generalized linear regression models were utilized. All of the above listed candidate predictors, except walking for exercise and menopausal status, were retained in the final prediction model. The correlation coefficient for predicted vitamin D score vs. observed 25(OH)D levels was 0.49 (standard deviation=0.026).[36]

Using beta estimates (Supplementary Table S1) from the prediction model[36] and participant values for each predictor at baseline, we calculated predicted vitamin D scores at baseline for each participant in the analytic sample. Values for predictor variables were updated every two years based on responses on biennial questionnaires, allowing for calculation of a predicted vitamin D score for every participant for each two-year period of follow-up. If a participant was missing predicted vitamin D score at a particular cycle, the predicted score from the previous two-year period was carried forward. Predicted scores were carried forward, on average, for 24% of cohort participants, primarily due to their not having completed a given biennial questionnaire. Because long-term vitamin D status may be better represented by using an average of two or more vitamin D measurements,[40] our primary analysis used the cumulative average method,[41,42] in which the exposure variable for each

timepoint was an average of the predicted vitamin D scores from previous timepoints up to and including the current timepoint. We conducted two sensitivity analyses; in one, baseline vitamin D score was the exposure variable, and in the other, the exposure was a simple update of vitamin D score, where predicted vitamin D score at baseline was updated at each subsequent two-year period. All three exposure variables were categorized into quartiles using cut points based on the distribution of predicted vitamin D score calculated at baseline in 1995. Predicted vitamin D score quartiles correspond to the quartile cut points of plasma 25(OH)D measured in blood samples provided by the subset of BWHS participants (21 ng/mL, 31 ng/mL, and 40 ng/mL).[36]

Outcome Ascertainment

Incident colorectal cancer was the outcome of interest. Primary colon or rectal cancer was defined based on the International Classification of Diseases 10 [ICD-10]; codes C18.0–C18.9 and C26.0 for colon and C19.9 and C20.0 for rectum. Colorectal cancer diagnoses were identified through self-report on baseline and follow-up questionnaires, as well as through linkage to the National Death Index and state cancer registries in the 24 states in which 95% of participants lived. Participants who reported cancer were asked for consent to obtain medical records and pathology reports. Trained study personnel blinded to exposure status reviewed pathology reports and cancer registry data to confirm diagnoses and collect information on diagnosis date and tumor location. Pathology data were collected from hospitals or cancer registries for ~85% of cases, of which ~99% were confirmed. All self-reported cases were included, unless they were determined to be incorrectly reported.

Statistical Analysis

We used Cox proportional hazards regression to calculate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between predicted vitamin D score and incident colorectal cancer, overall and according to anatomic location. Regression models were stratified by age in one-year increments and by questionnaire cycle, such that age was the underlying timescale. Participants accrued follow-up time beginning in 1995 and ending at colorectal cancer diagnosis, death, or end of the study period in 2017, whichever occurred first. In secondary analyses, we applied a 4-year and 10-year lag to exposure classification. With the 4-year lag, follow-up began in 1997. For each cycle, predicted vitamin D score was assigned based on the predicted score from two cycles prior. With the 10-year lag, follow-up began in 2003 and for each cycle, predicted vitamin D score was assigned based on the predicted score from five cycles prior. Covariate data were updated at each questionnaire cycle, except in the sensitivity analysis of baseline predicted vitamin D score. We assessed linear trends by assigning each quartile of predicted vitamin D score an ordinal value of 1–4 and then treating the parameter as a continuous variable in regression models.

To control for potential confounding, we adjusted for the following factors in multivariable models: family history of colorectal cancer (yes, no), calcium supplementation (yes, no), processed meat consumption (grams/day in quartiles) and current aspirin use (non-use, past, current). Other variables considered, but not included because estimates did not change by ≥10% with their inclusion, were years of education, history of type 2 diabetes, and fiber

intake. Missing indicator terms were used to account for missing covariate data. Variables that were used to derive predicted vitamin D score were not included in multivariable models because they were already accounted for in the predicted vitamin D score. However, in a sensitivity analysis, we additionally controlled for BMI (<25, 25–29, 30–34, ≥35 kg/m^2), vigorous exercise (none, <5, ≥5 hours/week), smoking status (never, past, current), alcohol consumption (not current, current 1–6, current ≥7 drinks/week), postmenopausal hormone use (ever, never), vitamin D supplementation (yes, no), and multivitamin use (yes, no) to adjust for possible confounding through pathways independent of vitamin D status.

In sensitivity analyses, we assessed associations between alternative exposure metrics—baseline predicted vitamin D score and updated predicted vitamin D score—and risk of overall and site-specific colorectal cancer.

Because African Americans are likely to be diagnosed with colorectal cancer at younger ages,[43] effect modification by age (<50, ≥50 years) was assessed by analyzing associations within strata of age.

Reported p-values are two-sided with a 0.05 level of significance. Analyses were performed using SAS 9.4 (Cary, North Carolina).

RESULTS

During follow-up from 1995 to 2017, 488 colorectal cancer cases were identified; 370 of the cancers were in the colon, 105 in the rectum, and subsite was unknown for 13 cases.

At baseline, women in the lowest quartile of predicted vitamin D score had a higher BMI, smoked more cigarettes, and consumed more alcoholic drinks compared to those in the highest quartile of predicted vitamin D score (Table 1). Additionally, women in the lowest quartile exercised less and took fewer vitamin D supplements and multivitamins. These distributions are as expected given these factors were included in the derivation of the predicted score. Being in the lowest quartile of predicted vitamin D score at baseline was also associated with older age, completing ≤12 years of education, not taking calcium supplements, and consuming more red and processed meat and less fiber.

Risk of colorectal cancer increased with decreasing quartile of cumulative average predicted vitamin D score in both age-adjusted (P_{trend}= 0.003) and multivariable (P_{trend}= 0.05, Table 2) models. In multivariable analyses, the HR for women in the lowest relative to highest quartile of predicted vitamin D score was 1.41 (95% CI 1.04–1.89). Additional control for variables that were used to create the predicted vitamin D score did not appreciably change the estimates; the greatest change was observed with additional adjustment for vitamin D supplementation, resulting in an HR of 1.46 (95% CI 1.08–1.98, Table 3). Results were similar in the 4-year lagged analysis (HR for lowest vs. highest quartile =1.30, 95% CI 0.96–1.76), but stronger associations were observed in the 10-year lagged analysis (HR=1.64, 95% CI 1.13–2.39, Supplementary Table S2). HRs for lowest vs. highest quartile of cumulative average predicted vitamin D score were 1.44 (95% CI 1.02–2.01) for colon cancer and 1.34 (95% CI 0.70–2.56) for rectal cancer.

Similar HRs were observed for associations of predicted vitamin D score with risk of colorectal cancer among women aged <50 years (HR=1.31, 95% CI 0.72–2.38 for lowest vs. highest quartile) and ≥50 years (HR=1.44, 95% CI 1.02–2.03, $P_{interaction}$=0.73, Table 4).

In sensitivity analyses that used either baseline predicted vitamin D score or a simple update of score as the exposure variable, we observed similar, though weaker, associations with colorectal cancer risk, overall and by site, as compared with results from the cumulative average predicted vitamin D score analysis (Supplementary Table S3).

DISCUSSION

Within this large prospective cohort study, African American women in the lowest quartile of predicted vitamin D score were estimated to have a 41% (HR=1.41, 95% CI 1.04–1.89) increased risk of colorectal cancer compared to those in the highest quartile. This would be equivalent to a 29% (HR=0.71, 95% CI 0.53–0.96) reduced risk of colorectal cancer among women in the highest quartile of predicted vitamin D score compared with women in the lowest quartile. The association was observed for both colon and rectal cancer, although the estimate for rectal cancer was less precise due to a relatively small number of cases. Results were similar among women under age 50 and those aged 50 and older.

These results, which relied on a proxy for vitamin D exposure, are consistent with previous observational studies among populations of mostly European ancestry that assessed the relation of circulating 25(OH)D with colorectal cancer risk. Two studies[21,28] reported that lower circulating levels of 25(OH)D were associated with a 15–32% increased risk of colorectal cancer. Similarly, low circulating levels of 25(OH)D were associated with an 18–150% increased risk in several other studies.[17–20,23–27] Additionally, the present results are consistent with previous studies that utilized a predicted vitamin D score,[22,44] as in the present study.

Low vitamin D levels are commonly observed in African Americans,[34,45] largely because darker skin pigmentation blocks UV light.[33] The three prior studies of 25(OH)D and colorectal cancer risk among African Americans reported inverse associations that were not statistically significant, possibly due in part to small sample sizes.[19,20,27] The largest of the three studies (224 cases) reported a statistically significant inverse association within the subgroup (83 cases) that developed cancer more than three years after blood draw.[27] These three studies used a one-time measure of vitamin D exposure, whereas the present study used a cumulative measure calculated at two-year intervals over the course of follow-up. Our results confirm the prior findings among African Americans and support the use of predicted vitamin D score as a proxy measure in large cohort studies that do not have prediagnositic blood samples on enough participants for informative analyses.

Experimental and animal studies provide evidence of biological mechanisms through which vitamin D influences carcinogenesis. For example, vitamin D inhibits cell proliferation and tumor growth by regulating cell cycle arrest and reducing expression of epidermal growth factor receptors, which fuel epidermal growth factor-stimulated cell growth.[7,8] Vitamin D promotes cell apoptosis by upregulating pro-apoptotic proteins and down-regulating anti-

apoptotic proteins.[7,8,10] Vitamin D enhances cell differentiation by increasing the expression of enzymes that inhibit cell proliferation and maintain differentiation.[8] Additionally, vitamin D exhibits anti-angiogenic properties by repressing the sprouting and elongation of cells and reducing the expression of proteins that enhance the migratory and invasive potential of cancer cells.[8,9] Many of the anti-cancer properties of vitamin D are mediated by vitamin D receptors, which are located on cell and nuclear surfaces. Vitamin D binds to vitamin D receptors, triggering a cascade of events that lead to its anti-cancer effects. Since vitamin D regulates the absorption of calcium in the gut, cells in the intestinal tract are equipped with vitamin D receptors,[8,46] thus, providing a pathway through which vitamin D can exert its anti-tumor effects in the colon and rectum.

It has been hypothesized that the higher prevalence of vitamin D insufficiency in African Americans may be a contributing factor to the disproportionately high rates of colorectal cancer incidence among African Americans.[3,4] Our findings provide evidence in support of this hypothesis. If low vitamin D levels increase risk of colorectal cancer, raising vitamin D levels through vitamin D supplementation may help remedy the adverse effects. Two randomized controlled trials conducted among populations that were largely White explored the effects of supplemental vitamin D treatment on colorectal cancer incidence.[11,12] Both reported no association. However, the lack of association may be explained by insufficient dosage of supplemental vitamin D, a follow-up period that was too short to observe an effect, and/or a small sample size.[47] Two other randomized placebo-controlled trials found no association between supplemental vitamin D and colorectal adenoma.[13,14] Based on current evidence, it is unclear whether supplemental vitamin D reduces colorectal cancer risk. Further research is needed, particularly among African Americans, to assess this relationship and determine the effective dose, duration, and timing of vitamin D supplement use.

Most prior studies reported risk of colorectal cancer in relation to a one-time measurement of 25(OH)D,[15–20,23–28] as collecting serum samples at multiple timepoints can be burdensome and sometimes infeasible, especially for large study populations. However, a single measurement of 25(OH)D may not accurately reflect long-term exposure status because 25(OH)D has a relatively short half-life, lasting approximately three weeks in the body.[48] Moreover, 25(OH)D varies by season, with higher levels in summer months and lower levels in winter months.[49] Thus, a single measurement of 25(OH)D may not capture exposure status during the relevant exposure window and may not represent average long-term vitamin D exposure, which could be important given the long and slow process of colorectal cancer development.[50] In the present prospective study, with over 20 years of follow-up data, we were able to create an exposure measure that averaged predicted vitamin D score from multiple timepoints prior to disease diagnosis or end of follow-up. As expected, we found that cumulative average predicted vitamin D score was more strongly associated with colorectal cancer risk than was a single baseline measure or a measure that relied on predicted vitamin D score from the most recent two-year period. Furthermore, our findings of a stronger association in analyses that used a cumulative average predicted vitamin D score from 10 years before the occurrence of cancer suggest that vitamin D status 10 years prior to colorectal cancer diagnosis may be more etiologically relevant than vitamin D status closer to the time of diagnosis.

In addition to examining overall risk of colorectal cancer, we also assessed associations with colon and rectal cancer separately, since colon and rectal cancer may be molecularly,[51] genetically,[52] and prognostically[53] dissimilar as a result of differences in embryologic origin[54] and physiology.[54] A positive association was observed for both sites, although the HR was not statistically significant for rectal cancer, with only 105 cases. Evidence regarding whether associations vary by location has been mixed. Some studies have reported stronger associations with colon cancer,[27,28] while others observed a stronger association with rectal cancer[17–19,24,55] or similar associations for the two cancer subsites.[20,21,26] Thus, there still remains some uncertainty as to whether the vitamin D-colorectal cancer association differs by cancer subsite.

Similarly, there have been inconsistent reports regarding effect modification by age, with some,[18,26] but not all[23] studies reporting varying associations by age group. In our analysis, there was no effect modification by age.

Although predicted vitamin D score appeared to be an effective proxy for vitamin D status, there are some notable limitations to this measure. Firstly, the measure is a score rather than a measurement of circulating vitamin D levels. Thus, we were unable to report the association of specific vitamin D levels and colorectal cancer risk, which would have more clinical significance. Nevertheless, the predicted score permitted us to rank participants and assess risk among those ranked lower compared to those ranked higher in vitamin D status. A second potential limitation is that skin pigmentation was not measured in the BWHS, and thus, could not be considered for inclusion in the prediction model. However, a previous study indicates that inclusion of skin color[56] may not substantially improve model prediction. Lastly, analyses of rectal cancer were underpowered due to the small number of rectal cancer cases.

Our analysis had a number of noteworthy strengths. Firstly, this study was prospective in design and included a large population of African American women, who are often underrepresented in epidemiologic research. The number of cases was appreciably greater than the number of African American cases in any previous study of vitamin D and colorectal cancer. Our use of predicted vitamin D score allowed us to assess vitamin D status in the entire study population rather than only in those who provided a blood sample. Furthermore, we estimated vitamin D status at multiple timepoints. We assessed vitamin D status in several ways, as a single measurement at baseline, a measurement updated every two years, and as a cumulative average, which had the strongest association with colorectal cancer risk, especially when assessed 10 years prior to cancer diagnosis. In addition, we examined potential confounding by vitamin D predictors and found no evidence of confounding.

In summary, in this large prospective cohort, African American women with the lowest values of predicted vitamin D score experienced an elevated risk of colorectal cancer relative to those with the highest scores. The magnitude of association was similar to what has been observed in White populations. Importantly, the results suggest that the greater prevalence of low vitamin D status in African Americans may contribute to the disproportionately high rates of colorectal cancer experienced by African Americans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list:

CRC	colorectal cancer
UV	ultraviolet
25(OH)D	25-hydroxyvitamin D
BWHS	Black Women’s Health Study
BMI	body mass index
ICD	International Classification of Diseases

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Table 1.

Age-standardized [a] characteristics of the study population at baseline in 1995 according to quartiles of predicted vitamin D score.

	Predicted vitamin D score at baseline			
	Quartile 1 (n=12,383)	**Quartile 2 (n=12,384)**	**Quartile 3 (n=12,384)**	**Quartile 4 (n=12,383)**
Factors included in the vitamin D prediction model				
Body mass index, kg/m²	32.0 (7.4)	28.3 (6.5)	26.3 (5.2)	25.0 (4.9)
Smoking status: Current smoker, %	26	15	12	7
Alcohol consumption: Current drinker, ≥7 drinks/week, %	13	7	4	3
Vigorous exercise: ≥5 hours/week, %	8	11	15	21
Vitamin D supplementation, %	0	0	1	29
Multivitamin use, %	14	52	80	93
Dietary vitamin D intake, kcal-mcg/day	2.4 (1.3)	2.6 (1.4)	3.0 (1.7)	3.1 (1.9)
Potential confounders				
Age	40.3 (10.1)	39.1 (10.6)	38.2 (10.6)	36.1 (10.3)
Years of education: ≤12 years, %	25	18	15	12
Family history of colorectal cancer, %	9	9	10	9
Calcium supplementation, %	9	16	22	46
Folate supplementation, %	3	4	6	8
Current aspirin use, %	10	9	9	8
Red meat consumption: Highest quartile, %	31	26	22	19
Processed meat consumption: Highest quartile, %	30	26	22	20
Total fiber intake: Highest quartile, %	18	23	28	32
Geographic region:				
Northeast, %	25	28	28	28
South, %	31	31	30	31
Midwest, %	22	23	23	24
West, %	21	18	19	17

[a] Values are means (SD) or percentages and are standardized to the age distribution of the study population.

Table 2.

Age- and multivariable-adjusted hazard ratios for the association between predicted vitamin D score and risk of colorectal cancer, overall and by cancer site, N=49,534.

	Overall colorectal cancer (n=488)				Colon cancer (n=370)			Rectal cancer (n=105)		
Predicted vitamin D score	**Cases**	**Person-years**	**Age-adjusted HR (95% CI) [a]**	**MV-adjusted HR (95% CI) [b]**	**Cases**	**Age-adjusted HR (95% CI) [a]**	**MV-adjusted HR (95% CI) [b]**	**Cases**	**Age-adjusted HR (95% CI) [a]**	**MV-adjusted HR (95% CI) [b]**
Quartile 1 (Lowest)	147	254,671	1.57 (1.19–2.08)	1.41 (1.04–1.89)	116	1.63 (1.18–2.25)	1.44 (1.02–2.01)	29	1.38 (0.74–2.57)	1.34 (0.70–2.56)
Quartile 2	133	276,186	1.34 (1.01–1.78)	1.23 (0.92–1.65)	98	1.30 (0.93–1.80)	1.17 (0.83–1.64)	30	1.38 (0.75–2.55)	1.34 (0.71–2.52)
Quartile 3	133	280,223	1.34 (1.01–1.78)	1.26 (0.95–1.68)	99	1.31 (0.95–1.82)	1.22 (0.88–1.71)	30	1.39 (0.75–2.55)	1.35 (0.73–2.50)
Quartile 4 (Highest)	75	206,819	1.00 (ref)	1.00 (ref)	57	1.00 (ref)	1.00 (ref)	16	1.00 (ref)	1.00 (ref)
P-trend			0.003	0.05		0.005	0.06		0.39	0.49

[a] Hazard ratios adjusted for age and time period.

[b] Hazard ratios adjusted for age, time period, family history of colorectal cancer, calcium supplementation, aspirin use, and processed meat consumption.

HR, Hazard ratio; CI, Confidence interval; MV, Multivariable.

Table 3.

Multivariable-adjusted hazard ratios for the association between predicted vitamin D score and risk of colorectal cancer, with additional control for variables that were included in the vitamin D prediction model.

	Multivariable-adjusted hazard ratios (95% CI) [a]							
Predicted vitamin D score	**Adjusted for physical activity**	**Adjusted for smoking status**	**Adjusted for alcohol use**	**Adjusted for postmenopausal hormone Use**	**Adjusted for BMI**	**Adjusted for vitamin D supplementation**	**Adjusted for multivitamin use**	**Adjusted for all 7 vitamin D predictors**
Quartile 1 (Lowest)	1.43 (1.06–1.94)	1.41 (1.04–1.90)	1.44 (1.07–1.94)	1.43 (1.06–1.92)	1.39 (1.01–1.90)	1.46 (1.08–1.98)	1.46 (1.07–2.00)	1.62 (1.13–2.33)
Quartile 2	1.25 (0.93–1.68)	1.23 (0.92–1.65)	1.24 (0.92–1.67)	1.24 (0.92–1.66)	1.22 (0.90–1.65)	1.27 (0.94–1.71)	1.25 (0.93–1.69)	1.35 (0.98–1.86)
Quartile 3	1.27 (0.95–1.70)	1.26 (0.95–1.68)	1.27 (0.95–1.69)	1.26 (0.95–1.69)	1.26 (0.94–1.68)	1.29 (0.96–1.73)	1.27 (0.95–1.69)	1.33 (0.99–1.79)
Quartile 4 (Highest)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
P-trend	0.04	0.05	0.03	0.04	0.08	0.03	0.03	0.02

[a] Hazard ratios also adjusted for age, time period, family history of colorectal cancer, calcium supplementation, aspirin use, and processed meat consumption.

CI, Confidence interval; BMI, Body mass index.

Table 4.

Multivariable-adjusted hazard ratios for the association between predicted vitamin D score and risk of colorectal cancer within strata of age. [a]

	Age <50 years			Age ≥50 years		
Predicted vitamin D score	**Cases**	**Person-years**	**MV-adjusted HR (95% CI)** [b]	**Cases**	**Person-years**	**MV-adjusted HR (95% CI)** [b]
Quartile 1 (Lowest)	35	145,622	1.31 (0.72–2.38)	112	109,049	1.44 (1.02–2.03)
Quartile 2	37	162,467	1.33 (0.74–2.39)	96	113,719	1.20 (0.85–1.68)
Quartile 3	39	166,919	1.47 (0.83–2.62)	94	113,304	1.19 (0.85–1.67)
Quartile 4 (Highest)	17	118,994	1.00 (ref)	58	87,825	1.00 (ref)
P-trend			0.65			0.04

[a] P-interaction=0.73

[b] Hazard ratios adjusted for age, time period, family history of colorectal cancer, calcium supplementation, aspirin use, and processed meat consumption.

MV, Multivariable; HR, Hazard ratio; CI, Confidence interval