Original Article

Racial Disparity in Death From Colorectal Cancer

Does Vitamin D Deficiency Contribute?

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BACKGROUND: The reasons blacks have higher mortality rates from colorectal cancer (CRC) than non-Hispanic whites are not fully understood. Blacks have higher rates of vitamin D deficiency than non-Hispanic whites, and vitamin D deficiency has been associated with CRC. The authors of this report investigated the association of vitamin D deficiency with excess risk for CRC mortality for blacks in the Third National Health and Nutrition Examination Survey (NHANES III) that was conducted from 1988 to 1994. **METHODS:** The association between serum 25(OH)D levels and CRC mortality and its contribution to elevated risk among blacks were studied using baseline data from NHANES III and CRC mortality data through 2006 from the National Death Index. By using survival models, the adjusted risk of death from CRC for African Americans was examined with and without adjusting for vitamin D deficiency, which was defined as an 25(OH)D level <20 ng/dL. **RESULTS:** Black race (hazard ratio [HR], 2.03; 95% confidence interval [95% CI], 1.04-3.95), age (HR, 1.12; 95% CI, 1.09-1.15), not having health insurance (HR, 2.45; 95% CI, 1.12-5.36), and a history of CRC (HR, 7.22; 95% CI, 2.12-24.6) predicted CRC mortality. When added to the model, vitamin D deficiency was associated significantly with CRC mortality (HR, 2.11; 95% CI, 1.11-4.00), and the effect of race was decreased (HR, 1.60; 95% CI, 0.87-2.93); the 40% attenuation was statistically significant ($F_{1,49} = 4.85$; $P = .03$). Similar results were observed when participants who had a history of CRC were excluded from the analysis. **CONCLUSIONS:** The current findings were consistent with the hypothesis that vitamin D deficiency contributes to excess African-American mortality from CRC. ***Cancer* 2011;117:1061–9**. © *2010 American Cancer Society.*

KEYWORDS: disparities, colorectal cancer, vitamin D, minorities, income, poverty.

African Americans have higher incidence and death from colorectal cancer (CRC) than non-Hispanic white Americans,[1] and disparities have been widening.[2] The reasons for this disparity remain uncertain.[3] Sociodemographic and insurance factors contribute but may not fully explain racial disparities in incidence and survival.[3,4] In addition, larger and more proximal colonic polyps are observed more often among blacks than among non-Hispanic whites.[2,5,6] These findings have led to speculation that differences in tumor biology,[4,7] in addition to differences in screening and follow-up,[8,9] may contribute to these disparities.

Low serum vitamin D levels represent a possible mechanism for the higher CRC incidence and mortality observed among blacks. Black Americans have significantly lower mean serum levels of vitamin D than whites across the lifespan.[10,11] This difference is attributable largely to darker skin pigmentation, which reduces the activation of oral vitamin D,[12] in addition to lower intake of foods that contain vitamin D[13] and less sun exposure.[14]

Growing observational data suggest that low serum vitamin D levels are associated with colonic adenomas, CRC, and CRC mortality.[15-18] The International Agency for Research on Cancer of the World Health Organization reviewed evidence and concluded that evidence for vitamin D levels in reducing cancer risk was strongest for CRC, but randomized controlled trials were needed to confirm a causal role.[19] Thus, if causality can be established, then it is plausible that low vitamin D levels might contribute to the observed racial disparity in CRC mortality.[20,21]

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The objective of the current study was to test the hypothesis that low serum vitamin D levels may help to explain the correlation between black race and CRC mortality. Specifically, we examined whether vitamin D deficiency assessed at baseline in a national US sample would be associated with CRC mortality and whether this association may partly mediate the racial disparity in CRC mortality.

MATERIALS AND METHODS

Participants

We constructed a retrospective cohort using publicly available data from the nationally representative Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994.[22] Our sample was restricted to participants aged ≥20 years who participated in the baseline examination and were eligible for mortality follow-up. Serum 25(OH)D levels were available for 15,772 individuals, corresponding to 95.2% of the target population (weighted).

Vitamin D

Serum 25(OH)D was measured using a radioimmunoassay kit (DiaSorin, Stillwater, Minn).[23] Although 1,25-dihydroxyvitamin D is the biologically active form of vitamin D, serum 25(OH)D is regarded as the best indicator of vitamin D status in individuals without kidney disease.[24] We defined vitamin D deficiency based on a 25(OH)D level <20 ng/dL.[25] This corresponds to the lowest quintile in the NHANES sample.

Race and Ethnicity

We assessed race and ethnicity based on self-reported race and ethnicity (white, black, Latino, and other).

CRC Deaths

Assessment of death continued from data collection until December 31, 2006 and was based on the NHANES III Linked Mortality file from the National Death Index using International Statistical Classification of Diseases, 10th Revision (ICD-10) 3-digit codes.[26] CRC mortality was based on codes C18 through C21. Publicly available data do not permit coding below this level. Follow-up was censored at the date of death for individuals who died of other diseases and at December 31, 2006 for those who were not identified as dead.

Covariates

To address confounding of the relation between vitamin D and CRC, we assessed a range of potential variables that have been associated previously with colonic neoplasia and/or CRC mortality. These included educational level (<high school, high school, or >high school),[27] household income as a percentage of the Federal Poverty Level (<100%, 100%-149%, 150%-199%, 200%-299%, or ≥300%),[28] health insurance status (insured or uninsured),[29,30] smoking status (current, former, or never),[31] body mass index (<20 kg/m^2, 20-25.5 kg/m^2, 25.5-29.9 kg/m^2, or ≥30 kg/m^2),[32] diabetes (based on self-report, a fasting glucose level >126 mg/dL, or glycohemoglobin >6%),[33] physical activity level (both self-reported physical inactivity [about the same or less than most individuals] and average metabolic equivalent task score per month),[33] alcohol intake (g/day),[33] dietary calcium intake (g/day),[34] meat intake (servings/day),[33] dietary fiber intake (g/day),[35] and dietary saturated fat intake (g/day).[36] We also included the region of the country (a series of dummy variables) and the month of vitamin D testing. Region is associated with vitamin D levels because of differences in sunlight (ie, ultraviolet [UV] radiation exposure)[2] and with rates of CRC screening.[37] Vitamin D levels fluctuate according to the time of year because of differences in UV exposure.[2] We also included a dichotomous variable for reported history of CRC at baseline.

Statistical Analyses

Analyses were conducted with the SUDAAN (version, 10.01; RTI International, Research Triangle Park, NC) and Stata (version 10.1; Stata, Inc., College Station, Tex) statistical software packages. The analyses were adjusted for the complex survey design of NHANES III to yield appropriate standard errors and population parameter estimates.

We implemented Cox semiparametric proportional hazards survival analyses and compared the results with proportional hazards parametric log-linear (Poisson) regression models.[38,39] In the Poisson models, each individual contributed an observation for each full or partial year of follow-up, and offset terms were used to control for variations in observation lengths. The adjusted hazard ratios (HRs) estimated in the Cox models were very similar to the adjusted incidence rate ratios estimated in the Poisson models. The parametric Poisson models were developed because they allow formal statistical comparison of parameter estimates among nested models. Two main models were developed. Model 1 excluded vitamin

D, and Model 2 included vitamin D. The parameter estimates for black individuals from the 2 Poisson models were compared using the method of Clogg et al[40] as a test for the hypothesis that vitamin D partly mediates the increased CRC mortality risk for African Americans.[41] The percentage attenuation was defined as $100*(\beta_{Model\ 1} - \beta_{Model\ 2})/(\beta_{Model\ 1})$, where β is the parameter estimate for black race.

Independent variables that were included in the analyses were age, sex, race/ethnicity (non-Hispanic white, black, Hispanic, and other), and serum 25(OH)D deficiency (present or absent). To minimize bias from missing data and avoid over fitting, we omitted potentially confounding variables that met the following criteria: 1) *P* values >.20 and 2) an effect on the parameter estimates of 25(OH)D or race by <10%. The final model included education, health insurance, BMI, and history of CRC. For each of the covariates in our regression models, we examined smoothed scatter plots of the scaled Schoenfeld residuals versus follow-up time to assess the appropriateness of our proportional hazards specification.[42]

Sensitivity analyses were used to examine the contribution of nonlinear components of all continuous covariates, including 25(OH)D as a continuous variable or by quintiles and excluding individuals who had CRC at baseline. We also examined interactions between 25(OH)D and age, sex, and race.

RESULTS

The mean serum 25(OH)D level in the sample was 29.5 ng/mL (73.6 nmol/L). Table 1 shows the distribution of baseline characteristics among individuals with and without deficient levels. In bivariate analyses, 25(OH)D deficiency was associated with older age; being a man or being black; region of the country; the time of year tested; less education; lower income; no health insurance; currently smoking; higher BMI; less physical activity; diabetes; and less intake of fiber, meat, saturated fat, and calcium.

There were 91 CRC deaths (0.4% of total mortality; population weighted) among individuals who had no missing data. The association of risk factors with CRC death is summarized in Table 2. In Model 1 (25[OH]D omitted), CRC death was associated with older age, black race, not having health insurance, and a history of CRC. Blacks had twice the risk of dying of CRC as non-Hispanic whites. This relation was not affected appreciably by forcing the inclusion of any of the covariates, including poverty, into the model. When vitamin D was added (Model 2), deficiency was associated with a 2-fold increased risk of CRC mortality. Notably, adding vitamin D deficiency to the model attenuated the CRC mortality risk associated with being black by 40%, and the attenuation was significant ($F_{1,49} = 4.85$; $P = .03$).

The sensitivity analyses produced no evidence for nonlinear effects for any of the continuous variables and revealed a significant effect for 25(OH)D when it was included as a continuous variable (and attenuation of the parameter estimate for black race was consistent with that reported). Analyses that excluded individuals who had CRC at baseline were consistent with those presented. There were no significant interactions between 25(OH)D and age, sex, or race.

DISCUSSION

By using a nationally representative sample of adults from the United States, we examined the hypothesis that vitamin D deficiency contributes to the black-white racial disparity in death from CRC. We observed that being black was associated with higher CRC mortality compared with being whites, and adjusting for vitamin D deficiency attenuated this race effect by 40%. The attenuation did not appear to be attributable to a range of potential confounders, including those related to socioeconomic status, health insurance, or behavioral risk factors. These findings are consistent with the hypothesis that vitamin D deficiency explains a portion of the observed black-white disparity in CRC mortality and raise the possibility that vitamin D supplementation may reduce this disparity.

The current study adds to a growing body of evidence indicating that there is an association between vitamin D and CRC incidence and/or mortality. The adjusted risk of vitamin D on CRC mortality observed in our study was slightly higher than the risk on CRC incidence derived from meta-analysis[18] but similar to an effect on mortality that was observed with a shorter follow-up period in this cohort.[43] The findings of the current study are consistent with prior observational studies but go beyond previous research to explore the relation between vitamin D deficiency and CRC disparities among African Americans.

A review of the published literature on the association between vitamin D and CRC revealed a lack of evidence from randomized controlled trials that vitamin D supplementation prevents CRC.[44] Therefore, causality has not been established definitively, and chemoprevention has been proven effective only for intermediate

Table 1. Sample Characteristics According to the Presence or Absence of Vitamin D Deficiency

Variable	Percentage (No.)			P[a]
	Total, n=15,772	Vitamin D Deficiency Present, n=5139	Vitamin D Deficiency Absent, n=10,633	
Age, y				.0002
20-29	3298	18.8 (1041)	22.6 (2257)	
30-39	3153	22.4 (1138)	24.2 (2015)	
40-49	2481	19.1 (905)	18.9 (1576)	
50-59	1795	14.5 (586)	12.2 (1209)	
60-69	2228	12.8 (693)	11.1 (1535)	
≥70	2817	12.4 (776)	10.9 (2041)	
Sex				.0000
Men	8358	65.8 (3291)	48.5 (5067)	
Women	7414	34.2 (1848)	51.5 (5566)	
Race/ethnicity				.0000
Non-Hispanic white	6558	51.7 (1059)	83.4 (5499)	
Non-Hispanic black	4298	29.3 (2475)	5.5 (1823)	
Hispanic	4282	7.2 (1401)	4.5 (2881)	
Other	634	11.8 (204)	6.6 (430)	
Region				.0000
Northeast	2157	16 (643)	22 (1514)	
Midwest	3096	17.9 (818)	25.8 (2278)	
South	6827	41.9 (2532)	32.2 (4295)	
West	3692	24.3 (1146)	20 (2546)	
Month of Vitamin D test				.0000
January	1401	10.0 (633)	6 (768)	
February	1215	7.1 (531)	4 (684)	
March	1561	8.4 (605)	4 (956)	
April	1447	9.1 (499)	6.4 (948)	
May	1347	8.3 (401)	8.5 (946)	
June	1279	9.3 (334)	11.3 (945)	
July	1012	5.5 (205)	10.3 (807)	
August	1546	8.6 (364)	14.9 (1182)	
September	1331	7.1 (341)	11.6 (990)	
October	1246	8.9 (388)	9.2 (858)	
November	1437	11.1 (502)	9.4 (935)	
December	950	6.7 (336)	4.5 (614)	
Education	15,672			.0008
<High school	6362	28.4 (2114)	23.9 (4248)	
High school	4798	35.8 (1656)	33.1 (3142)	
>High school	4512	35.8 (1333)	43.1 (3179)	
Federal poverty level, %	14,337			.0000
<100	3334	17.4 (1261)	11 (2073)	
100-<150	2149	12.3 (786)	9.5 (1363)	
150-<200	1845	11.3 (626)	11.0 (1219)	
200-<300	2699	20.8 (828)	21.5 (1871)	
≥300	4310	38.2 (1149)	47.0 (3161)	
Insurance	15,095			.0112
Any	12,535	85.6 (4065)	88.4 (8470)	
None	2560	14.4 (869)	11.6 (1691)	
Smoking status	15,771			.0001
Current	4067	31.2 (1517)	27.5 (2550)	
Former	3928	22.5 (1043)	26.9 (2885)	
Never	7776	46.3 (2579)	45.6 (5197)	

(Continued)

Table 1. (Continued)

Variable	Percentage (No.)			P[a]
	Total, n=15,772	Vitamin D Deficiency Present, n=5139	Vitamin D Deficiency Absent, n=10,633	
BMI, kg/m^2	15,736			.0000
<20	1002	7 (309)	7.3 (693)	
20-<25	5186	30.1 (1459)	39.2 (3727)	
25-<30	5514	31.1 (1689)	33.6 (3825)	
≥30	4034	31.9 (1668)	19.9 (2366)	
Diabetes	15,758			.0000
Yes	1927	12.4 (783)	7.1 (1144)	
No	13,831	87.6 (4352)	93 (9479)	
History of colorectal cancer	15,770			.0000
Yes	76	0.5 (23)	0.4 (53)	
No	15,694	99.5 (5115)	99.6 (10,579)	
Activity level compared with most individuals	15,464			.0000
More active	4938	28.2 (1378)	335.2 (3560)	
Less active	3427	27.9 (1326)	20.3 (2101)	
Approximately the same	7099	44 (2350)	44.5 (4749)	
Total METS per mo	12,272			.0000
<Median	6394	59.5 (2144)	47.8 (4250)	
≥Median	5878	40.5 (1491)	52.2 (4387)	
Alcohol, g/d	151,230			.0012
None	121,098	79.6 (4003)	74.7 (8095)	
>None	3132	20.4 (941)	25.3 (2191)	
Calcium, mg/d	151,230			.0000
<Median	8527	66 (3360)	45.7 (5167)	
≥Median	6703	34 (1584)	54.3 (5119)	
Dietary fiber, g/d	151,230			.0000
<Median	7844	59.6 (2949)	47.3 (4895)	
≥Median	7386	40.4 (1995)	52.7 (5391)	
Saturated fat, g/d	141,089			.0000
<Median	7792	57.4 (2871)	48.4 (4921	
≥Median	6297	42.6 (1959)	52 (4338)	
Meats, no. of servings/d	151,230			.0259
<Median	7603	52.9 (2528)	49.3 (5075)	
≥Median	7627	47.1 (2416)	50.7 (5211)	
Colorectal cancer death	151,772			.0230
Yes	91	0.6 (36)	0.3 (55)	
No	15,681	99.4 (5103)	99.7 (10,578)	

BMI indicates body mass index; METS, metabolic equivalent task score.
[a] Chi-square tests are weighted.

outcomes. However, the preponderance of evidence points to a link between vitamin D deficiency and CRC. These data include geographic incidence and UV exposure studies, biologic mechanism studies, and data from observational studies of serum levels on the incidence of adenomas and of CRC with accompanying dose-response relations.

To summarize these different lines of evidence, previous epidemiologic studies demonstrated a higher incidence of CRC at higher latitudes and/or with greater UV

Table 2. Risk Factors for Subsequent Colorectal Cancer Mortality Without and With Adjustment for Vitamin D[a]

Independent Variables	Model 1: Without Vitamin D		Model 2: With Vitamin D	
	HR	95% CI	HR	95% CI
Serum vitamin D, ng/Ml				
<20			2.11	1.11-4.00
20			1.00	
Age, y	1.12	1.09-1.15	1.12	1.09-1.15
Sex				
Women	1.62	0.78-3.38	1.87	0.89-3.92
Men	1.00		1.00	
Race/ethnicity				
Non-Hispanic white	1.00		1.00	
Non-Hispanic black	2.03	1.04-3.95	1.60	0.87-2.93
Hispanic	1.40	0.62-3.18	1.30	0.58-2.93
Other	1.10	0.42-2.93	1.06	0.39-2.88
Education				
<High school	1.33	0.51-3.47	1.32	0.51-3.43
High school	1.16	0.48-2.82	1.18	0.48-2.86
>High school	1.00		1.00	
Health insurance				
Any	1.00		1.00	
None	2.45	1.12-5.36	2.42	1.07-5.45
BMI, kg/m^2				
<20	0.53	0.16-1.75	0.54	0.16-1.78
20-<25	1.00		1.00	
25-<30	0.68	0.37-1.24	0.64	0.35-1.20
≥30	1.52	0.69-3.35	1.41	0.62-3.24
History of colorectal cancer				
Yes	7.22	2.12-24.59	7.19	2.15-24.02
No	1.00		1.00	

HR indicates hazard ratio; CI, confidence interval; BMI, body mass index.
[a] Models also were adjusted for month of vitamin D test and region.

exposure in the United States and Asia.[45-47] However, in the study from China, the effects were observed only in women.[46] In a study from Norway, no north-south gradient was observed for CRC mortality, but survival was improved among those who were diagnosed in summer and fall, when serum levels of vitamin D were highest.[48]

More recent studies explain possible mechanisms of vitamin D that protect against colorectal neoplasia. Vitamin D, possibly in combination with calcium intake, appears to promote colorectal epithelial cell differentiation and apoptosis, increase DNA mismatch-repair proteins, and reduce oxidative damage and adenoma recurrence.[49-54] Furthermore, polymorphisms in the vitamin D receptor have been associated with the risk of adenoma and cancer in various studies.[55,56] Although these data come from mostly studies that were conducted on participants without neoplasms at baseline, it is possible that similar processes accelerate the progression of cancer, potentially affecting both incidence and survival.

In contrast to geographic and mechanistic studies, the current study contributes to a body of research examining associations between serum vitamin D levels and CRC risk. A meta-analysis of serum 25(OH)D and the incidence of colonic adenomas revealed an inverse, graded response.[15] Gorham et al conducted a quantitative meta-analysis of nested case-control studies on serum levels of prediagnostic 25(OH)D and the subsequent incidence of CRC.[18] In 3 of the 6 studies, statistically significant associations were observed. A meta-analysis of all 6 studies revealed a significant effect and dose-response with the very lowest levels associated with the highest incidence. A subsequent meta-analysis that was conducted by different

investigators and included 8 studies reached similar conclusions.[57] A large, nested case-control study from Europe that was published after the meta-analyses were conducted also revealed a strong, inverse, linear relation between serum 25(OH)D and CRC incidence.[17] In addition, higher vitamin D levels predicted improved CRC survival.[58] Consistent with these studies, our findings reveal a significant association between low serum levels of 25(OH)D and CRC mortality.

To date, limited attention has been paid to the possible role of vitamin D deficiency in the black-white disparity in CRC[21] despite documentation of much higher rates of vitamin D deficiency among blacks of all ages.[10,11] The current results suggest that the racial disparity in CRC mortality is explained in part by vitamin D deficiency in the NHANES III cohort. We observed no interaction between race and serum 25(OH)D levels. Thus, given the high rates of vitamin D deficiency among blacks in this national sample and the finding of an overall effect of low levels with CRC mortality, it is not surprising that deficiency among blacks contributed to the racial disparity in CRC deaths. This finding is noteworthy. If it is demonstrated that vitamin D supplementation reduces CRC, then it could have a substantial impact on the racial disparity in CRC mortality.

Important limitations of these findings include the sample size, the ascertainment of CRC deaths, a single measurement of vitamin D, and the potential for unmeasured confounding. Consistent with previous studies,[29,30] lack of insurance remained a significant predictor of CRC death in the final model, yielding a 2.5-fold increase in risk. However, that variable was measured only at baseline, and subsequent changes in health insurance may have confounded the correlation between race and CRC mortality. Socioeconomic status is a multidimensional construct that arguably includes factors such as community of residence, which were not available in these data,[59] and residual confounding between race and socioeconomic status is possible. Furthermore, although our initial cohort was fairly large, the relatively small number of CRC deaths reduced our power to detect effects, and the confidence intervals were wide.

Death certificate data appear to be reasonably accurate for ascertaining CRC deaths but may over-report colon cancer deaths and under-report rectal cancer.[60] Findings from a meta-analysis demonstrated effects of vitamin D on both colon cancers and rectal cancers.[57] Thus, this misclassification may be moot. The level of coding of cancer permitted in public data may have included anal cancer. The pathophysiology of anal cancer differs fundamentally from that of CRC but likely had a negligible effect on our findings given its very low incidence.[61]

Although we measured vitamin D at a single point in time, prospective studies have revealed moderate correlations (0.7) over time.[58] Any change in levels likely would bias the results toward the null because of measurement error. Finally, although we controlled for multiple factors, confounding cannot be fully excluded in observational studies. Previous cancer protective effects observed for various nutrients have failed to hold up in randomized controlled trials and, in some cases (for example, beta carotene for smokers), has been associated with increased risk.[62]

In conclusion, the current findings add to the growing body of literature on the association between vitamin D and CRC[57] and provide the first direct evidence that high rates of vitamin D deficiency among blacks may account for some of the racial disparity in CRC deaths. These findings underscore the need for randomized controlled trials, such as the Vitamin D and Omega-3 Trial (VITAL) Study,[63] to assess whether supplementation with much higher doses than currently recommended not only will reduce deaths from CRC in general but also will reduce the black-white racial disparity in the second leading cause of cancer-related death in the United States.

CONFLICT OF INTEREST DISCLOSURES

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