Published in final edited form as:
Cancer. 2011 March 1; 117(5): 1061–1069. doi:10.1002/cncr.25647.

Racial Disparity in Death from Colorectal Cancer: Does Vitamin D Deficiency Contribute?

Kevin Fiscella, MD, MPH[1], **Paul Winters, MS**[2], **Daniel Tancredi, PhD**[3], **Samantha Hendren, MD, MPH**[4], and **Peter Franks, MD**[5]

[1]Departments of Family Medicine and, Community & Preventive Medicine, University of Rochester

[2]Department of Family Medicine, University of Rochester

[3]Center for Healthcare Policy and Research and Department of Pediatrics University of California at Davis

[4]Department of Surgery, Colorectal Division, University of Michigan School of Medicine

[5]Center for Healthcare Policy and Research, Department of Family & Community Medicine, University of California at Davis

Abstract

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. We 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) 1988–1994.

Methods—We examined the association of serum 25(OH) D levels with CRC mortality and its contribution to elevated risk among Blacks using baseline data from NHANES III and CRC mortality through 2006 from the National Death Index. Using survival models, we examined the adjusted risk for African Americans for CRC death with and without adjusting for vitamin D deficiency, defined as less 25(OH)D < 20 ng/dl.

Results—Black race (Hazard Ratio [HR] 2.03; 95% Confidence Interval [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 history of CRC (HR 7.22; 95% CI 2.12–24.6) predicted CRC mortality. When added to the model, vitamin D deficiency was significantly associated with CRC mortality (HR 2.11; 95% CI 1.11–4.00) and the effect of race was decreased (HR 1.60; 95% 0.87–2.93); the 40% attenuation was statistically significant ($F[1, 49] = 4.85$, $p = 0.03$). Similar results were seen when participants with a history of CRC were excluded from the analysis.

Conclusion—Our findings are consistent with the hypothesis that vitamin D deficiency contributes to excess African American mortality from CRC.

INTRODUCTION

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). Socio-demographic and insurance factors contribute, but may

Correspondence: Kevin Fiscella, MD, MPH, 1381 South Ave, Rochester, NY 14620;, Tel (585) 506-9484 ext 106;, Fax (585) 473-2245;, Kevin_Fiscella@URMC.rochester.edu.

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 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 in Blacks. Black Americans have significantly lower mean serum levels of vitamin D than Whites across the lifespan (10;11). This difference is largely attributable to darker skin pigmentation reducing activation of oral vitamin D (12), in addition to lower intake of food containing 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, it is plausible that low vitamin D levels might contribute to the observed racial disparity in CRC mortality (20;21).

The goal of this study was to test the hypothesis that low serum vitamin D levels might help to explain the relationship between Black race and CRC mortality. Specifically, we assessed whether vitamin D deficiency assessed at baseline in a national US sample would be associated with CRC mortality and whether this association might 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) conducted from 1988–1994 (22). Our sample was restricted to participants aged 20 and older, who participated in the baseline examination and were eligible for mortality follow-up. Serum 25(OH)D was available on 15,772 persons, corresponding to 95.2% of the target population (weighted).

Vitamin D

Serum 25(OH)D was measured using a radioimmunoassay kit (DiaSorin, Stillwater, MN) (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 25(OH)D less than 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, based on the NHANES III Linked Mortality file from the National Death Index, using International Statistical Classification of Diseases, 10th Revision (ICD-10) three digit codes (26). CRC mortality was based on codes C18–C21. Publically available data do not permit coding

below this level. Follow-up was censored at the date of death for persons who died of other diseases and at December 31, 2006 for those not identified as deceased.

Covariates

To address confounding of the relationship between vitamin D and CRC, we assessed a range of potential variables that have been previously associated with colonic neoplasia and/or CRC mortality. These included educational level (<high school, high school, > high school) (27); household income at federal poverty (<100%, 100–149%, 150–199%, 200–299%, ≥ 300%) (28); health insurance (insured or uninsured) (29;30); smoking (current, former, never) (31); body mass index (<20, 20–25.5, 25.5–29.9, ≥ 30 kg/m^2) (32); diabetes (based on self-report, a fasting glucose >126 mg/dl, or glycohemoglobin >6.0%.) (33); physical activity (both self-reported physical inactivity [about the same or less than most people] and average METS per month) (33), alcohol (gm/day) (33); dietary calcium (gm/day) (34); meat (servings/day) (33); dietary fiber (gm/day) (35); and dietary saturated fat intake (gm/day) (36). We also included region of the country (series of dummy variables) and month of vitamin D testing. Region is associated with vitamin D levels due to differences in sun light, i.e. ultraviolent radiation exposure (2), and also with rates of CRC screening (37). Vitamin D levels fluctuate by time of year due to differences in UV exposure (2). We also included a dichotomous variable for reported history of CRC at baseline.

Statistical Analyses

Analyses were conducted with SUDAAN (version, 10.01) and Stata (version 10.1, College Station, TX), adjusting for the complex survey design of NHANES III to yield appropriate standard errors and population parameter estimates.

We implemented Cox semi-parametric proportional hazards survival analyses and compared these results to proportional hazards parametric log-linear (Poisson) regression models (38;39). In the Poisson models each subject contributed an observation for each full or partial year of follow-up, using offset terms 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 (IRRs) 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 persons from the two 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 percent attenuation was defined as $100 *(\beta_{\text{Model 1}} - \beta_{\text{Model 2}})/(\beta_{\text{Model 1}})$; where β is the parameter estimate for Black race.

Independent variables 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 overfitting, we omitted potentially confounding variables meeting the following criteria: 1) p values >0.20 and; 2) 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 in order to assess the appropriateness of our proportional hazards specification (42).

Sensitivity analyses examined the contribution of non-linear components of all continuous covariates, included 25(OH)D as a continuous variable or by quintiles, and excluded subjects with baseline CRC. We also examined interactions between 25(OH)D with 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 those with and without deficiency levels. In bivariate analyses, deficiency of 25(OH)D was associated with older age, being male or Black, region of country, time of year, 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 (0.4 % of total mortality, population weighted) CRC deaths among subjects with 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 relationship was not appreciably affected by forcing inclusion of any of the covariates, including poverty, into the model. When vitamin D was added (model 2), deficiency was associated with a two-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%; the attenuation was significant ($F[1, 49] = 4.85$, $p = 0.03$).

The sensitivity analyses found no evidence for non-linear effects for any of the continuous variables and revealed a significant effect for 25(OH)D when included as a continuous variable (and attenuation of the parameter estimate for Black race consistent with that reported). Analyses excluding those with baseline CRC were consistent with those presented. There were no significant interactions between 25(OH)D and age, sex, or race.

DISCUSSION

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 found that being Black was associated with higher CRC mortality compared with Whites; 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 SES, 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 raises the possibility that vitamin D supplementation might reduce this disparity.

This study adds to a growing body of evidence showing an association between vitamin D and CRC incidence and/or mortality. The adjusted risk of vitamin D on CRC mortality observed in the present study is slightly higher than the risk on CRC incidence derived from meta-analysis (18), but similar to an effect on mortality observed with a shorter follow-up period of this cohort (43). Findings of the current study are consistent with prior observational studies, but go beyond prior research to explore the relationship between vitamin D deficiency and CRC disparities by African-American race.

A review of the published literature on the association between vitamin D and CRC reveals a lack of evidence from randomized controlled trials that vitamin D supplementation prevents CRC (44). Therefore, causality has not been definitively established and chemoprevention has been shown to be effective only for intermediate 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, biological mechanism studies, and data from observational studies of serum levels on incidence of adenomas and incidence of CRC with accompanying dose-response relationships.

To summarize these different lines of evidence, prior epidemiologic studies have shown a higher incidence of CRC at higher latitudes and/or greater UV exposure in the US and Asia (45–47). However, the study from China only observed effects in women (46). A study from Norway found no North-South gradient in CRC mortality, but survival was improved among those diagnosed in summer and fall, when serum levels of vitamin were highest (48).

More recent studies explain possible mechanisms of vitamin D protecting 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 are associated with adenoma and cancer risk in various studies (55;56). Although these data largely come from studies 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 geographical 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 incidence of colonic adenomas showed an inverse, graded response (57). Gorham *et al* conducted a quantitative meta-analysis of nested case-control studies of serum levels of 25(OH)D collected pre-diagnostically and subsequent incidence of CRC (18). Three of the six studies showed statistically significant associations. A meta-analysis of all six studies showed a significant effect and dose-response with the very lowest levels associated with the highest incidence. A subsequent meta-analysis conducted by different investigators that included eight studies reached similar conclusions (58). A large nested case-control study from Europe, published after these meta-analyses were conducted, also showed a strong inverse linear relationship between serum 25(OH)D and CRC incidence (17). In addition, higher vitamin D levels predict improved CRC survival (59). Consistent with this group of studies, our findings reveal a significant association between low serum levels of 25(OH)D and CRC mortality.

To date, there has been limited attention given 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 present study suggests that the racial disparity in CRC mortality is explained in part by vitamin D deficiency in the NHANES III cohort of patients. We observed no interaction between race and serum 25(OH) D. Thus, given high rates of Vitamin D deficiency among Blacks in this national sample, and the finding of an overall effect of low levels with CRC deaths, it is not surprising that deficiency among Blacks contributed to the racial disparity in CRC death. This finding is notable. If vitamin D supplementation is shown to reduce CRC, it could have a substantial impact on the racial disparity in CRC mortality.

Important limitations of these findings include sample size, ascertainment of CRC deaths, single measurement of vitamin D, and potential for unmeasured confounding. Consistent with prior studies (29;30), lack of insurance remained a significant predictor of CRC death in the final model, yielding a two and half fold increase in risk. However, it was only measured at baseline; subsequent changes in health insurance might have confounded the relationship 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 (60); 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 confidence intervals were wide.

Death certificate data appear reasonably accurate for CRC deaths, but may over-report colon cancer deaths and under-report rectal cancer (61). Findings from a meta-analysis show effects of vitamin D on both colon and rectal cancers (58). 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 is fundamentally different than that for CRC, but likely had negligible effect on our findings given its very low incidence (62).

Although we measured vitamin D at a single point in time, prospective studies show moderate correlations (0.7) over time (59). Any change in levels would likely bias results towards the null due to measurement error. Last, 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 (63).

In conclusion, these findings add to a growing literature on the association between vitamin D and CRC (58), and provide the first direct evidence that high rates of vitamin D deficiency among Blacks may account for some of the race disparity in CRC deaths. These findings underscore the need for randomized controlled trials such as the Vital Study (64), to assess whether supplementation with much higher doses than currently recommended will not only reduce deaths from CRC in general, but also reduce the Black-White racial disparity in the second leading cause of cancer related death in the United States.

Acknowledgments

American Cancer Society (RSGT-08-077-01) and National Cancer Institute (NIH U01CA116924-01), National Heart Lung Blood Institute (NIH R01 HL081066-01A2).

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59:225–249. [PubMed: 19474385]
2. Irby K, Anderson WF, Henson DE, Devesa SS. Emerging and widening colorectal carcinoma disparities between Blacks and Whites in the United States (1975–2002). Cancer Epidemiol Biomarkers Prev. 2006; 15:792–797. [PubMed: 16614125]
3. Alexander DD, Waterbor J, Hughes T, Funkhouser E, Grizzle W, Manne U. African-American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review. Cancer Biomark. 2007; 3:301–313. [PubMed: 18048968]
4. Davis CD. Vitamin D and cancer: current dilemmas and future research needs. Am J Clin Nutr. 2008; 88:565S–569S. [PubMed: 18689403]
5. Lieberman DA, Holub JL, Moravec MD, Eisen GM, Peters D, Morris CD. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. JAMA. 2008; 300:1417–1422. [PubMed: 18812532]
6. Thornton JG, Morris AM, Thornton JD, Flowers CR, McCashland TM. Racial variation in colorectal polyp and tumor location. J Natl Med Assoc. 2007; 99:723–728. [PubMed: 17668638]
7. Polite BN, Dignam JJ, Olopade OI. Colorectal cancer model of health disparities: understanding mortality differences in minority populations. J Clin Oncol. 2006; 24:2179–2187. [PubMed: 16682737]
8. Laiyemo AO, Doubeni C, Pinsky PF, et al. Race and Colorectal Cancer Disparities: Health-Care Utilization vs Different Cancer Susceptibilities. J Natl Cancer Inst. 2010; 102:538–546. [PubMed: 20357245]
9. Jerant AF, Fenton JJ, Franks P. Determinants of racial/ethnic colorectal cancer screening disparities. Arch Intern Med. 2008; 168:1317–1324. [PubMed: 18574089]

10. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007; 167:1159–1165. [PubMed: 17563024]
11. Seeman T, Merkin SS, Crimmins E, Koretz B, Charette S, Karlamangla A. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988–1994). Soc Sci Med. 2008; 66:72–87. [PubMed: 17920177]
12. Chen TC, Chimeh F, Lu Z, et al. Factors that influence the cutaneous synthesis and dietary sources of vitamin D. Arch Biochim Biophys. 2007; 460:213–217.
13. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr. 2005; 135:2478–2485. [PubMed: 16177216]
14. Santmyire BR, Feldman SR, Fleischer AB Jr. Lifestyle high-risk behaviors and demographics may predict the level of participation in sun-protection behaviors and skin cancer primary prevention in the United States: results of the 1998 National Health Interview Survey. Cancer. 2001; 92:1315–1324. [PubMed: 11571748]
15. Wei MY, Garland CF, Gorham ED, Mohr SB, Giovannucci E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008; 17:2958–2969. [PubMed: 18990737]
16. Giovannucci E. Epidemiological evidence for vitamin D and colorectal cancer. J Bone Miner Res. 2007; 22; (Suppl-5)
17. Jenab M, Bueno-de-Mesquita HB, Ferrari P, et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations:a nested case-control study. BMJ. 2010; 340:b5500. [PubMed: 20093284]
18. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med. 2007; 32:210–216. [PubMed: 17296473]
19. IARC. Vitamin D and Cancer. IARC Working Group Reports. Lyon, France: International Agency for Research on Cancer; 2008. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk5/index.php
20. Mai V, McCrary QM, Sinha R, Glei M. Associations between dietary habits and body mass index with gut microbiota composition and fecal water genotoxicity: an observational study in African American and Caucasian American volunteers. Nutr J. 2009; 8:49. [PubMed: 19845958]
21. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. Cancer Epidemiol Biomarkers Prev. 2006; 15:2467–2472. [PubMed: 17132768]
22. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94 Series I: programs and collection procedures. Bethesda: National Center for Health Statistics; 1994.
23. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone. 2002; 30:771–777. [PubMed: 11996918]
24. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008; 117:503–511. [PubMed: 18180395]
25. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–281. [PubMed: 17634462]
26. National Center for Health Statistics. [Accessed 7/2/2010] NHANES III Linked Mortality File. Available at http://www.cdc.gov/nchs/data_access/data_linkage/mortality.htm.
27. Albano JD, Ward E, Jemal A, et al. Cancer mortality in the United States by education level and race. J Nat Cancer Inst. 2007; 99:1384–1394. [PubMed: 17848670]
28. Byers TE, Wolf HJ, Bauer KR, et al. The impact of socioeconomic status on survival after cancer in the United States : findings from the National Program of Cancer Registries Patterns of Care Study. Cancer. 2008; 113:582–591. [PubMed: 18613122]
29. Roetzheim RG, Pal N, Gonzalez EC, Ferrante JM, Van Durme DJ, Krischer JP. Effects of health insurance and race on colorectal cancer treatments and outcomes. Am J Public Health. 2000; 90:1746–1754. [PubMed: 11076244]
30. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. 2008; 58:9–31. [PubMed: 18096863]

31. Tsoi KK, Pau CY, Wu WK, Chan FK, Griffiths S, Sung JJ. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol. 2009; 7:682–688. [PubMed: 19245853]
32. Wise LA, Rosenberg L, Palmer JR, Adams-Campbell LL. Anthropometric risk factors for colorectal polyps in African-American women. Obesity. 2008; 16:859–868. [PubMed: 18239567]
33. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer. 2009; 125:171–180. [PubMed: 19350627]
34. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer. 2009; 61:47–69. [PubMed: 19116875]
35. Nomura AM, Hankin JH, Henderson BE, et al. Dietary fiber and colorectal cancer risk: the multiethnic cohort study. Cancer Causes Control. 2007; 18:753–764. [PubMed: 17557210]
36. Mrkonjic M, Chappell E, Pethe VV, et al. Association of apolipoprotein E polymorphisms and dietary factors in colorectal cancer. Br J Cancer. 2009; 100:1966–1974. [PubMed: 19455140]
37. Haas JS, Fitzmaurice G, Brawarsky P, et al. Association of regional variation in primary care physicians' colorectal cancer screening recommendations with individual use of colorectal cancer screening. Prev Chronic Dis. 2007; 4:A90. [PubMed: 17875265]
38. Holford TR. The analysis of rates and of survivorship using log-linear models. Biometrics. 1980; 36:299–305. [PubMed: 7407317]
39. Laird N, Olivier D. Covariance Analysis of Censored Survival Data Using Log-Linear Analysis Techniques. J Am Stat Assoc. 1981; 76:231–240.
40. Clogg CC, Petkova E, Haritou A. Statistical methods for comparing regression coefficients between models. AJS. 1995; 100:1261–1293.
41. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods. 2002; 7:83–104. [PubMed: 11928892]
42. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994; 81:515–526.
43. Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. J Nat Cancer Inst. 2007; 99:1594–1602. [PubMed: 17971526]
44. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006; 354:684–696. [PubMed: 16481636]
45. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer. 2002; 94:1867–1875. [PubMed: 11920550]
46. Grant WB. Does solar ultraviolet irradiation affect cancer mortality rates in China? Asian Pac Cancer Prev. 2007; 8:236–242.
47. Mizoue T. Ecological study of solar radiation and cancer mortality in Japan. Health Phys. 2004; 87:532–538. [PubMed: 15551791]
48. Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control. 2004; 15:149–158. [PubMed: 15017127]
49. Fedirko V, Bostick RM, Long Q, et al. Effects of supplemental vitamin D and calcium on oxidative DNA damage marker in normal colorectal mucosa: a randomized clinical trial. Cancer Epidemiol Biomarkers Prev. 2010; 19:280–291. [PubMed: 20056649]
50. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin d and calcium on proliferation and differentiation in normal colon mucosa: a randomized clinical trial. Cancer Epidemiol Biomarkers Prev. 2009; 18:2933–2941. [PubMed: 19861511]
51. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. Cancer Prev Res. 2009; 2:213–223.
52. Kutuzova GD, DeLuca HF. 1,25-Dihydroxyvitamin D3 regulates genes responsible for detoxification in intestine. Toxicol Appl Pharmacol. 2007; 218:37–44. [PubMed: 17123563]

53. Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J Nat Cancer Inst. 2003; 95:1765–1771. [PubMed: 14652238]
54. Sidelnikov E, Bostick RM, Flanders WD, et al. Effects of calcium and vitamin D on MLH1 and MSH2 expression in rectal mucosa of sporadic colorectal adenoma patients. Cancer Epidemiol Biomarkers Prev. 2010; 19:1022–1032. [PubMed: 20332274]
55. Egan JB, Thompson PA, Ashbeck EL, et al. Genetic polymorphisms in vitamin D receptor VDR/RXRA influence the likelihood of colon adenoma recurrence. Cancer Res. 2010; 70:1496–1504. [PubMed: 20145122]
56. Slattery ML, Wolff RK, Herrick JS, Caan BJ, Potter JD. IL6 genotypes and colon and rectal cancer. Cancer Causes Control. 2007; 18:1095–1105. [PubMed: 17694420]
57. Wei MY, Garland CF, Gorham ED, Mohr SB, Giovannucci E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008; 17:2958–2969. [PubMed: 18990737]
58. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Ther. 2009; 30:113–125. [PubMed: 19392870]
59. Ng K, Wolpin BM, Meyerhardt JA, et al. Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. Br J Cancer. 2009; 101:916–923. [PubMed: 19690551]
60. Shavers VL. Measurement of socioeconomic status in health disparities research. J Natl Med Assoc. 2007; 99:1013–1023. [PubMed: 17913111]
61. Percy C, Stanek E III, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am J Public Health. 1981; 71:242–250. [PubMed: 7468855]
62. Garrett K, Kalady MF. Anal neoplasms. Surg Clin North Am. 2010; 90:147–161. [PubMed: 20109639]
63. Bardia A, Tleyjeh IM, Cerhan JR, et al. Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. Mayo Clin Proc. 2008; 83:23–34. [PubMed: 18173999]
64. Vital Study. Available at URL: http://www.vitalstudy.org.

Table 1

Sample characteristics by Vitamin D Deficiency or not.

Variable	Total (N)	Vitamin D Deficiency Present % (N)	Vitamin D Deficiency Absent % (N)	*p*-value*
Total	**15772**	**5139**	**10633**	
Age				0.0002
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				0.0000
Male	8358	65.8 (3291)	48.5 (5067)	
Female	7414	34.2 (1848)	51.5 (5566)	
Race/Ethnicity				0.0000
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				0.0000
Northeast	2157	16.0 (643)	22.0 (1514)	
Midwest	3096	17.9 (818)	25.8 (2278)	
South	6827	41.9 (2532)	32.2 (4295)	
West	3692	24.3 (1146)	20.0 (2546)	
Month				0.0000
Jan	1401	10.0 (633)	6.0 (768)	
Feb	1215	7.1 (531)	4.0 (684)	
Mar	1561	8.4 (605)	4.0 (956)	
Apr	1447	9.1 (499)	6.4 (948)	
May	1347	8.3 (401)	8.5 (946)	
Jun	1279	9.3 (334)	11.3 (945)	
Jul	1012	5.5 (205)	10.3 (807)	
Aug	1546	8.6 (364)	14.9 (1182)	
Sep	1331	7.1 (341)	11.6 (990)	
Oct	1246	8.9 (388)	9.2 (858)	
Nov	1437	11.1 (502)	9.4 (935)	
Dec	950	6.7 (336)	4.5 (614)	
Education	*15672*			0.0008
< 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)	

Variable	Total (N)	Vitamin D Deficiency Present % (N)	Vitamin D Deficiency Absent % (N)	*p*-value*
Total	**15772**	**5139**	**10633**	
Poverty	*14337*			0.0000
< 100 %	3334	17.4 (1261)	11.0 (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	*15095*			0.0112
Any	12535	85.6 (4065)	88.4 (8470)	
None	2560	14.4 (869)	11.6 (1691)	
Smoking Status	*15771*			0.0001
Current	4067	31.2 (1517)	27.5 (2550)	
Former	3928	22.5 (1043)	26.9 (2885)	
Never	7776	46.3 (2579)	45.6 (5197)	
Body Mass Index (Kg/m^2)	*15736*			
< 20	1002	7.0 (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	*15758*			0.0000
Yes	1927	12.4 (783)	7.1 (1144)	
No	13831	87.6 (4352)	93.0 (9479)	
History of Colorectal Cancer	*15770*			0.0000
Yes	76	0.5 (23)	0.4 (53)	
No	15694	99.5 (5115)	99.6 (10579)	
Activity Level (compared with most people)	*15464*			0.0000
More active	4938	28.2 (1378)	335.2 (3560)	
Less active	3427	27.9 (1326)	20.3 (2101)	
about the same	7099	44.0 (2350)	44.5 (4749)	
Total METS per Month	12272			0.0000
< median	6394	59.5 (2144)	47.8 (4250)	
>= median	5878	40.5 (1491)	52.2 (4387)	
Alcohol (gm/day)	15230			0.0012
None	12098	79.6 (4003)	74.7 (8095)	
> None	3132	20.4 (941)	25.3 (2191)	
Calcium (mg/day)	15230			0.0000
< median	8527	66.0 (3360)	45.7 (5167)	
>= median	6703	34.0 (1584)	54.3 (5119)	
Dietary Fiber (gm/day)	15230			0.0000
< median	7844	59.6 (2949)	47.3 (4895)	
>= median	7386	40.4 (1995)	52.7 (5391)	

Variable	Total (N)	Vitamin D Deficiency Present % (N)	Vitamin D Deficiency Absent % (N)	*p*-value*
Total	**15772**	**5139**	**10633**	
Saturated Fat (gm)/day)	14089			0.0000
< median	7792	57.4 (2871)	48.4 (4921)	
>= median	6297	42.6 (1959)	52.0 (4338)	
Meats (number of servings/day)	15230			0.0259
< median	7603	52.9 (2528)	49.3 (5075)	
>= median	7627	47.1 (2416)	50.7 (5211)	
Colorectal Cancer Death	*15772*			0.0230
Yes	91	0.6 (36)	0.3 (55)	
No	15681	99.4 (5103)	99.7 (10578)	

Notes:

* Chi-square test are weighted

Cancer. Author manuscript; available in PMC 2013 April 06.

Table 2

Risk factors for subsequent colorectal cancer mortality, without and with adjustment for vitamin D.

Independent Variables and Effects		Model 1 (without Vitamin D) Hazards Ratio	Lower 95% Limit	Upper 95% Limit	Model 2 (with Vitamin D) Hazards Ratio	Lower 95% Limit	Upper 95% Limit
Serum vitamin D (ng/mL)	Serum vitamin D < 20(ng/mL)				2.11	1.11	4.00
	Serum vitamin D ≥20(ng/mL)				1.00	1.00	1.00
Age	Years	1.12	1.09	1.15	1.12	1.09	1.15
Sex	Female	1.62	0.78	3.38	1.87	0.89	3.92
	Male	1.00	1.00	1.00	1.00	1.00	1.00
Race/Ethnicity	Non-Hispanic White	1.00	1.00	1.00	1.00	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	1.00	1.00	1.00	1.00
Health insurance	Any	1.00	1.00	1.00	1.00	1.00	1.00
	None	2.45	1.12	5.36	2.42	1.07	5.45
Body mass index (Kg/m^2)	<20	0.53	0.16	1.75	0.54	0.16	1.78
	20–<25	1.00	1.00	1.00	1.00	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	1.00	1.00	1.00	1.00

Notes: models also adjusted for month and region.