Cancer Incidence and Mortality and Vitamin D in Black and White Male Health Professionals

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Abstract

Blacks have been documented to have low vitamin D levels. We thus examined whether total cancer incidence and mortality rates differ between Blacks and Whites in a population of male health professionals, and particularly for digestive system cancers (oral, esophagus, stomach, pancreas, and colorectum), which have been most consistently linked to poor vitamin D status. Second, we examined whether Blacks might be more susceptible to these cancers if they concurrently had other risk factors for hypovitaminosis D. In the Health Professionals Follow-up Study, from 1986 to 2002, 99 of 481 Black men and 7,019 of 43,468 White men were diagnosed with cancer. Adjusting for multiple dietary, lifestyle, and medical risk factors, using Cox modeling, Black men were at higher risk of total cancer incidence [relative risk (RR), 1.32; 95% confidence interval (95% CI), 1.08-1.61; $P = 0.007$] and total cancer mortality (RR, 1.89; 95% CI, 1.40-2.56; $P < 0.0001$) and especially digestive system cancer mortality (RR, 2.24; 95% CI, 1.35-3.70). Compared with Whites with relatively few risk factors for hypovitaminosis D, Blacks also with few risk factors for hypovitaminosis D were not at appreciably higher risk of total cancer incidence (RR, 0.95; 95% CI, 0.60-1.51) or mortality (RR, 1.55; 95% CI, 0.91-2.62), but Black men with additional risk factors for poorer vitamin D status had a much higher cancer incidence (RR, 1.57; 95% CI, 1.16-2.11) and mortality risk (RR, 2.27; 95% CI, 1.57-3.28). This pattern was even more pronounced for digestive system cancer. Our results suggest that the high frequency of hypovitaminosis D in Blacks may be an important, and easily modifiable, contributor to their higher risk of cancer incidence and mortality. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2467–72)

Introduction

U.S. Black men have a 40% higher rate for total cancer mortality, and Black women have a 20% higher mortality rate compared with U.S. Whites (1). Differences in incidence may contribute to the higher mortality rate, but for many cancer sites, Blacks experience a more advanced stage at presentation and poorer survival across all stages than Whites (2). Many factors have been proposed to explain these differences, ranging from unequal access or use of medical care, differences in lifestyle and dietary practices, and differences in tumor biology. Vitamin D deficiency is one factor hypothesized to enhance risk of cancer incidence and progression (3-5), and hypovitaminosis D is common in Blacks (6-11). The possibility that poor vitamin D status contributes to excess cancer mortality in Blacks has been raised (12-14), but this hypothesis has not received adequate study. Recently, Grant showed that residential solar UVB radiation levels correlated inversely with numerous cancers in black Americans, including breast, colon, rectum, stomach, and esophagus (15). This finding is interesting in light of other epidemiologic evidence that digestive system malignancies may be particularly sensitive to hypovitaminosis D (3-5), although a biological basis for this sensitivity to vitamin D status for digestive malignancies is unclear as mechanisms proposed for anticarcinogenic effects of vitamin D are broad.

In this report, we examined cancer incidence and mortality rates for Black men compared with White men in the Health Professionals Follow-up Study (HPFS). Men in this cohort are all highly educated health professionals, with relatively uniformly high use of health care, and of relatively homogeneous demographic and lifestyle factors. Given that Blacks in general and in the HPFS cohort specifically have been documented to have low vitamin D levels (16), our first aim was to examine whether total cancer incidence and mortality rates differ between Blacks and Whites, and particularly for digestive system cancers, which have been most consistently linked to poor vitamin D status. Second, because of the marginal vitamin D status in Blacks, we examined whether they might more susceptible to these cancers if they had additional risk factors for hypovitaminosis D. Finally, we examined the potential contribution of specific medical, lifestyle, dietary, and hormonal factors other than vitamin D status as alternative explanations to any observed differences in cancer rates.

Materials and Methods

Study Population. The HPFS is an ongoing prospective study of heart disease and cancer among 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists. Men from these health professions who were age 40 to 75 years completed a questionnaire upon enrollment in 1986, which encompassed ancestry, medical history, diet, and other lifestyle exposures. We updated exposure and disease information biennially by mailed follow-up questionnaires. Deaths were reported by family members or by the postal system in response to the follow-up questionnaires or were identified through a search of the National Death Index. In 1986, we asked men to report their ''major ancestry'' (with the option to mark more than one category): southern European, Scandinavian, other Caucasian, Afro-American, Asian/Oriental, or other (unspecified) origin. The men who reported Afro-American ancestry were considered as Black, even if they reported an additional ancestry, and Whites were men who reported southern European, Scandinavian, or other Caucasian as their ancestry. For this analysis, we included 43,468 White men and 481 Black men who

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adequately completed the dietary questionnaire in 1986 and who did not have a diagnosis of cancer (except for non-melanoma skin cancer) at baseline. The HPFS was approved by the Human Subjects Committee of the Harvard School of Public Health, Boston, MA.

Variables. Self-administered semiquantitative food frequency questionnaires, described in detail previously (17), were given in 1986, 1990, 1994, and 1998. The questionnaires contained a list of about 130 food and beverage items, each with a specified commonly used unit or portion size, and an open-ended section for unlisted foods. The men reported how often, on average, over the past year, they typically consumed each item. In addition, they reported the brand of breakfast cereal, duration, frequency of use, and brand of ~1,400 distinct multivitamin supplements, including specific supplements (such as vitamin A or D). We computed nutrient intakes by multiplying the consumption frequency of each unit of food by its nutrient content, based on composition values from U.S. Department of Agriculture sources, supplemented with other data. The mean correlation coefficients between intakes determined by two 1-week diet records and the dietary questionnaire among a sample of 127 cohort members were 0.65 for nutrients, 0.63 for specific foods, and 0.86 for alcohol (17-19). We did not have data on vitamin D from the dietary records so we could not make direct comparison to the food frequency questionnaire, but we have previously shown that men with intake ≥400 IU/d had on average 10.4 ng/mL higher 25(OH)vitamin D [25(OH)D] level than those with intakes <100 IU/d ($P < 0.01$; ref. 3).

We asked the men to report height and weight in 1986. In a substudy, the correlation between self-report and technicians' measurements was 0.97 for weight and 0.99 for height (20). In 1986 and every 2 years thereafter, participants reported the average time per week that they engaged in various specific activities during the past year and the number of flights climbed daily and walking pace. To generate the total leisure-time physical activity score, we summed activity-specific MET-hours/wk based on the report of these activities. In a substudy of 238 study participants, the correlation between the questionnaire assessment of vigorous activity with four 1-week diary records was 0.58; reported vigorous activity predicted resting heart rate ($r = -0.45$; ref. 21). Cigarette smoking, body weight, physical examinations, digital rectal examinations, colonoscopy/sigmoidoscopy, and prostate-specific antigen screening (beginning in 1994) were assessed every 2 years. The number of teeth was asked in 1986.

Ascertainment of Cancers and Cause of Death. We asked for written permission to acquire relevant medical records and pathology reports from men (or next of kin) who reported a cancer. The follow-up rate with respect to the incidence of cancer was 97% of the total potential person-years, and death follow-up rate was >98%. Approximately 90% of cases were confirmed by medical record review, and the remaining cases were confirmed with information from the participant or family member, or by death certificate. Cause of death was based on medical record review by study physicians and by death certificate alone only rarely when medical records were not obtainable.

Statistical Analysis. The 43,949 White and Black men accrued follow-up time (person-months) beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis of cancer for incidence analyses (or month of death for the mortality analyses), month of death from other causes, or January 31, 2002, whichever came first. We used Cox modeling to control for multiple variables simultaneously and to compute hazard ratios which estimate relative risk (RR) and 95% confidence intervals (95% CI). Age was controlled for in 1-year increments and time period in 2-year intervals. The following covariables were included in the models: height, region, body mass index (BMI), physical activity, smoking history, alcohol, and, for dietary variables, quintiles of total calories, red meat, calcium, vitamin D, retinol, and total fruits and vegetables. Nutrients were energy-adjusted using residual analysis on the natural logarithm scale. In further analyses, we considered number of teeth (1986) as a surrogate of early life socioeconomic status, as race and socioeconomic status are strong determinants of tooth loss (22). We examined total cancer incidence, total cancer incidence excluding organ-confined prostate cancers because of their favorable prognosis, strong susceptibility to detection bias, and their high prevalence (accounting for about half of all non-skin cancers), and excluding all prostate cancers, which we already had shown to be more common in Blacks (16). We also considered as a group cancers of the digestive system (cancers of the oral cavity, esophagus, stomach, pancreas, colon, and rectum). We conducted parallel analyses for fatal cancer.

To assess whether Black men with other risk factors for hypovitaminosis D were at particularly high risk of cancer, we jointly classified men by race and possession of risk factors for vitamin D deficiency, outside of race, including residence in the northeastern United States, vitamin D intake <400 IU/d, BMI >25 kg/m^2, and physical activity level (a marker of outdoor sun exposure) below the median. These factors were determined to predict vitamin D status previously based on a sample of 1,095 HPFS men for whom we had measured plasma 25(OH)D (3). These factors, as well as race, were determined to be independent predictors of plasma 25(OH)D level.

Results

Table 1 displays various age-standardized characteristics of the Black and White men. BMI, height, physical activity level, and multivitamin use did not differ appreciably between the groups. Current smoking rates tended to be low in both groups, although higher in Blacks than in Whites; however, among men who had ever smoked, Whites accumulated more pack-years of smoking. Overall in the cohort, White men on average had more cigarette pack-years (13.8) than Blacks (10.9). Whites reported drinking more alcohol on average. Blacks ate more fish and less red meat than Whites. Intakes of various macronutrients, micronutrients, and fiber did not differ much between the two groups, although calcium tended to be lower in Blacks (due to lower milk consumption). To confirm that the higher reported intake of fruits and vegetables for Blacks was not due to reporting bias, we examined carotenoid levels in a sample of 40 Blacks and 53 Whites and found that mean levels of β-carotene, α-carotene, lycopene, lutein, and β-cryptoxanthin were higher in Blacks than in Whites.[4] Vitamin D intake (from supplements and dietary) did not differ substantially, but in a sample of men, circulating 25(OH)D levels were substantially lower in Black men ($P < 0.0001$; published previously, ref. 16). More Black men had a diagnosis of diabetes mellitus and high blood pressure, whereas high cholesterol diagnoses did not differ between groups. Blacks were more likely to suffer tooth loss than Whites. Use of the medical system seemed high and relatively similar in both groups. Black men reported more frequent physical and digital rectal examinations; sigmoidoscopy or colonoscopy procedures were slightly higher in Whites, and about 90% of Whites and Blacks had had a prostate-specific antigen test.

Up to the year 2002, we confirmed 7,118 cases of total cancers (including hematologic malignancies but excluding non-melanoma skin cancers) and 2,239 deaths from cancer

[4] Unpublished data.

Table 1. Age-standardized characteristics of the HPFS population at baseline 1986

	Blacks	Whites
No.	481	43,468
Age (not standardized)	54.4	54.0
Current married (%)	82.1	90.4
Current smoking (%)	14.1	9.9
Past smoking (%)	43.7	43.3
Never smoking (%)	41.1	46.2
Average pack-years (ever smokers only)	19.3	25.7
Alcohol (g/d)	8.1	11.5
BMI (kg/m^2)	26.1	25.5
Exercise (METS/wk)	17.8	20.0
Region (%)		
South	57.2	47.3
Northeast/Mid-Atlantic	20.2	20.2
Midwest/West	21.3	31.7
Hypertension (%)	33.7	21.8
High cholesterol (%)	10.6	12.5
High triglycerides (%)	6.0	10.6
Diabetes history (%) (up to 1/2002)*	18.0	9.3
No. teeth (%)		
≤10	5.5	3.2
1-16	2.4	1.3
17-24	17.1	11.4
≥25	68.7	82.2
Missing data	6.3	1.9
Total fat (g/d)	68.9	71.4
Total protein (g/d)	91.2	92.5
Total carbohydrates (g/d)	246	234
Saturated fat (g/d)	22.8	24.5
Fiber (g/d)	21.0	21.0
Calcium (mg/d)	763	904
Red meat (servings/day)	0.50	0.61
Fish (servings/day)	0.47	0.38
Fruits (servings/day)	2.7	2.4
Vegetables (servings/day)	3.6	3.6
Current multivitamin use (%)	38.9	41.9
Total folate (mg/d)	474	481
Total vitamin D (IU/d)	354	365
Screening variables (%) †		
Physical exam (previous 2 y)	85.5	77.7
Rectal exam (previous 2 y)	72.2	64.7
Colonoscopy/sigmoidoscopy	55.4	62.8
Prostate-specific antigen test	89.7	89.7

NOTE: Unless notified, all the variables are from 1986 baseline.
*Percentage of any self-reported diabetes up to January 2002.
†Physical exam and digital rectal exam are from 1990 questionnaire; colonoscopy/sigmoidoscopy is the percentage of any colonoscopy/sigmoidoscopy in the lifetime up to January 2002; Prostate-specific antigen is the percentage of any Prostate-specific antigen test in the lifetime up to January 2002.

(including from skin cancer) in the analytic cohort. Compared with Whites, Blacks had an elevated risk of total cancer incidence (Table 2). Multivariable adjustment did not alter the association appreciably. The association was similar when non-aggressive prostate cancer was excluded, although it became weaker and only borderline statistically significant when total prostate cancer was excluded. A strong association was observed for cancers of the digestive system. Associations were considerably stronger for total cancer mortality than for incidence (Table 3), especially for digestive system cancers. Multivariable adjustment had little influence on the association for total cancer mortality (age-adjusted RR, 1.99; 95% CI, 1.48-2.68; multivariable RR, 1.89; 95% CI, 1.40-2.56). In addition, excluding current smokers did not affect the results. For example, after excluding current smokers, the multivariable RR for Black compared with White men was 1.86 (95% CI, 1.35-2.57; $P = 0.0002$) for total cancer mortality and 2.21 (95% CI, 1.30-3.78; $P = 0.004$) for digestive cancer mortality.

Blacks had an increased risk of total mortality ($n = 84$ deaths; multivariable RR, 1.42; 95% CI, 1.14-1.77), but this was attributable largely to cancer mortality, as Blacks did not have an elevated risk of non-cancer mortality (multivariable RR, 1.08; 95% CI, 0.79-1.78). Of all the men who died, cancer was the cause for 35% of Whites but for 52% of Blacks. Among men diagnosed with any cancer at any time during the follow-up period, only 31% of Whites had died of the cancer by 2002 compared with 44% of Blacks. Excluding prostate cancer, these respective percentages were 46% and 70%, respectively.

Although adult socioeconomic status and use of health care did not seem to differ appreciably between Blacks and Whites in this cohort, socioeconomic status could have differed earlier in life for Blacks and Whites. When adding tooth loss as a surrogate of early life socioeconomic status to the multivariable models, the results for total and digestive cancer incidence did not change, and the results for total cancer mortality (RR, 1.85; 95% CI, 1.37-2.50; $P < 0.0001$) and digestive cancer mortality (RR, 2.20; 95% CI, 1.33-3.64; $P = 0.002$) were only slightly attenuated.

Table 2. RR of cancer incidence among Blacks compared with the Whites in HPFS 1986-2002

	Whites	Blacks	*P*
Person years	597,441	6,379	
Total cancer incidence			
Cases	7,019	99	
Age-adjusted RR	1.00	1.34 (1.10-1.63)	0.004
Multivariable-adjusted RR*	1.00	1.32 (1.08-1.61)	0.007
Total cancer incidence (excluding non-aggressive prostate cancer)			
Cases	4,628	63	
Age-adjusted RR	1.00	1.32 (1.03-1.69)	0.03
Multivariable-adjusted RR*	1.00	1.26 (0.98-1.62)	0.07
Total cancer incidence (excluding all prostate cancer)			
Cases	4,135	54	
Age-adjusted RR	1.00	1.26 (0.96-1.64)	0.10
Multivariable-adjusted RR*	1.00	1.19 (0.91-1.56)	0.21
Digestive system cancer incidence †			
Cases	1,275	23	
Age-adjusted RR	1.00	1.74 (1.15-2.63)	0.009
Multivariable-adjusted RR*	1.00	1.67 (1.10-2.53)	0.016

*Cox proportional hazards modeling was used to control for multiple variables simultaneously and to compute hazard ratios to estimate RR and 95% confidence intervals. Age was controlled for in 1-year increments and time period in 2-year intervals. The following covariables were included in the models: height (quintiles), region (South, Northeast-Mid-Atlantic, Midwest, and West), BMI (six categories), physical activity (quintiles), smoking history [never, quit <10 years, quit ≥10 years, current (1-14, 15-14, and ≥25 cigarettes per day)], alcohol (five categories), and, for dietary variables, quintiles of total calories, red meat, calcium, vitamin D, retinol, and total fruits and vegetables.
† Cancers of the oral cavity, esophagus, stomach, pancreas, colon, and rectum.

Table 3. RR of cancer mortality among Blacks compared with Whites in HPFS 1986-2002

	Whites	Blacks	*P*
Person-years	636,408	6,883	
Total cancer mortality			
Cases	2,195	44	
Age-adjusted RR	1.00	1.99 (1.48-2.68)	<0.0001
Multivariable-adjusted RR*	1.00	1.89 (1.40-2.56)	<0.0001
Total cancer mortality (excluding prostate cancer mortality)			
Cases	1,892	38	
Age-adjusted RR	1.00	1.96 (1.42-2.70)	<0.0001
Multivariable-adjusted RR*	1.00	1.82 (1.31-2.51)	0.0003
Digestive system cancer mortality †			
Cases	655	16	
Age-adjusted RR	1.00	2.34 (1.43-3.85)	0.0008
Multivariable-adjusted RR*	1.00	2.24 (1.35-3.70)	0.002

*Cox proportional hazards modeling was used to control for multiple variables simultaneously and to compute hazard ratios to estimate RR and 95% confidence intervals. Age was controlled for in 1-year increments and time period in 2-year intervals. The following covariables were included in the models: height, region, BMI, physical activity, smoking history, alcohol, and total calories, red meat, calcium, vitamin D, retinol, and total fruits and vegetables.
† Cancers of the oral cavity, esophagus, stomach, pancreas, colon, and rectum.

Finally, we cross-classified men by race and frequency of other determinants of poor vitamin D status. For Whites, each additional risk factor from none to four increased monotonically risk of cancer, especially digestive cancer mortality (for Whites with four risk factors compared with zero risk factors, the multivariable RR for digestive cancer incidence was 1.49; 95% CI, 1.05-2.12). Because of the much smaller numbers of Black men, for the racial comparisons, we could only dichotomize at those with zero or one risk factor (low risk) and those with two, three, or four risk factors (high risk). Black men were at 2- to 3-fold higher risk of cancer, especially digestive system cancers, if their vitamin D status was poor (i.e., ≥2 risk factors), but had similar risks to Whites if vitamin D status was relatively high (Table 4). Among men who provided blood samples, the following were the mean plasma 25(OH)D levels (and % with deficient values defined here as <16 ng/mL) in each group: Whites (≤1 risk factor), 25.8 ng/mL (6.8% deficient); Whites (≥2 risk factor), 23.1 ng/mL (12.6% deficient); Blacks (≤1 risk factor), 21.6 ng/mL (31.6% deficient); Blacks (≥2 risk factor), 17.2 ng/mL (62.1% deficient). Even in Whites with all four risk factors for hypovitaminosis D, vitamin D status was relatively good [mean 25(OH)D = 18.8 ng/mL; 17% deficient] compared with Black men in general.

Discussion

We found a higher risk of total cancer incidence and a considerably higher risk of total cancer mortality among Black men compared with White men in a study population that is relatively homogenous with respect to educational attainment (all highly educated medical professionals), use of the medical system, and lifestyle and dietary factors. Furthermore, controlling for various factors, including tooth loss as a surrogate of early life socioeconomic status, did not change the relative risks. The 2-fold higher cancer mortality rate in Blacks compared with Whites even exceeded the differential observed in the general population, where socioeconomic status heterogeneity is greater. If less frequent cancer screening examinations underlay the higher cancer mortality in Blacks, we would have expected them to have lower cancer incidence, but we observed a higher cancer incidence for Blacks. Besides colorectal cancer, other digestive system cancers are not susceptible to widespread screening. Mortality from other factors did not differ appreciably between Blacks and Whites. Furthermore, Blacks did not have higher non-cancer mortality despite much higher rates of hypertension and diabetes, indicating that in general they received comparable medical treatment to Whites.

We then sought to examine potential factors underlying this higher cancer risk, with an a priori focus on vitamin D. Previously in a subsample of this cohort (16), we have found low vitamin D levels in Blacks, results consistent with other studies (6-9, 11). The generally lower 25(OH)D in Blacks is a result mostly of a higher degree of skin melanin, which effectively filters UV-B radiation (23), although differences in metabolism could also contribute. The vast majority of the supply of vitamin D in individuals is generated by sun exposure. Lower intake of vitamin D may contribute somewhat to hypovitaminosis D, but vitamin D intakes in the Black men were comparable with those in White men (354 versus 365 IU/d) and were reasonably high in the context of current recommendations (200 IU for adults up to age 50 years, 400 IU for adults 50-70 years of age, and 600 IU for individuals ≥70 years).

Our findings are noteworthy in view of increasing evidence that hypovitaminosis D may increase cancer incidence and progression (12) and may perhaps even affect survival (24, 25). That low levels of vitamin D may account for higher prostate cancer (13), more aggressive prostate and breast cancer (14), and higher total cancer incidence and mortality (12) in Blacks has been hypothesized previously. Recently, an inverse association between regional solar UV-B radiation and mortality rate of breast, colon, rectum, esophageal, and gastric cancers was shown for Blacks in the United States (15). Of note, evidence suggests that incidence of digestive system malignancies may be particularly increased in the presence of hypovitaminosis D (3-5), and in our study, Blacks seemed to be at especially high risk for this group of cancers. Also supporting a role of vitamin D was that Blacks were at very high risk for these cancers if they concomitantly had other risk factors for low vitamin D status (based on region of residence, BMI, dietary vitamin D, and physical activity), but not if they had a relatively good vitamin D status. The prevalence of vitamin D deficiency was much lower in Whites, but as risk factors for vitamin D deficiency increased in Whites, the frequency of hypovitaminosis D increased, and cancer risk increased.

Table 4. RR of cancer incidence and mortality of Blacks compared with Whites jointly by risk factors of hypovitaminosis D in HPFS 1986-2002

	Cancer Incidence			
	Total		Digestive System	
	n (cases)	RR (95% CI)	*n* (cases)	RR (95% CI)
Whites (≤1 risk factor)	1,821	1.00	465	1.00
Whites (≥2 risk factors)	2,820	1.08 (1.01-1.04)	819	1.21 (1.08-1.36)
Blacks (≤1 risk factor)	18	0.95 (0.60-1.51)	4	0.84 (0.32-2.26)
Blacks (≥2 risk factors)	45	1.57 (1.16-2.11)	19	2.59 (1.63-4.11)
	Cancer Mortality			
	Total		Digestive System	
	n (cases)	RR (95% CI)	*n* (cases)	RR (95% CI)
Whites (≤1 risk factor)	874	1.00	268	1.00
Whites (≥2 risk factors)	1,349	1.09 (1.00-1.18)	398	1.02 (0.87-1.20)
Blacks (≤1 risk factor)	14	1.55 (0.91-2.62)	3	1.06 (0.34-3.31)
Blacks (≥2 risk factors)	30	2.27 (1.57-3.28)	13	2.99 (1.70-5.26)

NOTE: Cox proportional hazards modeling was used to control for multiple variables simultaneously and to compute hazard ratios to estimate RR and 95% confidence intervals. Age was controlled for in 1-year increments and time period in 2-year intervals. The following covariables were included in the models: height, region, BMI, physical activity, smoking history, alcohol, and total calories, red meat, calcium, vitamin D, retinol, and total fruits and vegetables. Each of the following was considered a risk factor for hypovitaminosis D: residence in the Northeastern United States, total vitamin D intake <400 IU/d, BMI >25 kg/m^2, and physical activity below the median.

Vitamin D has been proposed to influence cancer risk through a number of mechanisms, such as effects of cell proliferation, differentiation, apoptosis, and angiogenesis (12). Mechanisms whereby cancers of the digestive system seem to be most susceptible are currently obscure. The numbers of individual gastrointestinal cancers were too low for us to examine them individually, but for the most common colorectal cancer, the results were generally similar to the overall results. For example, Blacks with few risk factors for hypovitaminosis D were not at appreciably higher risk of colorectal cancer incidence (RR, 0.71; 95% CI, 0.18-2.87), but Black men with additional risk factors for poorer vitamin D status had an increased risk (RR, 2.43; 95% CI, 1.32-4.46).

We did not find any differences among various other dietary and lifestyle factors strong enough to explain these marked differences in cancer incidence and mortality (see Table 1). Furthermore, in a sample of the HPFS, we previously examined a number of plasma hormone levels, including total testosterone, dihydrotestosterone, estradiol, androstenediol glucuronide, sex hormone–binding globulin, insulin-like growth factor-1 (IGF-1), and IGF binding protein-3 (16, 26). None differed significantly between races, except for a 13% lower IGF binding protein-3 in Blacks. Although lower IGF binding protein-3 may theoretically increase risk of some cancers, the literature has been inconsistent (27), and the magnitude of the difference is probably not sufficient to contribute to substantial differences in risk. Moreover, the IGF-1/IGF binding protein-3 ratio, which presumably should increase risk, was slightly higher in Whites. The higher risk of type 2 diabetes mellitus suggests a relative hyperinsulinemia in Blacks, which is consistent with the literature (28). BMI was only marginally higher in Blacks and physical activity levels slightly lower; thus, Blacks were at higher risk for insulin resistance even at the same BMI level as Whites. Hyperinsulinemia could contribute to the marked racial difference in cancer rates, but to date, evidence is only reasonably strong that hyperinsulinemia is a factor for colon cancer (about 10% of total cancer deaths in U.S. men; ref. 29). Moreover, if the difference in insulin levels accounted for the 2-fold higher cancer mortality in Blacks in our cohort, we would expect that obesity, the strongest determinant of insulin resistance, would be an extremely strong risk factor for cancer mortality; however, as in the literature (30), we found obesity to be a moderate risk factor, and BMI was a much weaker risk factor for total cancer mortality than was Black ancestry. Thus, hyperinsulinemia could potentially contribute to the higher risk of cancer incidence and mortality in Blacks but probably is not the dominant factor.

Our study has several strengths and limitations. The detailed lifestyle and dietary data allowed us to examine potential factors that could contribute to racial differences in cancer incidence and mortality. The study design was prospective, averting recall bias, and our follow-up rates were high and essentially complete for mortality. Our major limitation was the relatively small number of Blacks, which substantially reduced our power to examine specific cancer sites. Nonetheless, we had adequate power to examine total and digestive cancer incidence and mortality. In addition, we did not have details for treatments for all cancer sites. However, treatment differences alone were unlikely to entirely explain our results because cancer incidence rates were higher in Blacks, and Blacks did not have higher mortality from non-malignant causes. Our study was limited to men; thus, we cannot generalize to women, although Black women also seem to be at relatively high risk for cancer mortality (2). Finally, we cannot prove that vitamin D explains the differences in races but can only state that Blacks who are likely to have poorer vitamin D status seem to be at very high risk for digestive system cancers.

The use of self-identified race in epidemiologic could serve multiple purposes, some of which are controversial (31). Our analysis focused on dietary and potential modifiable lifestyle factors as potentially contributing to some apparent racial disparities in cancer incidence and mortality rates. Our findings suggest that race could be acting, in part, as a surrogate of factors that influence vitamin D status. Although using race to characterize vitamin D status is imperfect, self-description as ''African-American'' was the strongest predictor of hypovitaminosis D. In fact, even Whites with all four risk factors of low vitamin D (other than race) had a lower prevalence of hypovitaminosis D than did Blacks with zero or one additional risk factor (17.7% versus 31.6%, respectively), and Blacks with at least two additional risk factors had a very high prevalence of hypovitaminosis D (63.1%). The generally higher degree of melanin is of obvious importance, but some studies indicate the existence of racial differences in the metabolism of vitamin D (32-34).

In a group of Black male health professionals characterized by high socioeconomic status, high degree of medical knowledge, high use of screening tests, and adherence to a healthful lifestyle and dietary practice comparable with their White counterparts, a marked difference in cancer incidence and especially mortality was found. We identified only vitamin D deficiency as a potentially relevant factor. Our results do not prove that vitamin D status is the causal factor underlying high cancer rates in Blacks. Such a conclusion could be drawn more directly if after controlling perfectly for lifetime vitamin D status, the higher risk in Blacks disappeared. What we showed was the Blacks have much higher rates of hypovitaminosis D than Whites, particularly if they had additional risk factors for poor vitamin D status, and that the prevalence of hypovitaminosis D based on a combination of race and other vitamin D risk factors corresponded to risk of cancer incidence and mortality, particularly of digestive cancer mortality. If hypovitaminosis D is indeed a causal risk factor for cancer, Blacks would be expected to be at particularly high risk. Thus, our results of higher risk of cancers suspected a priori to be associated with hypovitaminosis D in Blacks, especially those with additional risk factors for poor vitamin D status, are noteworthy, and further study of this topic should be a high priority.

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References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. American Cancer Society. Cancer facts and figures for African Americans, 2003–2004. Atlanta (GA): American Cancer Society; 2003.
3. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451–9.
4. Mizoue T. Ecological study of solar radiation and cancer mortality in Japan. Health Phys 2004;87:532–8.
5. Grant WB. An estimate of premature cancer mortality in the U S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002;94:1867–75.
6. Matsuoka LY, Wortsman J, Chen TC, Holick MF. Compensation for the interracial variance in the cutaneous synthesis of vitamin D. J Lab Clin Med 1995;126:452–7.
7. Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. Am J Clin Nutr 1998;67:1232–6.
8. 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;30:771–7.
9. Harris SS, Soteriades E, Coolidge JA, Mudgal S, Dawson-Hughes B. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. J Clin Endocrinol Metab 2000;85:4125–30.
10. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet 1982;1:74–6.
11. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of

reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 2002;76:187–92.
12. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 2005;16:83–95.
13. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 1990;10:1307–11.
14. Studzinski GP, Moore DC. Sunlight: can it prevent as well as cause cancer? Cancer Res 1995;55:4014–22.
15. Grant WB. Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. J Natl Med Assoc 2006;98:357–64.
16. Platz EA, Rimm EB, Willett WC, Kantoff PW, Giovannucci E. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals. J Natl Cancer Inst 2000;92:2009–17.
17. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of a expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
18. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
19. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810–7.
20. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
21. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.
22. Gilbert GH, Duncan RP, Shelton BJ. Social determinants of tooth loss. Health Serv Res 2003;38:1843–62.
23. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362–71.
24. 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;15:149–58.
25. Zhou W, Suk R, Liu G, et al. Vitamin D is associated with overall survival in early stage non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev 2005;14:2303–9.
26. Platz EA, Pollak MN, Rimm EB, et al. Racial variation in insulin-like growth factor-1 and binding protein-3 concentrations in middle-aged men. Cancer Epidemiol Biomarkers Prev 1999;8:1107–10.
27. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-1, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53.
28. Dagogo-Jack S. Ethnic disparities in type 2 diabetes: pathophysiology and implications for prevention and management. J Natl Med Assoc 2003;95:774, 9–89.
29. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109–20S.
30. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U S. adults. N Engl J Med 2003;348:1625–38.
31. Rebbeck TR, Halbert CH, Sankar P. Genetics, epidemiology, and cancer disparities: is it Black and White? J Clin Oncol 2006;24:2164–9.
32. Awumey EM, Mitra DA, Hollis BW, Kumar R, Bell NH. Vitamin D metabolism is altered in Asian Indians in the southern United States: a clinical research center study. J Clin Endocrinol Metab 1998;83:169–73.
33. Reasner CA, Dunn JF, Fetchick DA, et al. Alteration of vitamin D metabolism in Mexican-Americans. J Clin Endocrinol Metab 1990;5:13–7.
34. Awumey EM, Hollis BW, Bell NH. Evidence that decreased production rate and not increased metabolic clearance rate is probably responsible for low serum 25(OH)D in African Americans. In: Norman AW, Bouillon R, Thomasset M, editors. Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Horomone. Proceedings of the Tenth Workshop on Vitamin D, Strasbourg, France. Riverside (CA): University of California; 1997. pp. 701–8.

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