Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

Edward Giovannucci, Yan Liu, Eric B. Rimm, Bruce W. Hollis, Charles S. Fuchs, Meir J. Stampfer, Walter C. Willett

Background: **Vitamin D has potent anticancer properties, especially against digestive-system cancers. Many human studies have used geographic residence as a marker of solar ultraviolet B and hence vitamin D exposure. Here, we considered multiple determinants of vitamin D exposure (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure-time physical activity—to estimate sunlight exposure) in relation to cancer risk in the Health Professionals Follow-Up Study.** ***Methods:*** **Among 1095 men of this cohort, we quantified the relation of these six determinants to plasma 25-hydroxy-vitamin D [25(OH)D] level by use of a multiple linear regression model. We used results from the model to compute a predicted 25(OH)D level for each of 47 800 men in the cohort based on these characteristics. We then prospectively examined this variable in relation to cancer risk with multivariable Cox proportional hazards models.** ***Results:*** **From 1986 through January 31, 2000, we documented 4286 incident cancers (excluding organ-confined prostate cancer and nonmelanoma skin cancer) and 2025 deaths from cancer. From multivariable models, an increment of 25 nmol/L in predicted 25(OH)D level was associated with a 17% reduction in total cancer incidence (multivariable relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.74 to 0.92), a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83), and a 45% reduction in digestive-system cancer mortality (RR = 0.55, 95% CI = 0.41 to 0.74). The absolute annual rate of total cancer was 758 per 100 000 men in the bottom decile of predicted 25(OH)D and 674 per 100 000 men for the top decile; these respective rates were 326 per 100 000 and 277 per 100 000 for total cancer mortality and 128 per 100 000 and 78 per 100 000 for digestive-system cancer mortality. Results were similar when we controlled further for body mass index or physical activity level.** ***Conclusions:*** **Low levels of vitamin D may be associated with increased cancer incidence and mortality in men, particularly for digestive-system cancers. The vitamin D supplementation necessary to achieve a 25(OH)D increment of 25 nmol/L may be at least 1500 IU/day. [J Natl Cancer Inst 2006;98:451–9]**

In 1937, Peller and Stephenson *(1)* hypothesized that sunlight exposure lowers the risk of cancer, and in 1941, Apperly *(2)* demonstrated an association between latitude and cancer mortality. Four decades later, Garland and colleagues hypothesized that poor vitamin D status accounts for an elevated risk of risk of colon *(3)*, breast *(4)*, and ovarian *(5)* cancers at higher latitudes. Schwartz and colleagues *(6,7)* hypothesized a similar relationship for prostate cancer. More recently, Grant *(8)* demonstrated an inverse correlation between regional type B ultraviolet (UV-B) radiation levels and mortality rates of many cancers, particularly digestive-organ cancers, and found that in males approximately 80% of the cancers attributable to low regional solar UV-B were digestive-system cancers. Mizoue *(9)* also found an inverse correlation between averaged annual solar radiation levels and mortality from digestive system cancers (i.e., esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts) but not other cancer types in Japan. The vitamin D hypothesis (i.e., that poor vitamin D status increases cancer risk) has received strong experimental support over the past two decades from the almost ubiquitous expression in cells of vitamin D receptors and 1α-hydroxylase, which converts 25-hydroxy-vitamin D [25(OH)D] into 1,25-dihydroxy-vitamin D [1,25$(OH)_2$D], and the consistent demonstration that activation of the vitamin D receptor by 1,25$(OH)_2$D induces differentiation and apoptosis and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential *(10)*.

Latitude as a surrogate of solar UV-B radiation correlates inversely with vitamin D status *(8)*, but regional solar UV-B radiation is only one determinant of vitamin D status. Other determinants include vitamin D intake, skin pigmentation, adiposity [which lowers circulating 25(OH)D], and actual sunlight exposure *(10)*. No previous study, to our knowledge, has considered the combined influence of these major determinants of vitamin D status on cancer risk. To investigate this question, we analyzed a sample of men from the Health Professionals Follow-Up Study cohort who had measurements of circulating 25(OH)D levels available and used geographic region, skin pigmentation, dietary intake, supplement intake, body mass index (BMI), and leisure-time physical activity (a surrogate of exposure to solar UV-B) to develop a model to predict 25(OH)D score. We then calculated this score, which can be interpreted as an estimate of long-term 25(OH)D level, for each cohort member and investigated the relation between this score and the incidence of and mortality from total cancers, individual cancers, and digestive system cancers.

Subjects and Methods

Study Population

The Health Professionals Follow-Up Study, an ongoing prospective investigation of the causes of cancer and other chronic

Affiliations of authors: Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA (EG, EBR, CSF, MJS, WCW); Department of Nutrition (EG, YL, EBR, MJS, WCW), Department of Epidemiology (EG, EBR, MJS, WCW), Harvard School of Public Health, Boston, MA; Department of Pediatrics, Medical University of South Carolina, Charleston, SC (BWH); Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA (CSF).

Correspondence to: Edward Giovannucci, MD, ScD, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115 (e-mail: edward.giovannucci@channing.harvard.edu).

See "Notes" following "References."

DOI: 10.1093/jnci/djj101

diseases, is composed of 51 529 U.S. male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40–75 years in 1986. Through the baseline mailed questionnaire in 1986, these men provided information on age, marital status, height and weight, ancestry, medications, smoking history, medical history, physical activity, and diet. We updated nondietary exposures and medical history every 2 years and dietary information every 4 years. The study was approved by the institutional review board of the Harvard School of Public Health.

Determination and Assessment of Factors Potentially Influencing Circulating 25(OH)D Concentrations

From the existing literature, we identified factors that are known to influence circulating 25(OH)D concentrations, including region as a surrogate of UV-B radiation exposure, behaviors related to sun exposure, skin pigmentation, BMI, intake, season, and age *(10)*.

Regional UV-B radiation intensity. Solar UV-B radiation is the major source of vitamin D for most people. Being exposed to enough UV-B radiation to cause a slight pinkness to the skin in light-skinned persons with most of the skin uncovered (i.e., one minimal erythemal dose) produces a plasma vitamin D response equivalent to an oral dose of 20 000 IU of vitamin D *(11,12)*. A surrogate of vitamin D used in epidemiologic studies has been the average UV-B radiation in the geographic region of residence. We obtained state of residence in 1986 (baseline) from the study participant's mailing address.

Sun exposure. We did not assess actual behaviors in seeking or avoiding sunlight and instead used leisure-time physical activity as an indicator of outdoor sunlight exposure (because of the nature of their professions, most men in this cohort worked indoors and received minimal work-related sunlight exposure). 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, as well as the number of flights of stairs they climbed daily and their walking pace. To generate the total leisure-time physical activity score, we summed activity-specific metabolic-equivalents (MET)-hours/week. In a substudy of 238 study participants, the correlation between the questionnaire assessment of vigorous activity with four 1-week diary records was .58, and the correlation between the reported vigorous activity and the resting heart rate was –.45 *(13)*.

Skin pigmentation. The degree of skin pigmentation exerts a profound influence on vitamin D status because melanin effectively filters out UV-B radiation. A dark-skinned individual may require an exposure to UV-B radiation equal to 10 times or greater that of a light-skinned person to produce an equivalent amount of vitamin D *(14)*. It is thus not surprising that African Americans have much higher rates of vitamin D deficiency than whites *(14,15)*. We assessed self-reported race in 1986 and thus categorized men as African American, Asian, white, and other.

Dietary and supplemental vitamin D intake. Semiquantitative food-frequency questionnaires, described in detail previously *(16)*, were administered in 1986, 1990, 1994, and 1998. The self-administered 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, they typically consumed each item over the past year. Also, on each questionnaire, they reported the brand of breakfast cereal and the duration and frequency of its use and the brand of vitamin supplements, including specific supplements (such as vitamin A or D or multivitamin supplements). In addition to assessing specific vitamin D supplements, we used information on vitamin D content from approximately 1400 multivitamins, which was updated every 4 years to assess intake from these general supplements. We used these specific data on supplements to compute nutrient intakes by multiplying the consumption frequency of each unit of food by its nutrient content derived from composition values from U.S. Department of Agriculture sources and supplemented with other data. The mean correlation coefficients between intakes determined by two 1-week diet records and the dietary questionnaire (adjusting for week-to-week variation in the diet records) among a sample of 127 cohort members were .65 for nutrients and .63 for specific foods *(16,17)*. We assessed the major sources of dietary vitamin D (including various dairy products, fortified breakfast cereals, dark meat fish, and cod liver oil) and supplementary vitamin D (including multivitamins and specific vitamin D supplements). Specific vitamin D intake was not available from the dietary records, but the predominant sources of dietary vitamin D in this cohort showed good correlations (skim or low-fat milk, $r = .88$; whole milk, $r = .67$; dark-meat fish, $r = .58$; and cold breakfast cereal, $r = .86$) *(17)*.

BMI. Higher BMI or obesity has usually been found to be associated with substantially lower blood concentrations of 25(OH)D *(15,18,19)*, probably as a result of decreased bioavailability of 25(OH)D because of its deposition in body fat compartments *(19)*. We asked the men to report height and weight in 1986 and used these values to determine their BMI. In a substudy, the correlation between self-reported measurements and technicians' measurements was .97 for weight *(20)*.

Plasma 25(OH)D assessment. The 25(OH)D level in plasma was determined by radioimmunoassay, as previously described *(21)*. The samples were from 1095 participants in two substudies in this cohort, one a nested case–control study of prostate cancer (n = 952) *(22)* and the other to examine racial differences and reproducibility over time (n = 143) *(23)*. Thus, the second study was enriched with African American and Asian men. The prediction equation (see below) was then validated in another sample from a substudy for colorectal cancer risk in this cohort (n = 542). None of men for whom 25(OH)D levels were determined had a cancer diagnosis at the time of blood draw. The samples had acceptable laboratory coefficients of variation (<10%) *(22,23)*.

Ascertainment of Cancers

We asked for written permission to acquire relevant medical records and pathology reports from men (or their next-of-kin) who reported a cancer on our biennial questionnaires. The follow-up rate with respect to the incidence of cancer was 97% of the total potential person-years, and the death follow-up rate was more than 98%. Approximately 90% of cases were confirmed by medical record review, and the remaining cases were confirmed with information from the participant or a family member or by death certificate. Through January 31, 2000, we confirmed 4286 cases of total incident cancers (including hematologic malignancies but excluding nonmelanoma skin cancers and nonaggressive, organ-confined prostate cancer) and 2025 deaths from cancer (including from skin cancer). Also, we separately examined individual cancer sites for which at least 50 cases were diagnosed. We excluded the 2552 organ-confined prostate cancers because

of their favorable prognosis, high incidence, and the facts that their detection usually results from a prostate-specific antigen screening test and that definitions of abnormal values for prostate-specific antigen screening tests vary among institutions. If we included organ-confined prostate cancer, prostate cancer would have constituted about half of all incident cancers, but they account for only about 10% of cancer deaths.

Statistical Analysis

Analysis for predicting 25(OH)D level as a function of participants' characteristics. To develop the prediction model for plasma 25(OH)D level, we used the sample of 1095 men from the Health Professionals Follow-Up Study who had a measurement of their plasma 25(OH)D level available. The men were free of diagnosed cancer when they provided the blood sample, and they did not vary appreciably from other men in the cohort on diet and lifestyle factors. Using linear regression, with the measured plasma 25(OH)D level as the dependent variable, we examined the following independent variables in prespecified categories (given in Table 1): 1) geographic region, 2) dietary vitamin D intake, 3) supplementary vitamin D intake including that from multivitamins, 4) race (African American, Asian, white, or other), 5) BMI (expressed as kg/m^2), and 6) physical activity level. We also examined two-way interactions for all combination of variables. We included age (continuous), season of blood draw, and batch in the model, although these variables were not included in the predictor score. Then, on the basis of the predictors' regression coefficients from the sample, we calculated a predicted 25(OH)D score for each cohort member (see below). We assumed that any measurement error in the assessment of plasma 25(OH)D level was not correlated with measurement error in the reporting of the six surrogates. Finally, we used an independent dataset from the cohort to validate that the computed score derived from the initial dataset predicted circulating 25(OH)D levels.

Cohort analysis. At baseline, we excluded men with diagnosed cancer (except for nonmelanoma skin cancer), men with more than 70 food items missing, and men whose energy intake was outside the range of 800–4200 kcal/day (i.e., a total of 3% of the entire cohort). These exclusions left 47 800 men, who accrued follow-up time beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis of cancer (for incidence analyses only), month of death from other causes, or January 31, 2000, whichever came first. We used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute hazard ratios to estimate relative risks (RRs) and 95% confidence intervals (CIs). Proportional hazards assumptions were tested by modeling a predicted 25(OH)D and age interaction term; that term was not statistically significant, confirming the assumption. Age was controlled for in 1-year increments, and time was controlled for in 2-year intervals. The following covariables were included in the models: height (quintiles); smoking history (never, quit <10 years, quit ≥10 years, or current [1–14, 15–24, or ≥25 cigarettes per day]); alcohol (0, 0.1–14, 15–29.9, or ≥30 g/day); and quintiles of total calories, red meat (servings per day), calcium (milligrams per day), retinol (IU/day), and total fruits and vegetables (servings per day). [In the vitamin D regression model, these covariables were not appreciably correlated with plasma 25(OH)D measurements because all partial Spearman correlation coefficients were less than .10.] Nutrients were energy adjusted by use of residual analysis on the natural logarithm scale. We generally controlled for covariables as categorical variables. We used baseline values without updating because recent changes in BMI and physical activity may result from underlying disease.

For the main analysis, we used the predicted 25(OH)D level as a continuous variable and then calculated the relative risk for an increment of 25 nmol/L in the predicted 25(OH)D level—this value corresponds approximately to the difference between the medians in the high and low deciles. In alternative analyses, we used predicted 25(OH)D level categorized in deciles. All statistical tests were two-sided.

Table 1. Factors contributing to the predictors of age-adjusted plasma 25-hydroxyvitamin D [25(OH)D] level from a multiple linear regression model of 1095 men in the Health Professionals Follow-Up Study

Factor	Change in 25(OH)D, nmol/L
Intercept	90.8
Race	
White	0 (referent)
African American	−12.8
Asian	−13.3
Residence	
South	0 (referent)
Midwest/West	−2.4
Northeast/Mid-Atlantic	−6.4
Quintile of leisure-time physical activity*	
5	0 (referent)
4	−4.5
3	−7.7
2	−9.0
1	−13.5
Body mass index	
<22 kg/m^2	0 (referent)
22–24.9 kg/m^2	−1.0
25–29.9 kg/m^2	−4.5
30–34.9 kg/m^2	−6.5
≥35 kg/m^2	−8.6
Dietary vitamin D	
≥400 IU/day	0 (referent)
300–399 IU/day	−3.5
200–299 IU/day	−2.6
100–199 IU/day	−7.2
<100 IU/day	−10.4
Supplementary vitamin D†	
≥400 IU/day	0 (referent)
200–399 IU/day	−1.8
1–199 IU/day	+2.4
<100 IU/day	−2.1
Season‡	
Autumn	0 (referent)
Summer	−1.8
Spring	−12.1
Winter	−13.5

*Physical activity is used as a proxy for outdoor activities, which will tend to increase solar UV-B exposure.

†Not statistically significant.

‡Season was adjusted but not used in the predictive model because season is a strong determinant of 25(OH)D level and reflects the time of blood draw, but it is not a factor in determining long-term average between-person variation in 25(OH)D level.

Results

Using linear regression, we identified race, geographic region, vitamin D from diet, BMI, and physical activity as independent predictors of 25(OH)D level (Table 1). Our model identified a

wide range of predicted 25(OH)D levels, from a summer high of 90.8 nmol/L for a man with all favorable characteristics (i.e., highest intake categories, residence in the southern United States, lowest BMI, highest activity level, and low skin pigmentation) to a winter low of 22.8 nmol/L for a man with the opposite extreme characteristics. The model r^2 was 28%. No statistically significant interactions were observed among the variables. The mean actual circulating level of 25(OH)D for men in the highest decile of predicted 25(OH)D level was 27.8 nmol higher (95% CI = 22.9 to 32.7) than that in men in the lowest decile. In terms of the individual predictors, physical inactivity and darker skin were the strongest predictors of 25(OH)D level, followed by dietary intake, BMI, and region. Vitamin D from supplements increased 25(OH)D levels only slightly. The association with season was similar to that of race and physical activity, although we did not use season to compute the predicted 25(OH)D level for the cohort because it reflects time of blood draw, but it is not a factor in determining long-term average between-person variation in 25(OH)D level. Increasing age was not associated with a lower level of 25(OH)D, but in further analyses the reason appeared to be that retired men likely had more opportunity for sun exposure (data not shown).

To verify the precision of our empirical model by use of the scores derived from the initial cohort of 1095 men, we calculated the predicted 25(OH)D level of an independent sample of 542 men from the Health Professionals Follow-Up Study who also had measurements of their circulating 25(OH)D level available. The actual plasma 25(OH)D level rose across increasing deciles of predicted 25(OH)D score ($P_{trend}<.001$), and the difference in the mean actual 25(OH)D level between the extreme deciles was 25.0 nmol/L. This difference was similar to the difference of 27.8 nmol/L, which we calculated from the initial dataset.

Age-adjusted characteristics of men according to predicted 25(OH)D level are shown in Table 2. As expected, a higher predicted 25(OH)D level was associated with white race, higher vitamin D intake, residence in the southern United States, lower BMI, and more physical activity, compared with other races, low vitamin D intakes, residence in the northeastern/mid-Atlantic United States, high BMI, and low physical activity, respectively. Also, those with higher 25(OH)D levels were less likely to smoke, more likely to use multivitamins, and likely to eat more fish and less red meat.

Among the 47 800 men in the cohort, from 1986 through January 31, 2000, we documented 4286 incident cancers (excluding organ-confined prostate cancer and nonmelanoma skin cancer) and 2025 deaths from cancer. The association between an increment of 25 nmol/L in the predicted 25(OH)D level and risk of various cancers as determined from multivariable models is shown in Fig. 1. For each of the four major digestive organ cancers, we observed a statistically significant inverse association for colorectal cancer (RR = 0.63, 95% CI = 0.48 to 0.83), for pancreatic cancer (RR = 0.49, 95% CI = 0.28 to 0.86), and for esophageal cancer (RR = 0.37, 95% CI = 0.17 to 0.80), and we observed a non–statistically significant but suggestive inverse association for stomach cancer (RR = 0.58, 95% CI = 0.26 to 1.33). A statistically significant inverse association was also observed for oral or pharyngeal cancers (RR = 0.30, 95% CI = 0.11 to 0.81), and a suggestive inverse association was observed for leukemias (RR = 0.44, 95% CI = 0.20 to 1.00). We observed inverse non–statistically significant associations for lung, advanced prostate, and renal cancers and for non-Hodgkin lymphoma. For other cancers, no appreciable inverse or positive association was noted, except for non–statistically significant positive associations for melanoma and brain cancer.

Table 2. Age-standardized demographic characteristics of 1986 Health Professionals Follow-Up Study Population

Characteristic	Predicted 25(OH)D* Q1	Q3	Q5
Mean age, y	53.6	54.1	54.3
Physical activity, MET-h/wk	5.2	15.6	44.1
BMI†, kg/m^2	26.4	24.9	23.6
Alcohol in 1986, g/day	12.1	11.2	10.3
Current smoking, %	13.1	9.8	6.3
Height, in	69.7	70.2	70.4
White, %	82.4	92.9	93.8
African American, %	4.3	0.07	0.0
Asian, %	7.0	0.28	0.0
Other, %	6.5	6.45	6.1
South, %	28.4	47.1	65.9
Northeast, %	37.0	17.1	7.2
Midwest, %	31.9	35.2	26.6
Multivitamin use, %	28.2	40.6	59.7
Vitamin D, IU/day	245	358	508
Vitamin D from food, IU/day	148	220	297
Vitamin D from supplement, IU/day	90	130	202
Calories, kcal/day	1956	1984	2022
Calcium, mg/day	732	907	1078
Retinol, IU/day	4172	5321	7109
Folate, μg/day	406	471	573
Red meat, servings per day	0.70	0.62	0.48
Fruits and/or vegetables, servings per day	5.41	5.83	6.65
Fish, servings per day	0.34	0.38	0.47

*This score is based on a regression model using race, region, leisure time physical activity, body mass index, dietary vitamin D, and supplementary vitamin D. Q = quintile; MET = metabolic equivalents.
†BMI = body mass index.

Results for the predicted 25(OH)D level and total cancer incidence and mortality are shown in Table 3. A predicted 25(OH)D increment of 25 nmol/L was associated with a 17% reduction in total cancer incidence (relative risk [RR] = 0.83, 95% confidence

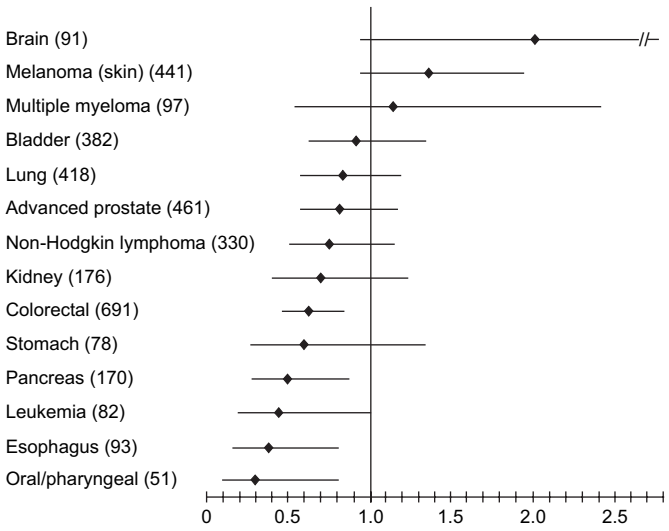

Fig. 1. Multivariable relative risks and 95% confidence intervals for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). Number in parentheses = number of cases. Covariables included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

interval [CI] = 0.74 to 0.92) and a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83). When we further controlled for BMI or for physical activity, the results did not change appreciably. The total cancer incidence annual rate was 758 per 100 000 people in the bottom decile of the predicted 25(OH)D level and 674 per 100 000 people in the top decile. When we conducted a categorical multivariable analysis for the predicted 25(OH)D level, in which the top versus bottom deciles were compared, we found that total cancer mortality was inversely associated with predicted 25(OH)D level (RR = 0.78, 95% CI = 0.64 to 0.97). The total cancer mortality annual rate was 326 per 100 000 people in the bottom decile of the predicted 25(OH)D level and 277 per 100 000 people in the top decile.

Results for the analysis of combined group of digestive cancers, which was selected a priori as the group expected to be most strongly related to vitamin D status, are shown in Table 4. Associations were stronger for digestive cancers than for total cancers. For digestive system cancers, an increment of 25 nmol/L in the predicted 25(OH)D level was associated with a 43% reduction in incidence (RR = 0.57, 95% CI = 0.46 to 0.71) and a 45% reduction in mortality (RR = 0.55, 95% CI = 0.41 to 0.74). Further control for BMI and physical activity did not alter these findings. When we conducted multivariable categorical analysis for the predicted 25(OH)D level by comparing the top decile with the bottom decile, we found an inverse association between digestive cancer mortality and predicted 25(OH)D level (RR = 0.58, 95% CI = 0.40 to 0.84). The digestive cancer mortality annual rate was 128 per 100 000 people in the bottom decile and 78 per 100 000 people in the top decile of the predicted 25(OH)D level.

The inverse association between a predicted 25(OH)D increment of 25 nmol/L and the risk of total cancer and digestive system cancer mortality across strata of various factors are shown in Table 5. These results were remarkably constant across all strata. For total cancer mortality, the associations were statistically significant for all strata of factors.

For the digestive system cancers, we examined a multivariable model [without predicted 25(OH)D levels in the model] that contained the five major components of predicted 25(OH)D level and found that increased risk was associated with African American (RR = 1.95, 95% CI = 1.26 to 3.02) and Asian (RR = 1.38, 95% CI = 0.86 to 2.24) race, compared with white race; residence in the Northeast/Mid-Atlantic region, compared with the South (RR = 1.24, 95% CI = 1.07 to 1.44); bottom versus top quintile of physical activity (RR = 1.30, 95% CI = 1.07 to 1.58); high versus low BMI (RR = 1.23, 95% CI = 0.83 to 1.82); and dietary vitamin D of less than 200 IU/day versus more than 400 IU/day (RR = 1.16, 95% CI = 0.91 to 1.48). For digestive cancer mortality, similar associations were observed (for African American race, RR = 2.34, 95% CI = 1.37 to 4.01; for Asian race, RR = 1.96, 95% CI =1.11 to 3.48; for residence in the Northeast/Mid-Atlantic region, RR = 1.25, 95% CI = 1.02 to 1.53; for dietary vitamin D intake, RR = 1.39, 95% CI = 0.97 to 1.97; for physical activity, RR = 1.20, 95% CI = 0.92 to 1.56; for BMI, RR = 1.02, 95% CI = 0.61 to 1.71).

Because the predicted 25(OH)D score was based on a sample within one cohort and thus subject to variability, we used measurement error–correction methods to calibrate the relative risk and 95% confidence intervals as previously described *(24,25)*. The predicted score, which was based on the initial subcohort of 1095 men and used in the entire cohort, was calibrated with plasma 25(OH)D levels from a second independent cohort of 542 men. With these methods, the actual plasma 25(OH)D level was regressed on the predicted 25(OH)D score, and the β coefficient and its standard error were used to calibrate the relative risks and 95% confidence intervals for total and digestive cancer incidence and mortality for the entire cohort. For an increment of 25 nmol/L in predicted vitamin D level, the corrected multivariable relative risks and 95% confidence intervals were as follows: for total cancer incidence, RR = 0.81, 95% CI = 0.71 to 0.93; for total cancer mortality, RR = 0.68, 95% CI = 0.55 to 0.84; for total digestive cancer incidence, RR = 0.54, 95% CI = 0.40 to 0.73; and for total digestive cancer mortality, RR = 0.52, 95% CI = 0.35 to 0.75. The corrected and uncorrected multivariable relative risks (see Tables 3 and 4) were not substantially different from each other, indicating that the predicted 25(OH) score was a robust measure.

Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D [25(OH)D] level for total cancer incidence and mortality in the Health Professionals Follow-Up Study (1986–2000)

Endpoint	RR (95% CI)
Total cancer incidence (N = 4286)	
Age-adjusted	0.78 (0.70 to 0.86)
Multivariable-adjusted*	0.83 (0.74 to 0.92)
Multivariable + BMI†	0.83 (0.73 to 0.94)
Multivariable + physical activity	0.84 (0.72 to 0.98)
Total cancer mortality (N = 2025)	
Age-adjusted	0.65 (0.56 to 0.76)
Multivariable-adjusted*	0.71 (0.60 to 0.83)
Multivariable + BMI†	0.71 (0.59 to 0.84)
Multivariable + physical activity	0.69 (0.55 to 0.86)

*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

†BMI = body mass index.

Table 4. Relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D [25(OH)D] level for digestive system cancer incidence and mortality in the Health Professionals Follow-Up Study (1986–2000)

Endpoint	RR (95% CI)
Digestive cancer incidence (n = 1123)	
Age-adjusted	0.54 (0.44 to 0.66)
Multivariable-adjusted*	0.57 (0.46 to 0.71)
Multivariable + BMI†	0.59 (0.47 to 0.75)
Multivariable + physical activity	0.52 (0.38 to 0.71)
Digestive cancer mortality (n = 594)	
Age-adjusted	0.51 (0.39 to 0.67)
Multivariable-adjusted*	0.55 (0.41 to 0.74)
Multivariable + BMI†	0.54 (0.39 to 0.75)
Multivariable + physical activity	0.45 (0.30 to 0.68)

*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

†BMI = body mass index.

Discussion

In the Health Professionals Follow-Up Study cohort, we quantified how v arious factors influence plasma 25(OH)D level for middle-aged to elderly men. When we used data from the 1095

Table 5. Multivariable* relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D level for total cancer mortality (n = 2025) and digestive system cancer mortality (n = 594) across strata of various factors in the Health Professionals Follow-Up Study (1986–2000)

Stratification variable	Total cancer mortality, RR (95% CI)	Digestive cancer mortality, RR (95% CI)
Age		
<70 y	0.67 (0.54 to 0.84)	0.57 (0.38 to 0.89)
≥70 y	0.75 (0.59 to 0.96)	0.52 (0.34 to 0.80)
Smoker		
Ever	0.72 (0.59 to 0.87)	0.52 (0.36 to 0.74)
Never	0.68 (0.50 to 0.92)	0.63 (0.36 to 1.08)
Body mass index		
<25 kg/m^2	0.66 (0.51 to 0.85)	0.47 (0.29 to 0.75)
≥25 kg/m^2	0.73 (0.57 to 0.93)	0.57 (0.37 to 0.88)
Physical activity		
Below median	0.71 (0.55 to 0.93)	0.36 (0.22 to 0.58)
Above median	0.73 (0.54 to 0.98)	0.63 (0.37 to 1.07)
Alcohol		
Below median	0.69 (0.55 to 0.87)	0.60 (0.39 to 0.92)
Above median	0.71 (0.52 to 0.97)	0.50 (0.33 to 0.76)
Region		
Northern latitude	0.76 (0.60 to 0.95)	0.49 (0.32 to 0.75)
Southern latitude	0.68 (0.53 to 0.88)	0.61 (0.38 to 0.97)
Multivitamin use		
No	0.69 (0.52 to 0.90)	0.46 (0.31 to 0.69)
Yes	0.73 (0.57 to 0.92)	0.63 (0.40 to 0.98)
Red meat consumption		
Below median	0.64 (0.52 to 0.80)	0.46 (0.31 to 0.69)
Above median	0.78 (0.61 to 0.99)	0.65 (0.41 to 1.03)
Fruit and vegetable consumption		
Below median	0.74 (0.59 to 0.94)	0.46 (0.29 to 0.71)
Above median	0.68 (0.54 to 0.85)	0.64 (0.42 to 0.76)
Fish consumption		
Below median	0.78 (0.61 to 0.98)	0.66 (0.42 to 1.03)
Above median	0.65 (0.52 to 0.81)	0.46 (0.30 to 0.69)

*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

men in our initial cohort, the range of predicted 25(OH)D levels was wide, from 22.8 nmol/L to 90.8 nmol/L. Vitamin D intake predicted a relatively small proportion of the variance in 25(OH)D, a finding that is consistent with the literature *(26)*, which indicates that the plasma level of 25(OH)D increases 1.75 nmol/L for every increment of 100 IU/day in vitamin D intake (cholecalciferol or D_3). Vitamin D from supplements predicted an even smaller rise. For example, from our estimates, a 400-IU vitamin D supplement daily would increase the plasma 25(OH)D level by only about 2 nmol/L. This finding may be consistent with the frequent use of ergocalciferol (D_2) in most multivitamin supplements (Dr. Walid Aldoori, personal communication), which is only one-fourth as potent as cholecalciferol (D_3) in raising plasma 25(OH)D levels *(27,28)*. Skin pigmentation (estimated by race), region of residence, adiposity level, and leisure-time physical activity were each comparable, if not greater, determinants of 25(OH)D level than was intake. Most notably, leisure-time physical activity, presumably a proxy of outdoor exposure to sun, was among the strongest determinants of 25(OH)D level, even though this variable did not take into account actually exercising outdoors, level of clothing, season, time of day, and use of sunscreen. Physical activity's strength likely lies in the fact that sunlight exposure is a considerably stronger determinant of 25(OH)D level than are typical dietary intakes. For example, a fair-skinned individual can produce 20 000 IU of vitamin D in the skin, which can be released to the circulation, through 20–30 minutes of sun exposure *(11,12)*.

In this cohort analysis, a 25(OH)D increment of 25 nmol/L was associated with a 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, and a 43% and 45% reduction in incidence and mortality, respectively, of digestive-system cancers. A further risk reduction is possible for even higher 25(OH)D increments, but larger increments were beyond the range of our data. We obtained similar results when we used a categorical analysis that compared high and low deciles of predicted 25(OH)D level, which represented a difference of about 25 nmol/L (e.g., a 22% reduction in total cancer mortality and a 42% reduction in digestive system cancer mortality). We had considered a priori that digestive cancers would most likely be sensitive to vitamin D status on the basis of previous ecologic geographic data in the United States and in Japan *(8,9)*. We similarly found colorectal, pancreatic, stomach, and esophageal cancers to be individually associated with predicted 25(OH)D levels. The strongest inverse association overall was for oral or pharyngeal cancers. Although we had not grouped these cancer types as digestive-system cancers, they can be considered as part of the oral–gastrointestinal tract. We did not study women, but previous ecologic studies have suggested similar relationships *(8)*.

Regarding specific cancer types, our findings for colorectal cancer are compatible with those of plasma-based, dietary-based, and ecologic studies, as reviewed by Grant and Garland *(29)*. Other cancers that were associated with predicted 25(OH)D levels have not received much study. The vitamin D–sensitive cancers that we found to be associated with predicted 25(OH)D levels are those of rapidly proliferating tissue, such as the oral–gastrointestinal tract and the bone marrow. These are tissues that are most susceptible to chemotherapeutic agents that block cell division. In animal models, vitamin D and calcium have been shown to inhibit the so-called Western diet–induced hyperproliferation in the intestines and pancreas *(30,31)*. Our findings for leukemia are of interest given that 1,25(OH)$_2$D induces differentiation of mouse myeloid leukemia cells *(32)* and improves survival *(33)* in mice inoculated with murine myeloid leukemia cells. In a case report *(34)*, adequate vitamin D intake (with apparently no other treatment) was associated with clinical remission of chronic lymphocytic leukemia for at least 16-years. Our results suggest that high levels of 25(OH)D were associated with reduced development of leukemia.

We found somewhat stronger inverse associations for total cancer mortality than for incidence. A large study *(35)* in Norway found that men and women diagnosed with breast, prostate, or colorectal cancer in the summer and autumn months, when 25(OH)D concentrations are highest, had statistically significantly better survival from these cancers. The authors of that study speculated that a high level of vitamin D at the time of diagnosis, and possibly during cancer treatment, may improve the prognosis of at least the three malignancies they considered. A recent analysis *(36)* suggests the same relationship for lung cancer. The association of vitamin D status at the time of diagnosis or thereafter with survival for some cancers deserves further study.

The vitamin D–cancer hypothesis has been studied in various ways, but each approach has had some limitations. Most epidemiologic approaches have focused on latitude or regional exposure to solar UV-B radiation *(3–9)*. For example, Grant *(8)* demonstrated that exposure to regional UV-B radiation was

inversely correlated with mortality rates of many cancers, particularly digestive-organ cancers, a finding confirmed in Japan *(9)*. A criticism of ecologic studies that were based on estimated regional UV-B exposure has been that other factors related to regional differences could explain the differences, although to date, no strong alternative explanation has been offered. A putative confounding factor would also have to be operative in populations as diverse as those of the United States and Japan. Another criticism is that regional UV-B exposure accounts for only a small proportion of the variation in 25(OH)D level. In fact, in our subsample analysis, region was a weaker predictor of 25(OH)D than was diet, race, physical activity level, and BMI. The effectiveness of region of residence as an indication of UV-B exposure and vitamin D status may be diminishing over time in part because of winter vacations in sunny climates and changes in sun exposure behavior, such as sun avoidance or use of sunscreen.

An innovative approach recently used to study the vitamin D-cancer hypothesis has been the use of a reflectometer to measure constitutive skin pigmentation on the upper underarm (a sun-protected site) and facultative pigmentation on the forehead (a sun-exposed site) to calculate a sun exposure index *(37)*. This measurement predicted risk of advanced prostate cancer in a case–control study *(37)*. Other investigators have used factors such as childhood sunburns, holidays in a hot climate, and skin type in a case–control study to predict prostate cancer risk *(38)*. Given the importance of sun exposure on vitamin D synthesis, it is reasonable to infer vitamin D status from these indirect measures, but the actual corresponding difference in vitamin D status was not estimated, and these approaches have been used only for prostate cancer.

To our knowledge, our study is the first to examine total cancer incidence and mortality by use of a comprehensive assessment of factors that determine 25(OH)D level. We examined six relevant factors and were able to predict a wide range of 25(OH)D levels and to quantify plasma levels of 25(OH)D. Perhaps the optimal approach is to measure 25(OH)D levels and monitor individuals for subsequent cancer risk. Although to date no such study has examined total cancer risk, some studies have examined circulating 25(OH)D levels in relation to risk of colorectal cancer *(39–41)* or risk of prostate cancer *(22,42–48)*. For these two cancer sites, our results provide similar results—clear inverse associations for colorectal cancer (40%–50% reduction in risk) and a suggestive but not statistically significant reduction in prostate cancer risk (approximately 20% reduction in risk).

The similarity of the findings (e.g., for colorectal cancer) that were based on one measurement of vitamin D in blood and those based on our predictor score indicates that each may provide approximately comparable information of long-term average 25(OH)D level (e.g., lifetime or over 20–30 years), the presumed factor of interest. A measurement of 25(OH)D level in blood has the advantage of potentially accounting for all sources of variability. However, the predicted measure may have some advantage over one measurement of 25(OH)D because some factors that influence the predicted 25(OH)D score are immutable (race) or relatively stable (region of residence or BMI), so that this score would tend to track well over time, whereas a substantial proportion of variability in one blood measurement would likely result from relatively recent exposures (for example, sun exposure from a recent vacation), season, and laboratory measurement error. These factors would make the single measurement less representative of actual long-term 25(OH)D level. In support of this supposition, in a sample of 143 of the men who provided a second blood sample 3–4 years later, the correlation between the two actual plasma 25(OH)D measurements was .70, whereas the correlation between the two predicted 25(OH)D levels for these men 4 years apart was .83.

The most apparent limitation of our approach is the possibility that our predicted 25(OH)D score was acting as a surrogate for the causal factor, such as BMI or physical activity, via alternative mechanisms. However, our results for predicted 25(OH)D level did not change appreciably when we controlled or stratified for BMI or physical activity. Controlling for these factors may be considered overcontrol because these variables are important determinants of 25(OH)D status. Our results, however, indicate that the inverse associations between predicted 25(OH)D level and cancer risk were not largely driven by BMI or physical activity. From the opposite perspective, however, a protective role of 25(OH)D level may partly account for some cancer risk factors for this disease. Colorectal cancer is worth examining in this regard because of previous evidence that obesity and physical inactivity are risk factors. When modeled without a predicted 25(OH)D level in the multivariable model, the risk of colorectal cancer was directly associated with BMI (comparing >30 kg/m^2 with <21 kg/m^2, RR = 1.59, 95% CI = 0.95 to 2.66) but inversely associated with physical activity (comparing high versus low physical activity, RR = 0.78, 95% CI = 0.61 to 0.99). When the predicted 25(OH)D level was included in the model, the strengths of these respective associations decreased (for BMI, RR = 1.49, 95% CI = 0.88 to 2.51; for physical activity, RR = 0.99, 95% CI = 0.71 to 1.39), whereas the associations for predicted 25(OH)D level did not change appreciably. These findings indicate that vitamin D status may explain some of the relationships of BMI, physical activity, and colon cancer risk. Our findings may also help explain why darker-skinned men (particularly African Americans) and men living in the northeastern or mid-Atlantic states are at higher risk of many cancers.

The Women's Health Initiative randomly assigned 36282 postmenopausal women to receive 1000 mg of calcium and 400 IU of vitamin D_3 daily or to receive placebo *(49)*. No association with colorectal cancer incidence was found with an average of 7 years of follow-up. Interestingly, suggestive non–statistically significant inverse associations were observed for colorectal cancer mortality (RR = 0.82, 95% CI = 0.52 to 1.29; P = .39), total cancer mortality (RR = 0.89, 95% CI = 0.77 to 1.03; P = .12), and total mortality (RR = 0.93, 95% CI = 0.83 to 1.01; P = 0.07). By use of data from that paper [28% higher level in 25(OH)D in women randomly assigned to receive vitamin D and a median baseline level of 42.3 nmol/L], we estimate the increase in the 25(OH)D level was 11.8 nmol/L. By use of our data, for such an increment of predicted 25(OH)D, we calculated a relative risk of 0.85 for total cancer mortality, which was not much different from that of 0.89 observed in the randomized trial. Thus, although the dose was relatively low and the duration relatively short in the trial, the suggestive findings for total cancer mortality are in line with our results and support further study with higher doses of vitamin D.

Confirming that vitamin D levels indeed account for the associations we observed is critical because current health recommendations typically discourage high intake of vitamin D and high levels of sun exposure, at least without use of sunscreen, which effectively blocks vitamin D production *(11)*. Achieving a 25(OH)D increment of 25 nmol/L may require a vitamin D

supplementation of at least 1500 IU/day, a safe but not generally encouraged level *(26)*. A glass of milk, although generally perceived as a good source of vitamin D, contains 100 IU, which would increase the plasma level of 25(OH)D by only about 2 to 3 nmol/L. Adult sun exposure is discouraged largely because of risk of melanoma, the most deadly form of skin cancer, but the melanoma risk associated with moderate sun exposure without burning in adults is unclear. Although melanomas account for approximately 7000 deaths annually in males in the United States, 295 000 men die annually of all cancers. We estimated a 29% lower cancer mortality rate (i.e., 85 550 fewer deaths) if the predicted 25(OH)D level is increased 25 nmol/L. Thus, because current recommendations are adequate only to prevent extremely low vitamin D levels, establishing definitively whether cancer incidence and mortality rates are increased by inadequate vitamin D status should be a high priority.

References

(1) Peller S, Stephenson CS. Skin irritation and cancer in the United States Navy. Am J Med Sci 1937;194:326–33.

(2) Apperly FL. The relation of solar radiation to cancer mortality in North American. Cancer Res 1941;1:191–5.

(3) Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980;9:227–31.

(4) Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med 1990;19:614–22.

(5) Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. Int J Epidemiol 1994;23:1133–6.

(6) Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 1990;10:1307–11.

(7) Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Cancer 1992;70:2861–9.

(8) 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.

(9) Mizoue T. Ecological study of solar radiation and cancer mortality in Japan. Health Phys 2004;87:532–8.

(10) Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 2005; 16:83–95.

(11) 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.

(12) Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135:317–22.

(13) Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.

(14) 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.

(15) Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, 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.

(16) 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.

(17) Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.

(18) Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, et al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004;89:1196–9.

(19) Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.

(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) Hollis BW, Kamerud JW, Selvaag SR, Lorenz JD, Napoli JL. Determination of vitamin D status by radioimmunoassay using I[125]-labelled tracer. Clin Chem 1993;39:529–33.

(22) Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. Cancer Causes Control 2004;15:255–65.

(23) 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.

(24) Willett WC. Correction for the effects of measurement error. Nutritional epidemiology, 2nd edition. New York (NY): Oxford University Press; 1998, p. 302–20.

(25) Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. Stat Med 1989;8:1051–69.

(26) Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204–10.

(27) Vieth R. The pharmacology of vitamin D, including fortification strategies. In Feldman D, Pike JW, Glorieux FH, editors. Vitamin D, 2nd edition. Amsterdam (The Netherlands): Elsevier Academic Press; 2005, p. 995–1015.

(28) Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004;89:5387–91.

(29) Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer 2004;48:115–23.

(30) Newmark HL, Lipkin M, Maheshwari N. Colonic hyperplasia and hyperproliferation induced by a nutritional stress diet with four components of Western-style diet. J Natl Cancer Inst 1990;82:491–6.

(31) Xue L, Lipkin M, Newmark H, Wang J. Influence of dietary calcium and vitamin D on diet-induced epithelial cell hyperproliferation in mice. J Natl Cancer Inst 1999;91:176–81.

(32) Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, et al. Differentiation of mouse myeloid leukemia cells induced by 1[alpha], 25-dihydroxyvitamin D3. Proc Natl Acad Sci U S A 1981;78:4990–4.

(33) Honma Y, Hozumi M, Abe E, Konno K, Fukushima M, Hata S, et al. 1[alpha],25-dihydroxyvitamin D3 and 1[alpha]-hydroxyvitamin D3 prolong survival time of mice inoculated with myeloid leukemia cells. Proc Natl Acad Sci U S A 1983;80:201–4.

(34) Politzer WM. Long-term clinical remission of chronic lymphocytic leukaemia by dietary means. South African Med J 2005;95:321–2.

(35) 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.

(36) Zhou W, Suk R, Liu G, Park S, Neuberg DS, Wain JC, 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.

(37) John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. Cancer Res 2005;65:5470–9.

(38) Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, et al. Associations between prostate cancer susceptibility and parameters of exposure to ultraviolet radiation. Cancer Lett 2003;200:141–8.

(39) Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet 1989;2:1176–8.

(40) Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, Virtamo J, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control 1997;8:615–25.

(41) Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004;13:1502–8.

(42) Corder EH, Guess HA, Hulka BS, Friedman GD, Sadler M, Vollmer RT, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomarkers Prev 1993;2:467–72.
(43) Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control 1995;6:235–9.
(44) Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomarkers Prev 1996;5:121–6.
(45) Nomura AM, Stemmermann GN, Lee J, Kolonel LN, Chen TC, Turner A, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer. Cancer Causes Control 1998;9:425–32.
(46) Jacobs ET, Giuliano AR, Martinez ME, Hollis BW, Reid ME, Marshall JR. Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. J Steroid Biochem Mol Biol 2004; 89–90:533–7.
(47) Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control 2000;11:847–52.
(48) Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer 2004;108:104–8.
(49) Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006;354:684–96.

Notes

Supported by research grant CA55075 from the National Institutes of Health, Bethesda, MD.

Dr. Hollis is a consultant for DiaSorin.

We are indebted to Elizabeth Frost-Hawes, Barbara Vericker, Stacy DeCaro, Mira Kaufman, and Al Wing for expert help.

Manuscript received September 7, 2005; revised January 26, 2006; accepted February 17, 2006.