JNCI Journal of the National Cancer Institute Advance Access published October 30, 2007

EDITORIALS

The "Sunshine Vitamin": Benefits Beyond Bone?

Cindy D. Davis, Johanna T. Dwyer

Although vitamin D is best known for its role in strengthening bone and preventing rickets, it is increasingly apparent that it may have beneficial health effects beyond the skeletal system, among them perhaps the prevention of a number of diseases, including cancer (1). These health effects have been the focus of two recent National Institutes of Health–sponsored conferences (2,3) and a number of reviews (4–6).

Could vitamin D also have a role in decreasing total mortality? A meta-analysis by Autier and Gandini (7) of 18 randomized clinical trials of supplemental intakes of vitamin D found a 7% reduction in total mortality from any cause (RR = 0.93, 95% confidence interval [CI] = 0.87 to 0.99). Supplement intakes in those studies generally ranged from 400 to 800 IU/day, which is within the range recommended by the Institute of Medicine's Food and Nutrition Board—up to 2000 IU/day. In this issue of the Journal, Freedman et al. (8), using data from the National Health and Nutrition Examination Study (NHANES III) of 1988–1992 with a 6- to 12-year follow up, found no differences in total cancer mortality by serum 25-hydroxy vitamin D [25(OH)D] levels but an intriguing difference in colon and possibly breast cancer mortality by baseline vitamin D status. Individuals with 25(OH)D levels of 80 nmol/L or more had a 72% lower risk of colon cancer mortality (95% CI = 0.11 to 0.68) compared with individuals whose 25(OH)D levels were less than 50 nmol/L (P_{trend}<.02).

Evidence from diverse sources, including in vitro, animal, ecologic, and epidemiologic studies, suggests a role for vitamin D in decreasing colorectal cancer incidence (9–13). In a recent meta-analysis of studies that prospectively examined serum 25(OH)D levels in relation to colorectal cancer, individuals with 25(OH)D concentrations of 82 nmol/L or more had a 50% lower incidence of colorectal cancer than those with 25(OH)D of 30 nmol/L or less (13). However, in the Women's Health Initiative (WHI) study vitamin D and calcium supplementation trial, daily supplementation of 18 176 women with 1000 mg calcium and 400 IU vitamin D for an average of 7 years was not associated with an altered risk of colorectal cancer (14). Possible explanations for the overall null effects could be that participants were allowed to take additional vitamin D supplements on their own, participants already had higher mean intake of vitamin D than the reported national average, and adherence was only approximately 65%. In contrast, a nested case–control study within the WHI found that lower baseline serum 25(OH)D levels were associated with an increased risk of colorectal cancer (14). Similarly, a recent pooled analysis from the Health Professional Follow-Up Study and the Nurses' Health Study found that higher plasma 25(OH)D levels were statistically significantly associated with a decreased risk of colorectal cancer (15). The study by Freedman et al. (8) expands these observations and suggests that vitamin D status is associated with decreased colorectal cancer mortality.

There are many plausible biological mechanisms that might mediate the association of vitamin D with reduced mortality from colorectal cancer. 1,25(OH)D plays an important role in the regulation of many cellular processes associated with carcinogenesis, including differentiation, proliferation, and apoptosis. Moreover, normal colonic cells, as well as malignant human cancer cell samples, contain 25(OH)D-hydroxylase (CYP27B1), the enzyme that converts 25(OH)D to the active metabolite $1,25(OH)_2D$ (16). These cells also possess the vitamin D receptor gene. Therefore, serum concentrations of 25(OH)D may be indicative of colonic exposure to 1,25(OH)D.

If vitamin D has effects on colorectal cancer, they are not likely to occur in isolation; rather, they may be modified by other dietary factors and energy balance. For example, vitamin D status is related to body mass index, body fatness, and physical activity (Fig. 1). In several studies, including NHANES III, both obesity and low physical activity have been associated with lower levels of serum 25(OH)D (17). Body fat is a storage site for vitamin D in humans, although the exact mechanism whereby higher body fat results in lower 25(OH)D is not known definitively (17). Moreover, both obesity and low physical activity have been linked to increased colorectal cancer risk (18–20). It is unknown whether the increased risk of colon cancer with obesity and low physical activity is mediated through decreased 25(OH)D levels. Thus, while serum 25(OH)D is a marker of vitamin D exposure, it may also be a marker of other risk factors for colorectal cancer, such as high body mass index levels, low physical activity levels, or perhaps a preexisting cancer that independently caused low 25(OH)D levels. Vitamin D should not be investigated in isolation because many other nutritional factors (e.g., high intakes of alcohol and fat, especially animal fat and processed meats, and low intakes of vegetables, calcium, fiber, folic acid, and selenium) are also associated with colorectal cancer risk.

In contrast to the results on colorectal cancer mortality, Freedman et al. (8) did not observe an association between 25(OH)D levels and total cancer mortality. It is unknown if or when during the carcinogenic process vitamin D might be most

Affiliations of authors: Nutritional Sciences Research Group, National Cancer Institute, National Institutes of Health, Bethesda, MD (CDD); Office of Dietary Supplements, National Institutes of Health, Bethesda, MD (JTD); School of Medicine and Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA (JTD).

Correspondence to: Johanna T. Dwyer, DSc, RD, NIH, Office of Dietary Supplements, 6100 Exec Blvd, MSC7517 Room 3B01, Bethesda, MD 20892 (e-mail: Dwyerj1@od.nih.gov.)

DOI: 10.1093/jnci/djm211

Published by Oxford University Press 2007.

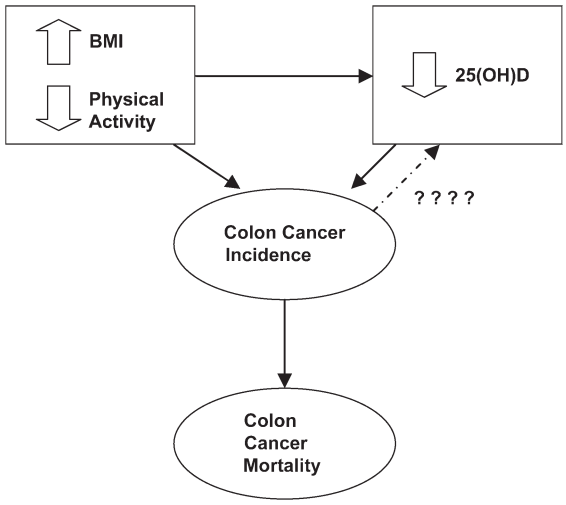

Fig. 1. Interrelationship among risk factors for colon cancer.

beneficial and if the potential beneficial effects may vary by the specific type of cancer. If the benefit of vitamin D is to prevent or slow the progression of cancer in its early stages and if some cancers have a latency of many decades for incidence, or even longer for mortality endpoints, the determination of cancer mortality in the 6- to 12-year period after assessment of vitamin D status may have been insufficient to demonstrate an effect. However, it is also possible that the potential beneficial effect of improved vitamin D status on colon cancer is stronger than for other cancers or that the study was limited by the small number of other cancer deaths. For example, even for lung cancer, the most common cause of cancer mortality in this cohort, only 153 deaths occurred. However, in a larger study of 447 patients with early stage non–small-cell lung cancer, higher circulating 25(OH)D was associated with increased survival (adjusted hazard ratio for mortality = 0.45; 95% CI = 0.24 to 0.82) for the highest versus lowest quartile of 25(OH)D (21). Similarly, in 15 166 patients with lung cancer, mortality was 15% lower in patients diagnosed during autumn than in those diagnosed in winter, suggesting that a high level of sun-induced 25(OH)D offers a survival advantage for lung cancer patients (22). Although these studies suggest that higher vitamin D status may decrease lung cancer mortality, it is important to note that both of these studies examined survival in patients with diagnosed lung cancer. In contrast, the study by Freedman et al. (8) examined the role of vitamin D status on cancer mortality in presumably healthy individuals.

The study by Freedman et al. (8) has several strengths. It used NHANES III, which is a population-based survey, to assess the health and nutritional status of noninstitutionalized individuals. This cohort is somewhat more representative of race/ethnicity, sex and income of US adult noninstitutionalized populations than many of the other large cohorts, making it useful for examining these differences and for hypothesis testing. NHANES III oversampled non-Hispanic blacks and Mexican Americans, groups thought to be at increased risk for many cancers. In addition, vitamin D nutriture was assessed by using both a single 24-hour dietary recall (which is problematic, since a single day's intake does not capture usual intakes) (23) and serum 25(OH)D, a marker of vitamin D nutritional status that also accounts for vitamin D synthesis from the pro-vitamin in the skin under the influence of sunlight (24).

There are also some limitations with the use of the NHANES III cohort. NHANES III was a cross-sectional study that identified associations but not causation. Residual confounding is a particular problem in this study owing to peculiarities in NHANES sampling that may have affected both measures of vitamin D exposure and outcomes. Season and latitude, both related to 25(OH)D levels, were linked in the dataset. That is, data were collected in southern latitudes in the cooler months of November through March (winter/lower latitude) and in the more northerly latitudes in warmer months (April–October) (summer/higher latitude). The 25(OH)D levels were determined on blood samples obtained only at one time point, and thus they may not have been representative of long-term chronic levels of 25(OH)D concentrations, nor would they reflect the nadir of 25(OH)D reached during the year. There also might be fewer lower 25(OH)D levels in the summer/higher latitude sample than would be the case if all subjects had been examined in the winter. This is a cause of concern because in Norway the maximal level of 25(OH)D is reached between the months of July and September and it is 20%–120% higher than the corresponding winter value, suggesting that season of diagnosis is a predictor of colon cancer survival (25,26).

From the research perspective, continued exploration of the effects of vitamin D beyond those on bone itself is warranted. The behavior of serum 25(OH)D levels as a biomarker of exposure, including what dietary vitamin D intakes are associated with various 25(OH)D levels and how these change from season to season, needs further attention. For example, are those who have low 25(OH)D levels in the summer also the individuals with low levels in the winter? A better understanding is also needed of the relationship between skin pigmentation and the response to UVB radiation in increasing 25(OH)D concentrations.

The relationship between nutritional factors and colorectal as well as other cancers is complicated. Therefore, these findings must be put into the context of total diet and lifestyle. There are many risk factors other than diet for colorectal cancer, and there are many possible dietary risk factors other than vitamin D that have been linked to cancer risk. From the clinical perspective, based on bone health markers, the Adequate Intake for vitamin D is 200 IU for adults younger than 50 years, 400 IU for those between the ages of 50 and 70, and 600 IU for those 71 years and older. It is recommended that intakes not exceed 2000 IU, the current safe Upper Level. Whether vitamin D reduces cancer risks and, if it does, whether these amounts suffice are actively being debated. Randomized clinical trials of the effects of vitamin D on the incidence of colonic polyps and invasive cancer are needed. While vitamin D may well have multiple benefits beyond bone, health professionals and the public should not in a rush to judgment assume that vitamin D is a magic bullet and consume high amounts of vitamin D. More definitive data on both benefits and potential adverse effects of high doses are urgently needed.

References

(1) Lappe JM, Travers-Gustafson DT, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85:1566–91.

(2) Davis CD, Hartmuller V, Freedman DM, Hartge P, Picciano MF, Swanson CA, et al. Vitamin D and cancer: current dilemmas and future needs. Nutr Rev 2007;65:S71–4.

(3) Raiten DJ, Picciano MF. Vitamin D and health in the 21st century: bone and beyond. Am J Clin Nutr 2004;80:1673S–77S.

(4) Holick MF. Vitamin D deficiency. New Engl J Med 2007;357:266–81.

(5) Bikle DD. What is new in vitamin D: 2006–2007. Curr Opin Rheumatol 2007;19:383–8.

(6) Mullin GE, Dobs A. Vitamin D and its role in cancer and immunity: a prescription for sunlight. Nutr Clin Pract 2007;22:305–22.

(7) Autier P, Gandini S. Vitamin D supplementation and total mortality. Arch Intern Med 2007;167:1730–7.

(8) Freedman DM, Looker AC, Chang S-C, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007;99:1594–602.

(9) Murillo G, Matusiak D, Benya RV, Mehta RG. Chemopreventive efficacy of 25-hydroxyvitamin D3 in colon cancer. J Steroid Biochem Mol Biol 2007;103:763–7.

(10) Gonzalez-Sancho JM, Larriba MJ, Ordonez-Moran P, Palmer HG, Munoz A. Effects of 1alpha,25-dihydroxyvitamin D3 in human colon cancer cells. Anticancer Res 2006;26:2669–881.

(11) Tangpricha V, Spina C, Yao M, Chen TC, Wolfe MM, Holick MF. Vitamin D deficiency enhances the growth of MC-26 colon cancer xenografts in Balb/C mice. J Nutr 2005;135:2350–4.

(12) Cross HS, Bises G, Lechner D, Manhardt T, Kallay E. The vitamin D endocrine system of the gut—its possible role in colorectal cancer prevention. J Steroid Biochem Mol Biol 2005;97:121–8.

(13) Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, et al. Optimal vitamin D status for colorectal cancer prevention. A quantitative meta analysis. Am J Prev Med 2007;32:210–6.

(14) 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. New Engl J Med 2006;354:694–6.

(15) Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case-control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. J Natl Cancer Inst 2007;99:1120–9.

(16) Lechner D, Kallay E, Cross HS. 1alpha,25-Dihydroxyvitamin D3 downregulates CYP27B1 and induces CYP24A1 in colon cells. Mol Cell Endocrinol 2007;263:55–64.

(17) Looker AC. Do body fat and exercise modulate vitamin D status? Nutr Rev 2007;65:S124–6.

(18) Samand AKA, Taylor RS, Marshall T, Chapman MAS. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7:204–13.

(19) Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate and pancreas. Gastroenterology 2007;132:2208–25.

(20) Gunter MJ, Leitzmann MF. Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. J Nutr Biochem 2006;17:145–56.

(21) Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. J Clin Oncol 2007;25:479–85.

(22) Porojnicu AC, Robsahm TE, Dahlback A, Berg JP, Christiani D, Bruland OS, et al. Seasonal and geographical variations in lung cancer prognosis in Norway: does vitamin D from the sun play a role? Lung Cancer 2007;55:263–70.

(23) Dodd KW, Guenther PM, Freedman LS, Subar AF, Kipnis V, Midthune D, et al. Statistical methods for estimating usual intake of nutrients and foods: a review of the theory. J Am Diet Assoc 2006;106:1640–50.

(24) Armas LAG, Dowell S, Akhter M, Duthuluru S, Huerter C, Hollis BW, et al. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. J Am Acad Dermatol 2007;57:588–93.

(25) Porojnicu A, Robsahm TE, Berg JP, Moan J. Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: a possible role of sun-induced Vitamin D. J Steroid Biochem Mol Biol 2007;103:675–8.

(26) Moan J, Porojnicu AC, Robsahm TE, Dahlback A, Juzeniene A, Tretli S, et al. Solar radiation, vitamin D and survival rate of colon cancer in Norway. J Photochem Photobiol B 2005;78:189–93.