Routledge
Taylor & Francis Group

Dietary Vitamin D Intake and Cancers of the Colon and Rectum: A Case-Control Study in Italy

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Epidemiologic evidence indicates that vitamin D is inversely associated with risk of colon or rectal cancer or both. Using data from a case-control study conducted in Italy between 1992 and 1996, we examined the relation between dietary intake of vitamin D and colon and rectal cancer risk. The study population comprised patients with incident colon cancer ($n = 1,225$) or rectal cancer ($n = 728$) and 4,154 hospital controls. Odds ratios (OR) and 95% confidence intervals (CI) according to deciles of vitamin D intake were estimated by multiple logistic regression. In addition, we adjusted for intensity of sunlight exposure through stratification by geographic region of residence, and we computed ORs separately by anatomic subsite within the colon. Adjusted ORs for colon cancer were seen to decrease after the 5th decile of vitamin D intake and reached 0.69 (95% CI = 0.50–0.96) for the 9th and 10th deciles, reflecting a statistically significant inverse trend. The inverse association appeared to be somewhat more pronounced for the proximal than the distal colon and was similar among strata of geographic region and calcium intake. Rectal cancer was unrelated to vitamin D intake in this population. In conclusion, we observed an inverse association between dietary vitamin D intake and colon cancer risk among those with the highest intake levels, which was somewhat unexpected given that these levels were still substantially below the levels considered optimal for colon cancer prevention.

INTRODUCTION

Accumulating epidemiologic evidence supports the suggestion by Garland and Garland (1), stemming from ecologic observations of geographic differences in cancer mortality rates, that vitamin D may account for the inverse association observed between ultraviolet (UV-B) radiation exposure and risk of colon cancer (2,3). Numerous epidemiologic studies that have evaluated either levels of the primary circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), or dietary or supplementary vitamin D intake have reported an inverse association with colon or rectal cancer or both (2–4). Colon cancer cells express vitamin

D receptors and the enzyme 1-α-hydroxylase, which converts 25(OH)D into the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)$_2$D). Although the specific mechanism is not clear, 1,25(OH)$_2$D is believed to be important in the regulation of cell differentiation, the inhibition of cell proliferation, angiogenesis, metastasis, and the enhancement of apoptosis (2–5), thereby providing a strong biologic basis for a protective role of vitamin D in colon cancer.

Vitamin D in humans is largely derived from exposure to sunlight, with major contributions, mainly in winter, from a few natural food sources (such as fatty fish and eggs) and fortified foods or from dietary supplements. The optimal level of vitamin D intake for the prevention of colon or other cancers is believed to be quite high, but quantification remains undefined in various populations.

We previously examined the influence of dietary intake of numerous micronutrients on the risk of developing colorectal cancer, and we reported an inverse association with vitamin D intake, with a significant trend of decreasing risk with increasing intake (6). The relatively large number of colorectal cancer cases in our study has enabled us to expand our earlier analyses to quantify in more detail any dose-response (or threshold) effect of vitamin D intake on the risk of colon and rectal cancers, to adjust for intensity of sunlight exposure through stratification by geographic region of residence, and to compute odds ratios (ORs) separately by anatomic subsite within the colon.

METHODS

A case-control study of cancers of the colon and rectum was conducted between January 1992 and June 1996 in 6 Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, the province of Forlì, the province of Latina, and the urban area of Naples (6). A detailed description of the study methods has been previously published (6).

In short, cases were patients with incident, histologically confirmed colon cancer ($n = 1,225$; 688 men and 537 women) or cancer of the rectum ($n = 728$; 437 men and 291 women) diagnosed within 1 yr before interview and with no prior history of cancer. The median age of cases was 62 yr (range $= 23$–74 yr). We have included rectal cancer cases in this analysis to allow for specific evaluation of distal colon and rectum combined. Controls were 4,154 patients (median age 58 yr; range $= 20$–74 yr) with no history of cancer admitted to the same major teaching and general hospitals as cases for acute, nonneoplastic conditions, unrelated to digestive tract diseases or to known long-term modifications of diet. Of these, 23% were admitted for traumas; 28% for other orthopedic disorders; 20% for acute surgical conditions; and 29% for eye, ear, nose and throat and other miscellaneous diseases. Overall, less than 4% of subjects (cases and controls) invited to participate in the study refused to participate.

Cases and controls were interviewed in the hospital by trained personnel using a standard structured questionnaire designed to collect information on sociodemographic characteristics, lifetime smoking and alcohol drinking habits, physical activity, anthropometric measures, a problem-oriented personal medical history, and family history of cancer. Usual diet during the 2 yr preceding diagnosis, or hospital admission for controls, was assessed using an interviewer-administered food frequency questionnaire (FFQ) that included 78 foods, groups of food, or recipes. The FFQ was divided into 7 sections: 1) bread, cereals, and first courses; 2) second courses (e.g., meat and other main dishes); 3) side dishes (i.e., vegetables); 4) fruits; 5) sweets, desserts, and soft drinks; 6) milk, hot beverages, and sweeteners; and 7) alcoholic beverages. Reproducibility and validity of the FFQ were demonstrated to be sufficient for epidemiologic studies of this type (7,8). Italian food-composition databases were integrated with information from manufacturers and other published data to compute energy and nutrient intake (6,9).

The data were modeled through unconditional multiple logistic regression to compute ORs and the corresponding 95% confidence intervals (CIs) (10). Adjusted models included terms for quintiles of age, sex, and study center as well as terms for education, physical activity, family history of colorectal cancer, body mass index (BMI) at age 50 yr, fruit and vegetable consumption, and total energy intake. Terms for lifetime smoking and alcohol drinking habits were not included because these factors do not appreciably modify the risk of colorectal cancer in this study population (11,12). We also fitted models across strata of age ($<$ or $\geq$ 60 yr), sex, anatomic subsite (proximal colon, distal colon, distal colon + rectum, or unspecified), geographic area of residence as a proxy for intensity of sunlight exposure (Northern or Southern Italy), and calcium intake ($<$ or $\geq$ median value among controls $= 962.56$ mg/day). Vitamin D was entered into the models as deciles of intake (based on distribution among controls) or as a continuous variable (with the increment of intake set as the SD among controls). Trend tests for risk of colon cancer according to deciles of vitamin D intake were based on a likelihood ratio test between models with and without a linear term for the vitamin D deciles.

RESULTS

Both colon and rectal cancer cases were older than controls and reported a slightly higher energy intake and more frequent positive family cancer history. Cases of colon cancer, but not rectal cancer, were more educated than controls and more often reported a low level of physical activity. Calcium intake was comparable between cases and controls.

Table 1 shows the distribution of colon and rectal cancer cases and controls as well as multiple logistic regression-derived ORs and corresponding 95% CIs according to deciles of vitamin D intake as well as continuous increments of intake. We observed a significant trend of decreasing colon cancer ORs with increasing intake of vitamin D ($P < 0.001$). Adjusted ORs for colon cancer remained close to 1 through the 5th decile of intake, after which they began to decrease; among those in the eighth decile of

TABLE 1

Multiple logistic regression-derived odds ratios (ORs) and corresponding 95% confidence intervals (CI) for 1,225 cases of colon cancer, 728 cases of rectal cancer and 4,154 controls according to deciles of intake of vitamin D, Italy, 1992–1996

	Deciles of intake,[a] OR[b] (95% CI)										P Value (Trend)	Continuous OR[c]
Vitamin D	1[d]	2	3	4	5	6	7	8	9	10		
Upper cut points (μg/day)	1.57	2.01	2.37	2.69	3.03	3.37	3.77	4.29	5.10	—		
No. Cases												
Colon[e]	126	145	132	129	133	104	125	113	104	114		
Proximal colon	34	27	25	33	26	23	29	25	23	25		
Distal colon	54	71	49	52	58	48	66	52	49	46		
Unspecified	38	47	58	44	49	33	30	36	32	43		
Rectum	67	72	81	69	94	69	61	60	71	84		
Controls	416	414	416	416	415	415	415	416	415	416		
Colon[e] OR (95% CI)	1	1.17 (0.88–1.55)	0.98 (0.73–1.32)	1.02 (0.76–1.37)	0.92 (0.69–1.25)	0.77 (0.56–1.05)	0.86 (0.63–1.17)	0.78 (0.57–1.06)	0.69 (0.50–0.96)	0.69 (0.50–0.96)	<.0001	0.87 (0.81–0.95)
Proximal colon	1	0.76 (0.44–1.30)	0.74 (0.42–1.28)	0.91 (0.54–1.54)	0.65 (0.37–1.15)	0.59 (0.33–1.06)	0.71 (0.41–1.24)	0.58 (0.33–1.04)	0.53 (0.29–0.97)	0.44 (0.24–0.80)	0.005	0.84 (0.72–0.97)
Distal colon	1	1.31 (0.88–1.93)	0.86 (0.56–1.32)	1.04 (0.68–1.59)	0.95 (0.63–1.45)	0.83 (0.53–1.28)	1.08 (0.71–1.64)	0.86 (0.56–1.33)	0.77 (0.49–1.20)	0.64 (0.40–1.02)	0.01	0.85 (0.76–0.95)
Unspecified	1	1.23 (0.77–1.96)	1.38 (0.88–2.17)	1.14 (0.70–1.83)	1.16 (0.72–1.86)	0.80 (0.48–1.34)	0.70 (0.41–1.19)	0.85 (0.51–1.42)	0.76 (0.45–1.30)	1.04 (0.63–1.74)	0.03	0.93 (0.83–1.06)
Rectum OR (95% CI)	1	1.18 (0.81–1.70)	1.32 (0.92–1.90)	1.17 (0.80–1.71)	1.53 (1.07–2.20)	1.13 (0.77–1.65)	0.99 (0.67–1.47)	0.96 (0.64–1.43)	1.14 (0.77–1.68)	1.22 (0.82–1.80)	0.70	1.01 (0.93–1.11)
Distal colon + Rectum	1	1.25 (0.94–1.67)	1.10 (0.82–1.48)	1.11 (0.82–1.49)	1.25 (0.93–1.67)	0.99 (0.73–1.35)	1.05 (0.77–1.42)	0.92 (0.67–1.26)	0.96 (0.70–1.32)	0.95 (0.69–1.31)	0.09	0.95 (0.88–1.02)

[a] Deciles based on distribution among controls.

[b] Adjusted for age, sex, study center, education, physical activity, family history, body mass index at age 50, fruit and vegetable consumption, and total energy intake.

[c] Estimated for an increment of intake equal to 1 SD among controls (1.47 ug/day).

[d] Reference category.

[e] Proximal colon (International Classification of Diseases, vol. 9 [ICD–9] = 1530, 1531, 1534–1537), distal colon (ICD–9 = 1532, 1533), and unspecified (ICD–9 = 1539).

intake, the OR for colon cancer was 0.78 (95% CI = 0.57–1.06), and it decreased to 0.69 (95% CI = 0.50–0.96) for both the 9th and 10th deciles of vitamin D intake. No association was observed between intake of vitamin D and cancer of the rectum (P trend = 0.70). The continuous ORs for colon and rectal cancer per 1.47 ug increase in vitamin D intake were 0.87 (95% CI = 0.81–0.95) and 1.01 (95% CI = 0.93–1.11), respectively.

When the association with vitamin D intake was examined separately according to anatomic subsite within the colon (Table 1), the inverse association appeared to be somewhat more pronounced for the proximal colon, with ORs decreasing to 0.58 (95% CI = 0.33–1.04), 0.53 (95% CI = 0.29–0.97), and 0.44 (95% CI = 0.24–0.80) in the 3 highest deciles of intake, respectively (P trend = 0.005). For the distal colon, most of the ORs were between 0.8 and 1.0; however, the ORs were nonsignificantly decreased for the 3 highest deciles of vitamin D intake (OR = 0.86, 0.77, and 0.64, respectively), and the dose-response trend was statistically significant (P trend = 0.01). The continuous ORs for proximal and distal colon per 1.47 ug increase in vitamin D intake were virtually identical (OR = 0.84, 95% CI = 0.72–0.97; and OR = 0.85, 95% CI = 0.76–0.95, respectively). When distal colon and rectum were combined, ORs for all levels of vitamin D intake were close to 1.

The relation between vitamin D intake and colon cancer risk was examined further in Table 2 in separate strata of age, sex, geographic area of residence, calcium intake, and family

history of colorectal cancer. The inverse association between vitamin D intake and colon cancer was more pronounced among women than among men (P value for heterogeneity between sexes = 0.003). The association also appeared stronger for those less than 60 yr of age, but the difference among age strata was not statistically significant. There was little evidence of effect modification by geographic area of residence or calcium intake. We also evaluated the interaction between calcium and vitamin D intake using a common reference group of calcium below median (<962.6 mg/day) and vitamin D below median (<3.03 ug/day). The ORs were 0.74 (95% CI = 0.60–0.90) for calcium below median and vitamin D above median, 0.87 (95% CI = 0.71–1.06) for calcium above median and vitamin D below median, and 0.68 (95% CI = 0.55–0.83) for both calcium and vitamin D above median, further suggesting that the association between vitamin D and colon cancer was not modified by calcium intake (data not shown).

DISCUSSION

This analysis, based on a large case-control study, confirms the inverse association between vitamin D and colon cancer, with a 30% reduction in risk among those with the highest levels of dietary intake. There was a statistically significant trend of decreasing colon cancer risk with increasing vitamin D intake in our study population, although the inverse association was statistically significant only among those in the 9th or 10th

TABLE 2

Multiple logistic regression-derived odds ratios (ORs)[a] and corresponding 95% confidence intervals (CIs) for 1,225 cases of colon cancer and 4,154 controls according to deciles of intake of vitamin D across strata of age, sex, geographic area of residence, and calcium intake, Italy, 1992–1996

Vitamin D	Cases:Controls	OR (95% CI) for Deciles of Intake vs. Decile 1 of Intake[b]			Continuous OR (95% CI)[c]
		8	9	10	
Gender					
Male	688:2,073	1.07 (0.69–1.68)	0.99 (0.63–1.57)	0.80 (0.51–1.28)	0.94 (0.85–1.04)
Female	537:2,081	0.53 (0.33–0.86)	0.46 (0.28–0.75)	0.60 (0.37–0.99)	0.78 (0.68–0.88)
Age (yr)					
<60	490:2,323	0.65 (0.39–1.07)	0.61 (0.37–1.00)	0.46 (0.27–0.79)	0.79 (0.70–0.89)
≥ 60	735:1,831	0.88 (0.59–1.33)	0.74 (0.48–1.14)	0.90 (0.59–1.37)	0.94 (0.85–1.04)
Geographic area of residence					
Northern	829:3,125	0.73 (0.49–1.07)	0.69 (0.47–1.02)	0.66 (0.45–0.98)	0.87 (0.79–0.95)
Southern	396:1,029	0.76 (0.43–1.34)	0.64 (0.35–1.16)	0.65 (0.35–1.21)	0.86 (0.75–0.99)
Calcium intake					
<962.6 mg	625:2,077	0.92 (0.59–1.41)	0.81 (0.52–1.28)	0.61 (0.36–1.04)	0.84 (0.74–0.94)
≥ 962.6mg	600:2,077	0.64 (0.38–1.06)	0.58 (0.35–0.97)	0.65 (0.39–1.08)	0.90 (0.81–1.00)

[a]Adjusted for age, sex, study center, education, physical activity, family history, body mass index at age 50, fruit and vegetable consumption, and total energy intake.

[b]Deciles based on distribution among controls.

[c]Estimated for an increment of intake equal to 1 SD among controls (1.47 ug/day).

decile of intake, corresponding to dietary vitamin D intake greater than 4.29 ug/day.

Our results contribute to the growing body of epidemiologic evidence that has demonstrated an inverse association between colorectal, colon, or rectal cancer and dietary or supplementary vitamin D intake. In studies that have accounted for supplementary as well as dietary vitamin D intake, risk reductions for the highest categories of intake (which generally correspond to an average of 700–800 IU/day, or 17.5 to 20 ug/day) vs. the lowest ones have ranged between 30% and 50% (2,13). It is somewhat surprising and perhaps suggestive that we observed a risk reduction of similar magnitude in this Italian population with substantially lower cutpoints for the top two intake deciles of only 4.29 and 5.10 ug/day, respectively, and little food fortification or use of supplements (14).

The main dietary sources of vitamin D in this population were fish (55.0%), meat (23.5%), cheese (6.8%), and eggs (5.6%). Of these, fish was found to have an inverse association with colorectal cancer in our data set, whereas no significant association was found with cheese, eggs, and meats (15). The inverse association between vitamin D and colon cancer became nonsignificant after adjustment for fish consumption; however, it is difficult to clearly disentangle the effects of fish consumption and dietary vitamin D intake given the high collinearity between these variables ($r = .84$).

This hospital-based case-control study was sufficiently large to obtain relatively precise risk estimates for vitamin D intake, and estimated intake of vitamin D was satisfactorily reproducible and valid (7,8). Cases and controls came from comparable catchment areas, participation was virtually complete, and both cases and controls were interviewed in the hospital setting, thereby reducing potential selection and recall bias (16). However, it is well established that vitamin D is essential to bone health, and low vitamin D levels are associated with osteoporosis and osteomalacia as well as muscle strength and falls (4,5,17). Because 23% of controls in our study were admitted to hospital for traumas, and another 28% for other orthopedic disorders, we cannot rule out the possibility that low vitamin D intake among those controls may have biased our colon cancer ORs away from the null. However, the association was not materially different when comparison was made separately with different categories of controls (data not shown).

In our study, we did not have measurements of serum concentration of 25(OH)D, the main circulating form of vitamin D, which is believed to be the best indicator of vitamin D status. Serum 25(OH)D level is influenced by dietary vitamin D intake and sunlight exposure as well as other factors such as BMI and skin pigmentation (2). Numerous studies, including two recent large studies in Finland and the United States, have reported a decreased risk for colon, distal colon, or colorectal cancer with higher 25(OH)D concentrations (18–24). There does not appear to be a threshold of 25(OH)D level for reduced risk in these studies, and a recent meta-analysis indicated a linear decrease

in colorectal cancer risk with increasing serum 25(OH)D levels, with odds ratios of 1.00, 0.82, 0.66, 0.59, and 0.46 from lowest to highest quintile, respectively (23).

Most experts agree that optimal vitamin D intake for a benefit in colon cancer prevention corresponds to at least 1,000 IU/day (25 ug/day) of vitamin D_3 (23,25–27); this is considerably higher than the highest levels of intake in most study populations including ours and is difficult to obtain on a daily basis without sun exposure or the use of supplements (17). In the United States, intake of 1,000 IU/day would be required to reach optimal 25(OH)D concentrations in the range of 30–50 ng/ml (75–125 nmol/l), particularly in the absence of substantial sunlight exposure (2,4). In the meta-analysis by Gorham et al. (23), serum 25(OH)D $\geq$ 33 ng/ml (83 nmol/l) was associated with a 50% lower risk of colorectal cancer incidence compared with <12 ng/ml. Vitamin D intoxication is an extremely rare occurrence and is not caused by sun exposure because the ultraviolet radiation itself destroys any excess vitamin D that is produced (4).

The inverse association between dietary vitamin D intake and colon cancer in our study did not appear to be modified by either dietary calcium intake or by geographic area of residence. However, the lowest ORs were observed among those with both the highest deciles of vitamin D intake and above-median calcium intake; a similar synergistic effect of calcium and vitamin D in reducing colon and rectum cancer risk has been observed in several other studies (28,29). With respect to geographic region, residence in northern versus southern Italy may not be an optimal surrogate for UV-B radiation exposure. A recent study in Australia reported a relatively high prevalence of vitamin D insufficiency in winter and spring across a wide range of latitude and suggested that season may be more important than latitude in predicting variation in 25(OH)D levels, although both accounted for less than one-fifth of the variation (30).

Whether the influence of vitamin D differs by colonic subsite is unclear, and those studies of dietary vitamin D that have evaluated proximal and distal colon and rectum separately have produced inconsistent results. We observed a somewhat stronger inverse association with vitamin D in the proximal colon than in the distal colon or rectum. The results of some (20,21), but not all (24), studies of plasma 25(OH)D have shown stronger risk reductions in the distal colon or rectum than in the proximal colon. There are differences across colonic subsites in molecular characteristics and in associations with genetic and environmental factors (31), but an explanation for site-specific differences in mechanisms of vitamin D anticarcinogenesis, if confirmed, is presently unavailable.

In conclusion, more than 50% of both children and adults in the United States and Europe are believed to be at high risk of vitamin D deficiency, which is defined by most experts as a 25(OH)D level of < 20 ng/ml (5,17). Even among healthy young individuals in southern and central Italy (32,33), vitamin D deficiency has been shown to be a common phenomenon, especially

in winter. We observed an inverse association between dietary vitamin D intake and colon cancer among those with the highest levels of intake, which were still substantially below the levels considered optimal for colon cancer prevention. The weight of the epidemiologic evidence supports an inverse association between vitamin D deficiency and colon cancer incidence, and it has been projected that 250,000 cases of colorectal cancer could be prevented annually worldwide with achievement of serum 25(OH)D levels ≥ 55 ng/ml (26).

ACKNOWLEDGMENTS

REFERENCES

1. Garland CF and Garland FC: Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* **9,** 227–231, 1980.
2. Giovannucci E: The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* **16,** 83–95, 2005.
3. Giovannucci E: The epidemiology of vitamin D and colorectal cancer: recent findings. *Curr Opin Gastroenterol* **22,** 24–29, 2006.
4. Holick MF: Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol* **92,** 49–59, 2006.
5. Holick MF: High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* **81,** 353–373, 2006.
6. La Vecchia C, Braga C, Negri E, Franceschi S, Russo A, et al.: Intake of selected micronutrients and risk of colorectal cancer. *Int J Cancer* **73,** 525–530, 1997.
7. Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, et al.: Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. *Ann Epidemiol* **6,** 110–118, 1996.
8. Franceschi S, Negri E, Salvini S, Decarli A, Ferraroni M, et al.: Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. *Eur J Cancer* **29A,** 2298–2305, 1993.
9. Salvini S, Gnagnarella P, Parpinel MT, Boyle P, Decarli A, et al.: The food composition database for an Italian food frequency questionnaire. *J Food Composition Anal* **9,** 57–71, 1996.
10. Breslow NE and Day NE: *Statistical methods in cancer research. Vol. I: The analysis of case-control studies.* IARC Sci Publ 32. Lyon, France: International Agency for Research on Cancer, 1980.
11. Tavani A, Ferraroni M, Mezzetti M, Franceschi S, Lo Re A, et al.: Alcohol intake and risk of cancers of the colon and rectum. *Nutr Cancer* **30,** 213–219, 1998.
12. Tavani A, Gallus S, Negri E, Franceschi S, Talamini R, et al.: Cigarette smoking and risk of cancers of the colon and rectum: a case-control study from Italy. *Eur J Epidemiol* **14,** 675–681, 1998.
13. Grant WB and Garland CF: A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr Cancer* **48,** 115–123, 2004.
14. Istituto Nazionale di Statistica: *Indagine multiscopo sulle famiglie. Anni 1987–1991, Vol 10. Condizione di salute e ricorso ai servizi sanitari.* Rome, Italy: ISTAT, 1994.
15. Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, et al.: Food groups and risk of colorectal cancer in Italy. *Int J Cancer* **72,** 56–61, 1997.
16. D'Avanzo B, La Vecchia C, Katsouyanni K, Negri E, and Trichopoulos D: An assessment, and reproducibility of food frequency data provided by hospital controls. *Eur J Cancer Prev* **6,** 288–293, 1997.
17. Holick MF: Vitamin D deficiency. *N Engl J Med* **357,** 266–281, 2007.
18. Garland C, Comstock G, Garland F, Helsing K, and Shaw E: Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* **2,** 1176–1178, 1989.
19. Braun MM, Helzlsouer KJ, Hollis BW, and Comstock GW: Colon cancer and serum vitamin D metabolite levels 10–17 years prior to diagnosis. *Am J Epidemiol* **142,** 608–611, 1995.
20. Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, et al.: Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* **8,** 615–625, 1997.
21. Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, et al.: Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* **13,** 1502–1508, 2004.
22. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, et al.: Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* **354,** 684–696, 2006.
23. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, et al.: Optimal vitamin D status for colorectal cancer prevention: a quantitative meta-analysis. *Am J Prev Med* **32,** 210–216, 2007.
24. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, et al.: A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst* **99,** 1120–1129, 2007.
25. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, and Dawson-Hughes B: Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* **84,** 18–28, 2006.
26. Garland CF, Grant WB, Mohr SB, Gorham ED, and Garland FC: What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev* **65,** S91–S95, 2007.
27. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, and Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* **85,** 1586–1591, 2007.
28. Garland C, Garland F, and Gorham E: Calcium and vitamin D: their potential roles in cancer prevention. *Ann NY Acad Sci* **889,** 107–119, 1999.
29. Jacobs ET, Martinez ME, and Alberts DS: Research and public health implications of the intricate relationship between calcium and vitamin D in the prevention of colorectal neoplasia. *J Natl Cancer Inst* **95,** 1736–1737, 2003.
30. Van der Mei IAF, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, et al.: The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. *Environ Health Perspect* **115,** 1132–1139, 2007.
31. Iacopetta B: Are there two sides to colorectal cancer? *Int J Cancer* **101,** 403–408, 2002.
32. Carnevale V, Modoni S, Pileri M, Di Giorgio A, Chiodini I, et al.: Longitudinal evaluation of vitamin D status in healthy subjects from southern Italy: seasonal and gender differences. *Osteoporos Int* **12,** 1026–1030, 2001.
33. Romagnoli E, Caravella P, Scarnecchia L, Martinez P, and Minisola S: Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. *Br J Nutr* **81,** 133–137, 1999.