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Review

Epidemiology of vitamin D and colorectal cancer: Casual or causal link?☆

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ABSTRACT

Introduction: Since Garland and Garland hypothesized that better vitamin D status lowered risk of colorectal cancer in 1980, the relation between vitamin D status and colorectal cancer risk has been investigated in epidemiologic studies. These studies are reviewed.
Materials and methods: Various approaches have been used to estimate vitamin D status, including direct measures of circulating 25(OH)vitamin D levels, surrogates or determinants of vitamin D (including region of residence, intake, and sun exposure estimates, or a combination of these). These measures of vitamin D status have been studied in relation to colorectal adenoma, cancer incidence and mortality.
Results: In general, all lines of inquiry from observational studies indicate that an association between better vitamin D status and lower colorectal cancer risk exists. While most of the studies have examined vitamin D status in relation to risk of cancer, some evidence suggests that vitamin D may be additionally important for colorectal cancer progression and mortality.
Discussion: Although confounding factors cannot be entirely excluded, the consistency of the association using various approaches to measure vitamin D, for diverse endpoints and in diverse populations shows high consistency and is suggestive of a causal association. Thus, improving vitamin D status could be potentially beneficial against colorectal cancer incidence and mortality.

Contents

1. Introduction

In 1980, Garland and Garland hypothesized that poor vitamin D status accounted for the higher mortality rates of colon cancer in geographical areas in the United States that receive relatively low solar UV-B radiation [1]. Since 1980, numerous studies have addressed the biologic basis of this hypothesis, and epidemiologic studies have addressed the relationship between vitamin D status and subsequent risk of colorectal cancer or adenoma, the cancer precursor. Three decades later, a substantial body of literature now addresses the relationship between vitamin D and colorectal cancer risk. It is thus timely to address whether the evidence supports a causal association. Important criteria to be considered are the consistency of evidence, strength and the temporality of the relationship, and the biological plausibility. From an epidemiologic basis, the relationship has been studied using a variety of surrogates of vitamin D status. These surrogates include estimates of solar radiation at the population (ecologic) level or individual level, studies

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based on circulating 25(OH)vitamin D (25(OH)D) levels, dietary and supplementary intakes, predicted 25(OH)D, and limited evidence for randomized trials. Endpoints considered have been colorectal adenoma incidence, colorectal cancer and mortality, and survival in patients with colorectal cancer. While evidence from vitamin D gene pathway polymorphisms may prove useful in the future [2], the evidence to date is largely inconclusive [3] and will not be considered here.

2. Geographic studies

The relationship between solar UV-B and risk of colon cancer initially proposed by Garland and Garland [1] has been confirmed in subsequent analyses. Grant demonstrated that regional UV-B radiation correlated inversely with mortality rates of numerous cancers, particularly digestive organ cancers [4]; the strongest association (in terms of number of cancers potentially preventable) was for colorectal cancer. In another ecologic study of solar UV-B and colorectal cancer, an inverse association was stronger for colorectal cancer mortality than for incidence [5]. Importantly, the association has been observed in different populations outside of the United States. For example, Mizoue calculated Pearson correlation coefficients between averaged annual solar radiation levels for the period from 1961 through 1990 and cancer mortality in the year 2000 in 47 prefectures in Japan [6]. Adjusting for regional per capita income and dietary factors, an inverse correlation was found between averaged annual solar radiation levels and mortality from colon cancer in men ($r = -0.53$) and in women ($r = -0.46$), and for rectal cancer ($r = -0.53$ in men, and $r = -0.47$ in women).

Geography (as a surrogate of solar UV-B and presumably vitamin D status) has been sparsely examined in individual based studies. The largest study by far was a death certificate based case–control study conducted in the United States [7]. This study examined mortality from colon cancer in relation to residential and occupational exposure to sunlight; non-melanoma skin cancer served as a positive "control." The cases consisted of all colon cancer deaths between 1984 and 1995 in 24 states of the United States. The controls were age-frequency matched (deaths from cancer and certain neurological diseases were excluded because of possible relationships with sun exposure). Based on 153,511 cases of colon cancer deaths, those with high compared to low exposure to sun based on residence were at decreased risk (relative risk (RR) = 0.73; 95% confidence interval (CI), 0.71–0.74). In addition, individual who had had outdoor occupations (RR = 0.90; 95% CI, 0.86–0.94) and occupations that required more physical activity (RR = 0.89; 95% CI, 0.86–0.92) were at lower risk, and the inverse association with outdoor occupation was strongest among those living in the highest sunlight region. The multivariate analyses controlled for age, sex, race, and mutual adjustment for residence, occupation (outdoor versus indoor), occupational physical activity levels and socioeconomic status.

3. Nested case–control studies of 25(OH)D and colorectal cancer or adenoma risk

Some studies have examined levels of circulating 25(OH)D in relation to risk colorectal cancer. Typically, these studies are based on a cohort with archived blood samples. After a specified follow-up period, blood samples from cases who developed colorectal cancer and selected controls are retrieved and 25(OH)D is measured. Analyses then compare 25(OH)D levels in cases and controls to calculated the odds ratio, which is an estimate of the relative risk or RR. Studies that have examined circulating 25(OH)D levels prospectively in relation to risk of colorectal cancer have generally supported an inverse association [8–16]. In a recent meta-analysis of the colorectal cancer studies, based on 535 cases, individuals with ≥82 nmol/L (33 ng/mL) serum 25(OH) level had 50% lower incidence of colorectal cancer ($P < 0.01$) compared to those with relatively low levels of less than 30 nmol/L (12 ng/mL) [17]. The dose–response appears linear up to a 25(OH)D level of at least approximately 90 nmol/L (35 ng/mL), with no obvious threshold or non-linear relationship, and controlling for multiple covariates have had little influence on the findings. The results are somewhat inconsistent in distinguishing whether the association is stronger for colon cancer or for rectal cancer, possibly due to small numbers, but in general the association has been observed for both anatomic sites.

The two largest studies included in the meta-analysis were from the Nurses' Health Study and the Women's Health Initiative. The Nurses' Health Study [10] was based on 193 incident cases of colorectal cancer. Two controls were matched per case on year of birth and month of blood draw. The main analysis adjusted for age, body mass index, physical activity, smoking, family history, use of hormone replacement therapy, aspirin use, and dietary intakes of various factors. The RR decreased in a monotonic fashion across quintiles of plasma 25(OH)D concentration, and the RR for quintile 5 versus 1 was 0.53 (95% CI = 0.27–1.04). The Women's Health Initiative was based on a total of 322 cases of colorectal cancer [16]. In that study, an inverse association was observed between baseline 25(OH)D level and colorectal cancer risk; however, detailed analyses on potential confounders were not reported. Of note, the Women's Health Initiative was a randomized placebo-controlled trial of 400 IU vitamin D plus 1000 mg a day of elemental calcium in 36,282 post-menopausal women; the interventional component of this study is discussed below.

Three additional studies on colorectal cancer have been published after this meta-analyses was completed. The Health Professionals Follow-Up Study [18], a large cohort of men, showed a non-statistically significant inverse association between higher plasma 25(OH)D concentration and risk of colorectal cancer and a statistically significant inverse association for colon cancer (highest versus lowest quintile: RR = 0.46; 95% CI = 0.24–0.89; P(trend) = .005). After the results from the Health Professionals Follow-Up Study and the Nurses' Health Study were pooled, higher plasma 25(OH)D levels were associated with decreased risks of both colorectal cancer (RR = 0.66; 95% CI = 0.42–1.05; P(trend) = .01) and colon cancer (RR = 0.54; 95% CI = 0.34–0.86; P(trend) = .002). The results for rectal cancer were inconsistent, though the number of cases was small.

Plasma 25(OH)D and colorectal cancer incidence risk was examined in The Japan Public Health Center-based Prospective Study [19], a nested case–control study of 375 incident cases of colorectal cancer during 11.5 years of follow-up after blood collection. Two controls were matched per case on sex, age, study area, date of blood draw, and fasting time. The multivariate analysis further adjusted for smoking, alcohol consumption, body mass index, physical exercise, vitamin supplement use, and family history of colorectal cancer. Plasma 25(OH)D was not significantly associated with colorectal cancer but the lowest category of plasma 25(OH)D was associated with an elevated risk of rectal cancer in both men (RR = 4.6; 95% CI = 1.0–20) and women (RR, 2.7; 95% CI, 0.94–7.6), compared with the other quartiles combined. Finally, the association between 25(OH)D and colorectal cancer mortality was examined in 16,818 participants followed from 1988–1994 through 2000 in the Third National Health and Nutrition Examination Survey [20]. Serum 25(OH)D level measured at baseline was inversely associated with colorectal cancer mortality ($n = 66$ cases). Specially, those with levels of 80 nmol/L (32 ng/mL) or higher associated had a 72% risk reduction (95% CI = 32–89%) compared with those levels <50 nmol/L (20 ng/mL) (P(trend) = .02).

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Several studies have examined circulating 25(OH)D levels and risk of colorectal adenoma, which are precursors to colorectal cancer. Most of the studies were based on comparing 25(OH)D levels in adenoma cases to controls who were adenoma-free on colonoscopy or sigmoidoscopy. The studies were based either on initial adenomas or in adenomas among individuals who had had an adenoma and were then followed for subsequent (recurrent) adenomas. In general, these studies suggest an inverse association with 25(OH)D and possibly $1,25(OH)_2D$ [11–14,21], particularly for advanced adenomas [14]. A recent meta-analysis summarized the results for circulating 25(OH)D and adenoma risk [22]. In the summary analysis, higher circulating 25(OH)D was associated with lower risk of colorectal adenomas; the odds ratio = 0.70 (95%, 0.56–0.87) for high versus low circulating 25(OH)D. The inverse associations was stronger for advanced adenoma (odds ratio, 0.64; 95% CI, 0.45–0.90) though this was based on relatively limited numbers.

4. Predicted 25(OH)D level

One study used an estimate of circulating 25(OH)D based on how various factors predicted 25(OH)D levels. The predicted 25(OH)D score was then associated with risk of colorectal cancer in men of the Health Professionals Follow-Up Study [23]. First, in a sample of 1095 men, actual plasma 25(OH)D levels was the dependent variable in a multiple linear regression. The independent (predictor) variables were geographical region, skin pigmentation, dietary intake, supplement intake, body mass index, and leisure-time physical activity (a surrogate of potential exposure to sunlight UV-B) [23]. Based on the regression coefficients, a score was calculated for each of approximately 47,000 cohort members who had information on these variables. This variable was then examined in relation to subsequent risk of incident colorectal cancer cases ($n = 691$). In the multivariate analysis, a 25 nmol/L (10 ng/mL) increment in 25(OH)D was associated with a 37% reduced risk of colorectal cancer (RR = 0.63; 95% CI, 0.48–0.83). This association persisted after controlling for body mass index and physical activity.

5. Studies based on dietary and supplementary vitamin D intake

The association between colorectal cancer risk and dietary or supplementary vitamin D has been investigated in cohort studies of men [24,25] and women [26–28] or both sexes [29,30], and in case–control studies [31–38]. A limitation of these studies is that vitamin D intake in most population accounts for a relatively small proportion of the variation in 25(OH)D as it does not include vitamin D generated from sun exposure. Nevertheless, the majority of these studies found inverse associations for colon or rectal cancer, or both [24–27,30,32,34,36,37,39]. This finding was especially evident in studies that took into account supplementary vitamin D and where milk in fortified; these are generally the studies in the United States as compared to Europe. In the studies conducted in the United States, the cutpoint for the top category was from approximately 500–600 IU/day, with an average intake in this category of approximately 700–800 IU/day in this category. This level of intake is expected to increase circulating 25(OH)D level by about 7–8 ng/mL and has been shown in randomized trials to reduce risk of fractures and falls [40,41]. The risk reduction of the colorectal cancer in the top versus bottom category was generally marked (in the various studies, risk reduction: 46% [26], 34% [25], 58% [27], 24% [28], 30% [37], 29% male, 0% female [30], 50% males, 40% females [38], and 28% male, 11% female [39]). Similar risk reductions were also observed for colorectal adenoma. A recent meta-analysis of 12 studies based on vitamin D intake [22] found that compared with the lowest quantile of vitamin D intake, the highest quantile was associated with an 11% marginally decreased risk of colorectal adenomas (Odds ratio, 0.89; 95% CI, 0.78–1.02) and recurrent adenomas, (odds ratio = 0.88; 95% CI, 0.72–1.07), particularly for advanced adenoma (OR, 0.77; 95% CI, 0.63–0.95).

An important consideration of studies in the United States is that high vitamin D intakes are generally associated with high calcium intakes. Thus, some of the apparent benefit may be related to calcium intake, although some evidence shows that vitamin D intake remains associated with lower risk even after statistical adjustment for calcium intake [42]. Some studies indicate that vitamin D and calcium may interact and both may be required to minimize risk. In a randomized trial of calcium intake and risk of recurrent adenoma, 25(OH)D concentration was much more strongly associated with a reduced risk of adenoma only among subjects randomized to receive calcium [14]. Some proposed mechanisms are based on interactive functions of vitamin D and calcium [43].

6. Randomized controlled trials

Data from randomized controlled trials may more definitively establish a causal association, but the current data are sparse. The largest study on this issue is the Women's Health Initiative, which was a randomized placebo-controlled trial of 400 IU vitamin D plus 1000 mg/day of elemental calcium in 36,282 post-menopausal women [16]. The incidence of invasive colorectal cancer over a 7-year period did not differ between women assigned to calcium plus vitamin D supplementation and those assigned to placebo (168 and 154 cases; hazard ratio, 1.08; 95% confidence interval, 0.86–1.34; $P = 0.51$). Of note, this trial had some important limitations. First, the vitamin D dose of 400 IU/day was probably inadequate to yield a substantial contrast between the treated and the control groups. For example, the expected increase of serum 25(OH)D level following an increment of 400 IU/day would be approximately 7.5 nmol/L (3 ng/ml). Further, the adherence for this trial was sub-optimal and a high percentage of women took non-study supplements, so the actual contrast of 25(OH)D tested between the treated and the placebo group in the intent-to-treat analysis was likely further reduced. In comparison, in the epidemiologic studies of 25(OH)D, the contrast between the high and low quintiles of 25(OH)D was generally at least 50 nmol/L (20 ng/mL). Secondly, whether the 7-year duration for the trial was sufficiently long to show an effect is unclear. The epidemiologic data on duration are limited, but one study suggested that at least 10 years may be required for an effect of calcium and vitamin D intake for colorectal cancer to emerge [27].

A third consideration is that the study was based on a factorial design along with hormonal replacement use, and a post hoc analysis suggested that women on hormones did not benefit from the vitamin D and calcium, but women not taken hormones may have benefited [44]. Although this result could have been a chance finding, some subsequent observational studies support this interaction. For example, in the Nurses' Health Study of colorectal adenomas, no material association with vitamin D intake was observed for pre-menopausal women or for current users of post-menopausal hormones (HRT), but adenoma risk was significantly reduced among past users of HRT (RR = 0.56; 95% CI: 0.36, 0.89; P trend = 0.03) and suggestively so among never users (RR = 0.82; 95% CI: 0.54, 1.27; P trend = 0.37) [42]. Also, a recent study found no association between outdoor time or ambient UV measure and colorectal cancer risk in current HRT users, but in never/past HRT users, an inverse association with higher ambient UV exposure was found (RR for highest versus lowest tertile = 0.40; 95% CI, 0.17, 0.93; P for trend = 0.04) [45]. Further data are required to evaluate this potential interaction between vitamin D and HRT. Of interest, a recent study of global gene expression in rectal mucosal biopsies

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suggested that the preventive action of HRT on colon neoplasia results, at least in part, from changes in vitamin D activity [46].

The other randomized controlled trial with relevant data was a United Kingdom study of 2686 subjects 65–85 years old who received 100,000 IU of vitamin D_3 every 4 months for 5 years [47]. This amount averages to 820 IU of vitamin D daily, and a fairly substantial 21 nmol/L difference in 25(OH)D was documented between the treated and control groups. Based on 53 cases of colorectal cancer, no association was associated with treatment relative to placebo (RR = 1.02; 0.60–1.74).

7. Vitamin D and survival from colorectal cancer

Some evidence suggests that any association of solar radiation or vitamin D on colorectal cancer risk may be stronger for cancer progression or for survival from cancer. As noted above, the geographical association between 25(OH)D and colorectal cancer was stronger for mortality than for incidence [5] and a study of 25(OH)D and colorectal mortality found a 72% reduction in risk [20], which is a greater reduction than is found in studies of incidence. Mortality is a function of incidence rate and survival. A study examined the influence of season of diagnosis on survival from colon cancer in Norway, where solar generated vitamin D is minimal during the winter months [48]. In this study, 12,823 men and 14,922 women with colon cancer were included, and the period of observation was from 1964 to 1992. There was no significant seasonal variation in the incidence rates of colon cancer, with 25% of the cancers diagnosed in each season. Death rates at 18 months, 36 months and 45 months were significantly lower in those with colon cancers diagnosed in autumn months compared with those diagnosed in the winter months. The magnitude was about 20–30% lower, with maximal benefit at 18 months. This finding suggests that high vitamin D level at the time of diagnosis, and presumably treatment, may improve survival from colon cancer. Late anti-cancer effects of vitamin D, such as reduction in metastases, are observed in numerous animal models. Some evidence from animal models suggests that vitamin D analogues may improve tumor control by radiation treatment, in part by promoting apoptosis [49]. Although these data are provocative, other micronutrients related to fruits and vegetables may be consumed in the summer months only, so an effect cannot necessarily be attributed solely to vitamin D.

Pre-diagnostic 25(OH)D levels were examined in relation to mortality among 304 participants in the Nurses' Health Study and the Health Professionals Follow-Up Study who were diagnosed with colorectal cancer from 1991 to 2002 and followed until 2005 [50]. Patients diagnosed within 2 years of blood collection were excluded from the analysis. In multivariate analyses, compared with those in the lowest quartile, participants in the highest quartile had a multivariate adjusted hazards ratio (HR) of 0.52 (95% CI, 0.29–0.94) for overall mortality and HR = 0.61 (95% CI, 0.31–1.19) for colorectal cancer-specific mortality. The results persisted after excluding patients diagnosed within 5 years of blood collection. Further, predicted 25(OH)D level was examined in relation to mortality among 1017 participants in these same cohorts who were diagnosed with colorectal cancer from 1986 to 2004 [51]. Higher predicted 25(OH)D levels were associated with a significant reduction in colorectal cancer-specific and overall mortality; compared with those with levels in the lowest quintile, participants with predicted 25(OH)D levels in the highest quintile had an adjusted HR of 0.50 (95% CI, 0.26–0.95) for cancer-specific mortality and 0.62 (95% CI, 0.42–0.93) for overall mortality. These associations persisted even after adjusting for pre-diagnostic predicted 25(OH)D level.

The suggested relationship between vitamin D and colorectal cancer mortality and survival prompted an examination of the results from the Women's Health Initiative and the United Kingdom randomized trials for colorectal cancer morality, where no association was observed for colorectal cancer incidence. Although based on small numbers, a suggestive reduction in colorectal cancer mortality was observed in those randomized to vitamin D (and also calcium in the Women's Health Initiative) and colorectal cancer mortality (pooled RR = 0.78; 95%CI = 0.52–1.17).

8. Biologic plausibility of an association between vitamin D and colorectal cancer

While not considered in detail in this review, reasonable biologic plausibility supports an effect of vitamin D on colorectal carcinogenesis. Some animal models indicate that vitamin D status influences growth of intestinal tumors [52–55]. Vitamin D is a transcription factor and vitamin D status modulates various genes in the colorectal mucosa that may influence cancer risk [43,56]. In humans, there is some evidence that vitamin D (and/or calcium) intakes may influence marker of differentiation and apoptosis, which are indicators of risk of developing an adenoma or cancer [57,58]. In human colorectal adenoma and cancer cell lines, 1,25(OH)D induces apoptosis in a dose-dependent manner [59]. The relationship between vitamin D level and calcium intakes was studied in relation to apoptosis determined in rectal biopsies in 498 adenoma patients and 324 individuals without adenoma [60]. Dietary calcium intake was associated with higher apoptosis scores in patients with adenomas whereas level of 25(OH)D was associated with higher apoptosis in adenoma-free patients. In a randomized trial, 92 men and women with at least one pathology-confirmed colorectal adenoma were treated with 2.0 g/day calcium or 800 IU/day vitamin D_3, alone or in combination, versus placebo over 6 months. Calcium and vitamin D, individually or together, appeared to enhance apoptosis in the normal human colorectal epithelium, especially in the upper sections of the colorectal crypts, and in the calcium, vitamin D, and calcium plus vitamin D groups relative to the placebo, p21 (waf1/cip1) (a marker of differentiation) expression increased by 201% ($P = 0.03$), 242% ($P = 0.005$), and 25% ($P = 0.47$), respectively, along the full lengths of colorectal crypts after treatment [61,62].

9. Conclusions

The relation between vitamin D status and colorectal cancer risk has been investigated in a number of epidemiologic studies, while data from interventional studies remain scarce. The various approaches to estimate vitamin D status have included direct measures of circulating 25(OH)D levels, surrogates or determinants of 25(OH)D, including region of residence, intake, and sun exposure estimates, or a combination of these. In general, all lines of inquiry from observational studies indicate that an association between better vitamin D status and lower colorectal cancer risk exists. While most of the epidemiologic studies have examined vitamin D status in relation to risk of cancer, some evidence suggests that vitamin D may be an important factor for cancer progression and mortality, independently of any effects on incidence. Although confounding factors cannot be entirely excluded, the consistency of the association using various approaches to measure vitamin D, for diverse endpoints and in diverse populations shows high consistency and is suggestive of a causal association. For example, while circulating 25(OH)D level could potentially be confounded by physical activity level (if not adequately controlled for) as outdoor exercise will tend to increase sun exposure, confounding by exercise should not be a major issue in studies of vitamin D intake or of regional sun exposure as a surrogate for vitamin D. The criteria of dose–response and temporality are generally met. The magnitude

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of the association is moderate, up to about two-fold differences in risk. While an association of this magnitude for a common cancer such as colorectal cancer is of major public health importance if causal, uncontrolled or residual confounding cannot be ruled out. However, in studies that have controlled for established or suspected risk factors for colorectal cancer, associations with 25(OH)D and colorectal cancer persisted.

The entire body of evidence summarized above is supportive of a causal association between vitamin D status and risk of colorectal cancer. Thus, improving vitamin D status could be potentially beneficial against colorectal cancer incidence and mortality. High-risk groups for deficient or inadequate D include individuals with low intakes, who live in regions with low sunlight intensity, who avoid sunlight or thoroughly use sunscreen, who have darker skin, who are old, who live in a nursing home, and who are overweight or obese. The current recommended intakes of vitamin D (e.g., 200–600 IU/day) may be too low to provide maximal benefits, though the precise optimal dose remains unestablished. For most people, solar UV-B exposure remains the major source of vitamin D, with the only feasible alternative being supplements with higher than traditional doses. However, unprotected sun exposure is usually discouraged because of the increased risk for skin damage and cancer. Given the potential benefits from this vitamin against colorectal cancer, further research should be a priority. Other potential benefits and risks also need to be considered in formulating recommendations and guidelines.

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