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REVIEWS

A Critical Review of Studies on Vitamin D in Relation to Colorectal Cancer

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Abstract: *Vitamin D intake has been hypothesized to reduce the risk of several types of cancer. Vitamin D and its analogues have demonstrated anticancer activity in vitro and in animal models. However, the risk of colorectal cancer in relation to dietary vitamin D remains controversial. A literature search was performed for articles on epidemiologic studies of vitamin D and colorectal cancer and the mechanisms involved. Studies that combine multiple sources of vitamin D or examine serum 25(OH)D_3 usually find that above-average vitamin D intake and serum metabolite concentrations are associated with significantly reduced incidence of colorectal cancer. A number of mechanisms have been identified through which vitamin D may reduce the risk of colorectal and several other types of cancer. Although studies that include vitamin D from all sources or serum 25(OH)D_3 usually show significantly reduced incidence of colorectal cancer in association with vitamin D, analyses limited to dietary vitamin D tend to have mixed results. The likely reason that dietary vitamin D is not a significant risk reduction factor for colorectal cancer in many studies is that dietary sources provide only a portion of total vitamin D, with supplements and synthesis of vitamin D in the skin in association with solar UV-B radiation providing the balance. There is strong evidence from several different lines of investigation supporting the hypothesis that vitamin D may reduce the risk of colorectal cancer. Further study is required to elucidate the mechanisms and develop guidelines for optimal vitamin D sources and serum levels of vitamin D metabolites.*

Introduction

More than two decades ago, Garland and Garland (1) suggested that sunlight, through the production of vitamin D, could explain the geographic distribution of colon cancer mortality rates in the United States. Today, there is still debate over whether solar UV-B and vitamin D reduce the risk of cancer and, if so, the amount and source of vitamin D required.

The objective of this article is to review the epidemiologic literature regarding the relationship between vitamin D and colorectal cancer and to summarize the mechanisms proposed to explain any links. There are several approaches used to determine whether and the extent to which solar UV-B radiation and vitamin D reduce the risk of colorectal cancer and colorectal adenomas. These include ecologic studies of UV-B, vitamin D, and colorectal cancer; case-control and cohort studies of dietary vitamin D, total consumed vitamin D, including supplements, and serum vitamin D; animal studies; and in vitro studies. Each approach has strengths and weaknesses. The various studies are critically reviewed here.

Methods and Materials

To further examine the role of vitamin D in the etiology of colon cancer, a literature search was undertaken. The PubMed database was searched for epidemiologic and other studies of dietary and total vitamin D and serum 25(OH)D_3 in relation to colon cancer. The terms "vitamin D" and "colon cancer" were used, and the "related articles" feature was used to find additional articles related to the topic. A total of 20 case-control and cohort studies were found that examined the link between vitamin D and colon cancer, rectal cancer, colorectal cancer, or colon adenomas. These 20 are likely to represent the vast majority of the work done in this field.

The studies were evaluated using accepted criteria for causality for biological systems. These criteria were originally described in the Surgeon General's report on smoking and health

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(2), were expanded on by A. B. Hill in his Presidential Address (3), and have been discussed by many authors since then (4,5). The primary criteria are: consistency, strength of association, dose response, biological plausibility, temporality, and exclusion of confounding factors from the analysis. Other criteria, such as analogy, coherence, experiment, plausibility, and specificity, are generally either assumed implicitly or ignored. Not all criteria need to be satisfied, but the more that are, the greater the confidence in the result.

Review of Results in the Literature

Ecologic Approach

The ecologic approach was the first to identify sunlight through the production of vitamin D as a risk reduction factor for colon cancer (1). This approach is still being applied today (6). The results of ecologic studies for colorectal cancer are shown in Table 1 (6–9). The adjusted r^2 for the portion of the variance attributed to UV-B radiation varies from 0.38–0.73. A recent study by Grant (submitted) considered factors in addition to solar UV-B associated with colon and rectal cancer in the United States, including urban or rural residence, alcohol, Hispanic heritage, poverty, and smoking; this study found that the fraction of the variance associated with UV-B radiation (incident UV-B plus rural or urban residence) increased by 0.07 –0.28, except for rectal cancer in women. Living in an urban area is associated with reduced UV-B exposure compared with living in a rural area; thus, reducing the effect of incident UV-B. Doll (10) identified UV radiation as one of the factors explaining the lower cancer rates in rural regions compared with urban regions. Also, urban residence was identified as a risk factor for colon cancer in other studies (11). A recent study in New York State reported reduced rates of colorectal cancer among women living on farms (12). Thus, ecologic studies consistently give strong (inverse) associations between solar UV-B radiation and colorectal cancer.

Solar UV-B radiation is arguably the most important source of vitamin D in the United States (13,14), with seasonal variations in solar UV-B explaining the seasonal variations in serum vitamin D (15–17). Solar UV-B radiation is inversely correlated with 12–13 types of cancer in ecologic studies (6,9). Because various types of cancer have some shared and some unique risk factors, it would be surprising if a factor other than vitamin D explained the solar UV-B link, especially because the mechanisms whereby vitamin D reduces the risk of cancer are well known (18).

Cohort and Case-Control Studies

Results from various cohort and case-control studies are summarized in Tables 2–5 (19–37). First, we considered cohort and case-control studies that attempted to correlate dietary vitamin D with colon cancer, rectal cancer, colorectal cancer, or colon adenomas (Tables 2 and 3). The odds ratios (OR) or risk ratios (RR) were < 1.0 in six cohort studies, but > 1.0 in five cohort studies. The 95% confidence interval (CI) included 1.0, and the *P* value (for trend) was insignificant at the 0.05 level in all but one case, that of Garland et al. (19). However, in the case-control studies, five of the seven studies reported OR < 1.0, with the 95% CI < 1 in three studies. One study reported a *P* value (for trend) of < 0.01, and two reported a *P* value of < 0.10.

Table 1. Ecologic and Case-Control Study Results on Solar UV-B Radiation and Colorectal Cancer[a]

Reference	Disease Outcome	Study Region	Regressed Factors	Data Sources	Findings
1	Colon cancer		Mortality, sunlight	Atlas of Cancer Mortality	
6	Colon cancer	USA	Mortality and solar UV-B	TOMS, Atlas of Cancer Mortality	Adj. r^2 = 0.38 (M); 0.40 (F)
6	Rectal cancer	USA	Mortality and solar UV-B	TOMS, Atlas of Cancer Mortality	Adj. r^2 = 0.40 (M); 0.48 (F)
7	Colon cancer	Canada; 20 cities	Mortality, aerosols	Aerosols, mortality rates	Adj. r^2 = 0.55 (M); 0.37 (F)
8	Colon cancer	USA; 9 population centers	Incidence rates and solar radiation	SEER	40–90% increase with decreasing radiation, P = 0.03 (M); 10–60% increase, P = 0.24 (F)
8	Rectal cancer	USA; 9 population centers	Incidence rates and solar radiation		50–80% increase with decreasing radiation (M); no change (F)
9	Colon cancer	USA; 24 states		Death certificates, residence, high vs. low sunlight	Odds ratio = 0.73 (95% CI 0.71–0.74)
Grant, submitted	Colon cancer	USA	Mortality with UV-B, smoking	Lung cancer for smoking	Adj. r^2 = 0.73 (M) (+ urban); 0.59 (F) (+ poverty)
Grant, submitted	Rectal cancer	USA	Mortality with UV-B, Hispanic heritage, poverty	Census Bureau data	Adj. r^2 = 0.76 (M) (+ smoking); 0.60 (F)

a: Abbreviations are as follows: M, male; F, female; adj., adjusted; SEER, XXXXXXXXXXXXX; TOMS, XXXXXXXXXXXX.

Table 2. Cohort Studies of Dietary Vitamin D and Colon, Rectal, or Colorectal Cancer or Colorectal Adenoma[a]

Reference	Outcome	Type of Study (Location)	Vitamin D Range (IU/day; 1 μg = 40 IU)	Study Period (years)	OR or RR, Highest to Lowest (95% CI where available)	*P* (for trend)
19	Colorectal cancer	Cohort (USA)	<30 IU/1000 kcal/d–>75 IU/1000 kcal/d (quartiles)	19	RR = 0.55	0.05
20	Colon cancer	Cohort (Iowa, USA)	<127–>373 (quintiles)	4	RR = 0.77 (0.50–1.16)	0.25
21	Colon cancer	Cohort (USA)	<134–>356 (quintiles)	6	RR = 0.88 (0.54–1.42)	0.55
22	Colorectal cancer	Cohort (USA)	<85–>280 (septiles)	12	RR = 0.72 (0.34–1.54)	0.29
23	Colon cancer	Cohort (Finland)	<103–>196 (quartiles, M); <72–>137 (F)	24	RR = 1.18 (0.40–3.45)	0.65
23	Rectal cancer	Cohort Finland	<103–>196 (quartiles, M); <72–>137 (F)	24	RR = 2.54 (0.89–7.27)	0.10
24	Colon cancer	Cohort (Sweden)	<104–>152 (quartiles)	11.3	RR = 1.24 (0.92–1.66)	0.17
24	Rectal cancer	Cohort (Sweden)	<104–>152 (quartiles)	11.3	RR = 0.74 (0.49–1.10)	0.15
25	Colorectal cancer	Cohort (USA)	<90–>240 (quintiles)	5	RR = 0.83 (0.60–1.15) (M); 1.08 (0.72–1.62) (F)	0.13 (M); 0.99 (F)
26	Colorectal adenoma	Cohort, HPFS (USA)	Not given	4	RR = 1.05 (0.74–1.49)	0.82
26	Colorectal adenoma	Cohort, NHS (USA)	101–470 (M, means, quintiles); 61–653 (F)	8	RR = 0.97 (0.68–1.38)	0.93

a: Abbreviations are as follows: OR, odds ratio; RR, relative risk; M, males; F, females; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Table 3. Case-Control Studies of Dietary Vitamin D and Colon, Rectal, or Colorectal Cancer[a]

Reference	Outcome	Type of Study (Location)	Vitamin D Range (IU/day; 1 μg = 40 IU)	OR or RR, Highest to Lowest (95% CI)	*P* (for trend)
27	Colon cancer	Case-control (Wisconsin, USA)	<122 – >336 (quintiles)	OR = 0.8 (0.5–1.3)	0.45
28	Colon cancer	Case-control (N. Calif.; Minn.; Utah)	7.7 vs. 7.6 μg/d–cases, controls (M); 5.6, 5.8 (F)	RR = 1.4 (1.0–2.2) (M); 1.0 (0.7–1.3) (F)	
29	Colorectal cancer	Case-control (Italy)	<316 – >788	RR = 0.74 (0.58–0.95)	$\chi^2 = 4.1$
30	Colorectal cancer	Case-control (Sweden)	<112–280 (quartiles)	OR = 0.6 (0.4–1.0)	0.076
30	Rectal cancer	Case-control (Sweden)	<112–280 (quartiles)	OR = 0.5 (0.3–0.9)	0.083
31	Colorectal cancer	Case-control (Italy)	<81–>171 (quintiles)	OR = 0.77 (0.6–0.9)	<0.01

Although most of the cohort studies were not able to demonstrate that dietary vitamin D reduced the risk of colorectal cancer, the case-control studies did show a correlation, at least at the $P < 0.10$ level. Thus, dietary vitamin D may be sufficient to significantly reduce the risk of colorectal cancer. But the reduction may not be robust enough to appear in all types of studies.

Second, we examined studies in which both dietary and supplemental sources of vitamin D were considered together (Table 4). Both cohort and case-control studies always found that high levels of total ingested vitamin D had an OR or RR < 1.0 (mean value = 0.65), with the 95% CI < 1.0 in three of the nine cases and the *P* value (for trend) < 0.05 in six of the nine studies. The cohort studies of colorectal adenoma were inconclusive. Thus, most studies found that dietary plus supplemental vitamin D is associated with a reduced risk of colorectal cancer.

One interesting finding was that when males and females were considered separately, total ingested vitamin D was a statistically significant risk reduction factor for males but not for females. For dietary vitamin D, only one study (25) reported different values for males and females, and the *P* value (for trend) was 0.13 (0.60–1.15) for males and 1.08 (0.72–1.62) for females. These results are consistent with a recent ecologic study of solar UV-B doses and colon cancer mortality rates in the United States for the period 1970–94: the adjusted r^2 for the variance was 0.73 for males but only 0.59 for females; rural versus urban residence, a factor also

Table 4. Studies of Total Ingested Vitamin D (Diet and Supplements) and Colon, Rectal, or Colorectal Cancer or Colorectal Adenoma[a]

Reference	Outcome	Type of Study (Location)	Vitamin D Range (IU/day)	Study Period (years)	OR or RR, Highest to Lowest (95% CI)	*P* (for trend)
20	Colon cancer	Cohort (Iowa, USA)	<159–>618 (quintiles)	4	RR = 0.54 (0.35–0.84)	0.02
21	Colon cancer	Cohort (USA)	<161–>613 (quintiles)	6	RR = 0.66 (0.42–1.05)	0.02
22	Colorectal cancer	Cohort (USA)	<120–>550 (septiles)	12	RR = 0.42 (0.19–0.91)	0.04
32	Rectal cancer	Cohort, postmenopausal women (Iowa)	<224–>476 (tertiles)	7	RR = 0.76 (0.50–1.16)	0.20 (F)
25	Colorectal cancer	Cohort (USA)	<110–>525 (quintiles)	5	RR = 0.71 (0.51–0.98) (M); 1.00 (0.68–1.47) (F)	0.02 (M); 0.62 (F)
27	Colon cancer	Case-control (Wisconsin, USA)	<148–>557 (quintiles)		OR = 0.7 (0.4–1.1)	0.05
28	Colon cancer	Case-control (N. Calif., Minn., Utah)	Supplements (Never vs. ever)		OR = 0.5 (0.2–1.1) (M); 0.6 (0.4–1.1) (F)	0.01 (M); 0.21 (F)
26	Colorectal adenoma	Cohort, HPFS (USA)	118–954 (means, quintiles)	4	RR = 1.29 (0.87–1.93)	0.32
26	Colorectal adenoma	Cohort, NHS (USA)	59–744 (means, quintiles)	8	RR = 0.68 (0.41–1.13)	0.09

a: Abbreviations are as follows: OR, odds ratio; CI, confidence interval; M, males; F, females; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Table 5. Studies of Serum 25(OH)D_3 and Colon Cancer or Colorectal Adenomas[a]

Reference	Outcome	Type of Study (Location)	Serum 25(OH)D Range	Serum 25(OH)D Cases, Controls (ng/ml)	Study Period (years)	OR or RR Highest to Lowest (95% CI, where available)	*P* (for trend)
33	Colon cancer	Cohort/nested case-control (Maryland, USA)	<20–>41 (quintiles)		9	RR = 0.21 (4th quintile); 0.73 (5th quintile)	0.05
34	Colon cancer	Case-control (Maryland, USA)		23.6 ± 9.2, 23.2 ± 7.8	17	OR = 0.4 (0.1–1.4; 5th quintile)	0.57
35	Rectal cancer	Case-control (Finland)		12.2 ± 13.8		RR = 0.37	0.06
36	Colorectal adenomas	Case-control (USA)	16.3–38.0 (quartiles)	26.4 ± 10.6, 26.8 ± 10.2	7	OR = 1.04 (0.66–1.66)	1.0
37	Colorectal adenomas	Case-control (Maryland, USA)	Per 10 ng/ml	24.7 ± 12.0, 26.5 ± 11.3	1	OR = 0.43 (0.23–0.81) (5th quintile)	0.21

a: Abbreviations are as follows: OR, odds ratio; RR, relative risk; CI, confidence interval.

affecting UV-B exposure, contributed almost as much as geographic UV-B dose for males, but did not contribute to the results for females (Grant, submitted). For rectal cancer, the corresponding values were 0.76 for males and 0.60 for females. The fact that vitamin D provides less protection against colorectal cancer for females than for males may be due to reduced solar UV-B exposure for females or to the fact that estrogen also reduces the risk of colorectal cancer (38–40). The combined effect of estrogen and vitamin D on colorectal cancer is also the subject of current research interest, such as in the interplay among estrogen, vitamin D, and estrogen- and vitamin D-receptor (VDR) genotypes (41). Thus, the effects of vitamin D on colorectal cancer should be reported separately for males and females.

Third, we considered studies that examined serum 25(OH)D_3 and colon or rectal cancer or colorectal adenomas (Table 5). Serum 25(OH)D_3 represents the sum of vitamin D from diet, supplements, and exposure to solar and artificial UV-B radiation. However, because solar production of vitamin D has strong seasonal variations (37,42), it is important to ensure that the sera used in each study were drawn either at the same time or in a random fashion. The sera in the studies by Garland et al. (33) and Braun et al. (34) were drawn within a four-month period, August through November 1974. Because the data used in the studies by Platz et al. (36) and Peters et al. (17) were from case-control studies, the seasonal variations should be unimportant. However, Peters et al. did find that the odds ratio for serum samples drawn in winter/spring (0.70) had a stronger inverse correlation with colorectal adenomas than did those drawn in summer/fall (0.77); in the absence of solar UV-B radiation, diet likely had a greater influence. The results for two of the colorectal cancer studies had *P* values (for trend) of 0.05 and 0.06 (33,35), whereas the third had a *P* value of 0.57 (34). The mean value of 25(OH)D_3 for the Garland et al. (33) study was 30 ng/ml (75 nmol/l), whereas that for the Braun et al. (34) study was

25 ng/ml (63 nmol/l) for cases and 20 ng/ml (50 nmol/l) for controls. It could be that the lower values in the Braun et al. study were below the threshold for effectively reducing the risk of colorectal cancer. Colon cancer mortality rates in Maryland were about twice as high as in southwestern states in the period 1970–94 (43).

In Vitro Studies

In vitro studies involving human colonic tissue provide an additional avenue to explore the roles of calcium and vitamin D in tumor progression. Some results from the literature are summarized here briefly. $1,25(OH)_2D_3$ decreases the proliferation of Caco-2 cells (44) and enhances certain parameters of differentiation (45). Vitamin D was found to make colon cancer cells less prolific and to have enhanced differentiation (46). The stimulatory effect of epidermal growth factor on cell division was effectively counteracted by $1,25(OH)2D_3$ (47). The effects of vitamin D were correlated with the expression of VDR. In vitro studies have also shown the importance of the Ca^{2+}-sensing receptor in inhibiting cell replication (48).

Discussion

The sources of vitamin D for humans are well known but difficult to study in an accurate, quantitative manner. Vitamin D is obtained from diet, dietary supplements, and solar UV-B radiation (280–320 nm). Vitamin D may be found in the serum both as $25(OH)D_3$ and $1,25(OH)_2D_3$. Thus, studies considering vitamin D and cancer usually do not fully account for all relevant sources and forms. It should be noted that assessments of dietary vitamin D are difficult. In New York State, the vitamin D content of milk was found to be out of compliance with current regulations, generally underfortified (49). Vitamin D supplementation is a complicating factor. And vitamin D consumption and production 10–25 yr prior to the detection of cancer may be much more important than more recent consumption and production (50,51). A study in Japan found a 23-yr lag between changing to a more Western, lower-fiber diet and the peak development of colon cancer (52). Also, the amount of serum vitamin D required to significantly reduce the risk of cancer is not well known. More recent studies suggest that levels of $25(OH)D_3$ of up to 100 nmol/l (40 ng/ml) are considered to be adequate for a number of conditions (53,54). Supplementation with 400 IU/day for postmenopausal Dutch women was approximately equal to that provided by solar UV-B in summer (55).

There have been many studies of mechanisms whereby vitamin D reduces the risk of cancer. These proposed mechanisms include effects on cell differentiation, apoptosis, cell cycle regulation, metastasis, proliferation, and angiogenesis (18,56–59). It is beyond the scope of this review to evaluate the strength of the evidence for each proposed mechanism, but there are several promising areas of investigation. Colon cells have the ability to convert circulating $25(OH)D_3$ into $1,25(OH)_2D_3$ (60), as do cells in a number of other organs (61). In an Israeli study, serum $25(OH)D_3$ levels were found to vary insignificantly between cases and controls of rectal cancer; however, serum $1,25(OH)_2D_3$ levels were found to decrease with advancing stage of the colorectal carcinoma, whereas PTH levels increased accordingly (62). The reason for this finding was not clear. Vitamin D also interacts with calcium to enhance the reduction of colon cancer risk (48,63,64). Finally, polymorphisms in vitamin D receptors may play a role in colon cancer risk (37,65,66). The polyA (short), BsmI (BB), and TaqI (tt) variants of the vitamin D receptor (VDR) gene were found to be in linkage disequilibrium in a mostly Caucasian population. These variants were associated with reduced risk of colon cancer (OR = 0.5, 95% CI = 0.3–0.9). The FokI variant was not associated with colon cancer risk (65). However, another paper found that VDR FokI genotype influences development of colorectal adenomas and that the effect may be modified by calcium and vitamin D status (66). Increased VDR and 1-α-hydroxylase m RNA expression was found in low-grade malignancies of the human colon (67). VDR also functions as a receptor for the secondary bile acid lithocholic acid (LCA) (68), which is hepatotoxic and a potential enteric carcinogen. Activation of VDR by LCA or vitamin D induced expression in vivo of CYP3A, a cytochrome P450 enzyme that detoxifies LCA in the liver and intestine. These studies offer a mechanism that may explain the proposed protective effects of vitamin D and its receptor against colon cancer.

In addition, vitamin D plays a role in reducing the risk of colorectal cancer through interactions with calcium. There is a growing body of evidence that calcium restrains growth of and induces differentiation and apoptosis of normal and tumor cells (33,57,59). One of the well-documented effects of vitamin D is to increase the absorption of calcium (69).

There are several reasons why examining only dietary sources of vitamin D is not a reliable method for assessing the value of vitamin D in reducing the risk of colon, or any other, cancer. First, dietary vitamin D is one of three sources of vitamin D, the other two being solar UV-B radiation and supplements. Second, dietary vitamin D levels are often below those that provide strong risk reduction for cancer and other conditions and diseases (53,54). Third, dietary assessments for vitamin D are difficult to perform accurately. These assessments rely on questionnaires along with vitamin D estimates for the foods, and both of these are inherently inaccurate (70,71). A more accurate method would be to measure biomarkers for dietary intake, but biomarkers are not available for all factors. Fourth, dietary assessments represent a snapshot of vitamin intake at one point in time. However, the effect of vitamin D on cancer development may have occurred years earlier. Therefore, these assessments may not accurately represent the dietary vitamin D during the time when it would have had the greatest impact on cancer risk. Fifth, genetics affect how vitamin D and calcium are absorbed or metabolized. Vitamin D receptor genotypes affect the utilization of vitamin D (72).

A sixth reason that dietary vitamin D may not always show up as reduced cancer risk is that many dietary sources of vitamin D contain confounding components that also strongly affect the risk of cancer. Animal products are correlated with colorectal cancer, whereas vegetable products are generally inversely correlated (73). These confounding factors are not always addressed (74). Fish, which is an important source of vitamin D for Scandinavian countries (75), is also an important source of n-3 oils, as well as being an animal source of protein. N-3 oils reduce the risk of many types of cancer (76,77). Milk, which is fortified with vitamin D in some countries such as the United States but not in many European countries, contains calcium, which reduces the risk of colon cancer (25). However, it also contains fat and protein, both of which increase the production of insulin-like growth factor-I (78). Neither fish nor milk has much fiber, an important risk reduction factor for colon cancer (79,80). Thus, both fish and milk have components that increase and decrease the risk of colon cancer, and these components should be considered in the analysis along with vitamin D. It appears as if all the studies in this review included calcium in the analysis, whereas many considered saturated fat and other micronutrients. However, given the importance of various dietary factors on the risk of colorectal cancer, other dietary factors may outweigh vitamin D.

Even the inclusion of supplementary vitamin D in the data is subject to confounding factors. Vitamin A is antagonistic to vitamin D (81,82) and leads to reduced calcium absorption when both are administered together. Despite this, vitamin A is often combined with vitamin D in supplements.

Evaluation of Vitamin D Based on the Criteria for Causality

Now that the evidence has been presented, it can be evaluated for causality. The criteria for causality in a biologic system are generally based on Hill (3), with later interpretations (4,5). The primary criteria used are strength, consistency, biologic gradient or dose-response, biologic plausibility, temporality, and testing for confounding factors. Each of these criteria is applied to the various approaches and tabulated in Table 6.

Strength is generally assumed to mean the magnitude of the relative risk estimates in published results. For ecologic studies, this should refer to the adjusted r^2 of the regression of the variance. The strength was rated high if both the risk ratio and the 95% CI were generally < 1.0 or the adjusted r^2 was always relatively high. Strength was high for all approaches except for serum $25(OH)D_3$ in case-control studies.

Consistency refers to the extent to which the findings are similar in direction across the entire body of evidence. Consistency was high for all approaches except diet in cohort and serum $25(OH)D_3$ in case-control studies.

Biologic gradient or dose-response is defined as having a generally linear relationship between the factor and the outcome. Biologic gradient was high for all approaches except diet in cohort and serum $25(OH)D_3$ in case-control studies.

Biologic plausibility refers to whether mechanisms exist that explain the action of the factor. For vitamin D, the proposed mechanisms are well known and include cell differentiation, increased apoptosis of cancer cells, reduced metastasis, and angiogenesis (18,59). Biologic plausibility was high for all approaches except diet in cohort studies.

Temporality means that the causal factor has to be applied before the effect is detected. For the ecologic study of geographic distribution of cancer mortality in the United States (6), the values of UV-B for July 1992 were used under the assumption that the July values have not changed significantly in either absolute or relative terms. Stratospheric ozone losses have been minimal over the United States and have occurred primarily after 1990 (83), which is mostly after the period for the data used (1970–94). In fact, using the July 1992 UV-B data with the cancer mortality data from 1950–69 yielded higher correlations for most cancers than mortality data from the latter period (Grant, submitted). For the other studies, the vitamin D values occurred prior to the detection of cancer, although the lag between determining the vitamin D values and the detection of cancer varied; because colorectal cancer can take over 20 years to go from initiation to discovery (50–52), the longer the lag, the better the results will be. Temporality was high for all approaches.

Table 6. Evaluation of the Various Approaches for Determining the Effect of Vitamin D on Colorectal Cancer Based on Hill's Criteria for Causality (3)

Factor	Strength	Consistency	Biologic Gradient	Biologic plausibility	Temporality	Confounding Factors Included	Analogy
Approach							
Ecologic	High	High	High	High	High	High	High
In vitro	High	High	High	High	High	High	High
Cohort							
Diet	Low	Low	Low	Medium	High	Low	Medium
Diet plus supplements	High	High	High	High	High	Medium	Medium
Case-control							
Diet	High	High	High	High	High	Medium	High
Diet plus supplements	High	High	High	High	High	Medium	High
Serum	Medium	Medium	Medium	High	High	Medium	High
All, based on the best approaches	High	High	High	High	High	High	High

Confounding factors for vitamin D and colorectal cancer may include diet, supplements, solar UV-B exposure (both incident radiation and time spent in the sun), alcohol consumption, smoking, exercise, body mass index, among others. The ecologic study in Grant (submitted) accounted for as many factors as possible and assumed that dietary factors were similar for all states. The primary problem with studies of dietary sources of vitamin D is that supplements and UV-B exposure are also important sources of vitamin D (84). Thus, the low findings for dietary sources of vitamin D are most likely due to failure to include the other sources of vitamin D.

Analogy refers to using results from related studies for the present study. In this case, the results for the 11 other cancers for which solar UV-B has been identified as a risk reduction factor (6,9,85) can be used. Analogy was high for all approaches except for cohort studies.

It should be noted that, whereas the ecologic approach (79,86,87) has generally not enjoyed a good reputation (88), it has been vindicated recently after cohort studies confirmed ecologic studies that showed dietary fiber is a risk reduction factor for colon cancer (80) and animal fat is a risk factor for breast cancer (89). The primary problem with cohort studies in this regard is that because relatively homogeneous populations are studied, variations of the important dietary values are often too small for significant correlations to be found, just as in the case of dietary vitamin D and colorectal cancer.

Because well-designed studies have consistently shown that vitamin D is associated with reduced risk of colorectal cancer, and to a lesser extent of other cancers, the implications for public health policy should be examined. Where solar UV-B levels are high enough during a good fraction of the year and outdoor exposure is possible, humans can synthesize sufficient vitamin D to meet physiological needs. However, there are many regions and seasons where this is impossible (42). Dietary vitamin D is found in small quantities in butter, some types of margarine, some fortified cereal and grain products, eggs, fish, and milk in a few countries (90,91). A serum level of 65–100 nmol/l (25–40 ng/ml) of $25(OH)D_3$ is now considered adequate for reduction of risk of cancers of the colon, breast, and others based on epidemiologic data (92). Where solar exposure and dietary vitamin D levels are not sufficient to achieve this level, vitamin D supplementation is suggested, although the amount varies depending on a number of factors.

Guidelines for supplementation for reducing the risk of cancer have not been established. Various evidence points to a general vitamin D deficiency in the United States (93,94). The U.S. National Institutes of Health held a conference October 9–10, 2003, entitled "Vitamin D in the 21st Century: Bone and Beyond" (95). This conference considered surveillance/monitoring, specific vitamin D and health issues, and developmental/ethnic/racial considerations for calcemic and noncalcemic diseases. It has raised the level of interest in vitamin D, and it is expected that revised vitamin D guidelines will be developed in the next few years.

Conclusion

If measures of vitamin D that relate to total vitamin D are considered, significant inverse correlations with colorectal cancer are generally found. However, if only dietary vitamin D is considered, significant inverse correlations are only occasionally found. Future studies of vitamin D and cancer or any other condition or disease should include the determination of total vitamin D intake and production, or serum vitamin D metabolite levels. In addition, because many conditions and diseases take a decade or more to develop to clinical levels, long-term studies are indicated. Eventually, revised guidelines for vitamin D and calcium should be established, but more information is required before this can be done.

Acknowledgments and Notes

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