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Optimal Vitamin D Status for Colorectal Cancer Prevention

A Quantitative Meta Analysis

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Background: Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.

Methods: Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Peto's Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose–response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.

Results: Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.82, 0.66, 0.59, and 0.46 ($p_{trend}<0.0001$) for colorectal cancer. According to the DerSimonian-Laird test for homogeneity of pooled data, the studies were homogeneous ($chi^2=1.09$, $df=4$, $p=0.90$. The pooled odds ratio for the highest quintile versus the lowest was 0.49 ($p<0.0001$, 95% confidence interval, 0.35–0.68). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level ≥33 ng/mL, compared to ≤12 ng/mL.

Conclusions: The evidence to date suggests that daily intake of 1000–2000 IU/day of vitamin D_3 could reduce the incidence of colorectal with minimal risk.

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Introduction

The Women's Health Initiative[1] demonstrated that a low dose of vitamin D did not protect against colorectal cancer within 7 years of follow-up; however, a meta-analysis indicates that a higher dose may reduce its incidence.

There were approximately 145,300 new cases and 56,300 deaths from colorectal cancer in the United States during 2005.[2] An observation of higher age-adjusted mortality rates of colorectal cancer in the northern and northeastern United States compared to the southwest, Hawaii, and Florida led to a theory that vitamin D of mainly solar origin may reduce risk of colorectal cancer[3] through a mechanism involving calcium metabolism, intercellular adherence, and contact inhibition. Since then, five observational studies have explored the association of serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25[OH]D) with risk of colorectal cancer.[1,4–7] However, an overall dose–response gradient for the effect of serum levels of 25(OH)D on colorectal cancer risk has not been determined. This meta-analysis provides an estimated dose–response gradient that may be of help in planning for a useful role of vitamin D in control of colorectal cancer.

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Methods

Study Inclusion

The PubMed database was searched for the period from January 1966 to December 2005 by using the terms ("vitamin

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D," or "25-hydroxyvitamin D"), and ("cohort" or "case–control" or "case–cohort" or "incidence" or "occurrence" or "epidemiology") and "human" as medical subject heading (MeSH) terms and words in the abstract. Articles were included if they were published in medical journals and included measures of association by quantile. A total of five studies were identified and all five met the inclusion criteria.[1,4–7] Information on study design, participant characteristics, multivariate adjustment, and serum levels of 25(OH)D was abstracted by two investigators. Data were abstracted and analyzed in 2006.

Statistical Analysis for 25(OH)D

Summary odds ratio. A summary odds ratio of the highest versus lowest quintile for all studies was obtained using Peto's Assumption-Free Method for combining odds ratios.[8] This method provides a weighted average of the natural logarithms of the odds ratios from each study. The weights were the inverse of the variances of the logarithms of each odds ratio.[9]

The *p* value for the summary odds ratio was calculated using a *z*-test, where the numerator was the natural logarithm of the pooled odds ratio and the denominator was the standard error of the pooled odds ratio, which is the standard method for calculating the *p* value when using Peto's Assumption-Free Method.[8] Odds ratios comparing the highest with the lowest quantiles for each study were displayed in a forest plot.[10,11] Confidence intervals were computed using the method of Woolf.[12] The DerSimonian-Laird statistic was calculated to assess homogeneity.[13] The calculations were performed using Rev Man (Oxford, England: The Cochrane Collaboration).

Dose–response gradient. A data set was created consisting of one record per participant in each study. The records in this data set identified whether the participant was a case or noncase, the median or midpoint of the participant's quantile of serum 25(OH)D at baseline, in ng/mL, a number identifying the study, and a serial number for each individual. If the median value was provided by the study,[1,7] it was used. If not,[4–6] midpoint values were calculated by computing the arithmetic mean of the upper and lower bounds of the quantiles.

Data presented in nmol/L were converted to ng/mL using the conversion factor 1 ng/mL=2.5 nmol/L. The records were put into order by serum 25(OH)D level, then divided into five quintiles, with each quintile containing approximately one fifth of the records.

Odds ratios were then calculated for the association between quintile of serum 25(OH)D and risk of colorectal cancer in the pooled data, using the lowest quintile as the reference group. Confidence intervals were computed using the method of Woolf.[12] A dose–response curve was then plotted using the odds ratios for each quintile of the pooled data.[12] A least-squares trend line was constructed to examine the dose–response relationship[14,15]; *p* values for trend were calculated using the Mantel-Haenszel chi^2 test.[16,17] Serum 25(OH)D concentrations associated with a 50% reduction in colorectal cancer risk, compared to the lowest quintile of 25(OH)D, were obtained by drawing a vertical line from the point on the dose–response curve corresponding to an odds ratio 0.50 to the point of intersection with the horizontal axis. Computations were performed using SAS, Version 9.1 (SAS Institute, Cary NC, 2004).

When the upper limit of the top quantile was not provided,[5,6] the median of that quantile was estimated based on an assumption that the median of the values above the lower limit were so close to that limit that the value of the lower limit that was provided was the best available estimate of the median of the quantile. This is an adaptation of a general procedure for handling open intervals.[8] Further corrections might have raised the assumed value of this limit by 1%–2%, which would have had virtually no detectable effect on the slope of the dose–response curve.

Results

Five studies of the association of serum 25(OH)D with risk of colorectal cancer were identified.[1,4–7] All were nested case–control studies of prediagnostic serum collected from healthy volunteer donors who were then followed from 2–25 years for incidence (Table 1). Three studies reported statistically significant trends toward lower odds ratios in individuals with higher levels of 25(OH)D,[1,6,7] while two reported trends in the same direction that were of borderline significance or not significant.[4,5] All studies were included in the meta-analysis.

The anatomic site of interest was the colon for the studies by Garland et al.[4] and Braun et al.,[5] and colon and rectum combined for the studies by Feskanich et al.[7] and Wactawski-Wende et al.[1] The association reported by Tangrea et al.[6] was limited to the distal colon.

There was a downward linear gradient in risk of colorectal cancer with increasing serum 25(OH)D in the meta-analysis (R^2=0.98, *p* for trend <0.0001) (Figure 1). The odds ratios for the pooled data were, from lowest to highest quintile: 1.00, 0.82, 0.66, 0.59, and 0.46 (*p* trend <0.0001 (Table 1).

A serum 25(OH)D ≥33 ng/mL (83 nmol/L) was associated with a 50% lower risk of colorectal cancer incidence, compared with <12 ng/mL (Figure 1). The five studies were homogeneous (DerSimonian-Laird chi^2=1.09, *df*=4, *p*=0.90). The overall Peto odds ratio summarizing the estimated risk in the highest compared to the lowest quantile across all studies was 0.49 (*p*<0.0001) (Figure 2).

Discussion

A meta-analysis increases power by combining the results of many studies. All known published studies of serum 25(OH)D and risk of colorectal cancer were included, and the results were homogenous. Pooling of such independent studies increases precision, because random fluctuation in any one study tends to be counterbalanced by results of other studies.

The data from two different studies of serum 25(OH)D in the Johns Hopkins cohort in Washington County MD had trends that were uneven but consistent

Table 1. Serum 25-hydroxyvitamin D [25(OH)D] concentration associated with colorectal cancer, according to observational studies[a]

Authors (year) ref	Cancer site	Gender	Quantile cutpoints (25(OH)D, ng/mL)	Total	Odds ratio by quantile	*p* for trend
Garland et al. (1989)[4]	Colon	Both	4–19, 20–26, 27–32, 33–41, 42–91		1.00, 0.48, 0.25, 0.21, 0.73	—
No. of cases per quintile			9, 7, 5, 4, 9	34		
No. of noncases per quintile			8, 13, 18, 17, 11	67		
Braun et al. (1995)[5]	Distal colon and rectum	Both	<17, 18–20, 21–24, 25–29, 30+		1.00, 0.33, 0.54, 0.70, 0.41	0.13
No. of cases per quintile			16, 8, 11, 13, 9	57		
No. of noncases per quintile			18, 26, 23, 21, 25	113		
Tangrea et al. (1997)[6]	Distal colon and rectum	Men	<10, 10–13, 14–18, 19+		1.00, 0.83, 0.61, 0.48	0.03
No. of cases per quartile			33, 29, 23, 18	103		
No. of noncases per quartile			47, 50, 54, 53	204		
Feskanich et al. (2004)[7]	Colorectal	Women	16, 22, 27, 31, 40[b]		1.00, 0.86, 0.68, 0.55, 0.55	0.01
No. of cases per quintile			53, 47, 35, 29, 29	193		
No. of noncases per quintile			77, 79, 75, 77, 75	383		
Wactawski et al. (2005)[1]	Colorectal	Women	12, 14.7, 20.2, 23.4[b]		1.00, 0.73, 0.71, 0.40	0.01
No. of cases per quintile			42, 45, 34, 27	148		
No. of noncases per quintile			28, 41, 32, 45	146		
Pooled data			6, 16.2, 21.8, 26.8, 37		1.00, 0.82, 0.66, 0.59, 0.46	<0.01
95% confidence intervals for odds ratios			(0.59–1.14), (0.47–0.92), (0.41–0.82), (0.32–0.64)			
No. of cases per quintile			129, 121, 107, 98, 80	535		
No. of noncases per quintile			151, 172, 190, 195, 205	913		

[a]All were nested case–control studies.
[b]Medians of quantiles are shown; cut points were not provided.
Dash (—) denotes no statistically significant association ($p>0.05$).

with lower risk of colon cancer in association with higher serum 25(OH)D. One of these reported on the first 8 years of follow-up[4] and another reported on later years.[5] The slightly stronger association that was present in the first study suggests that 25(OH)D may exert an effect on cancer risk rather quickly, in the promotional stage.

Because data on serum 25(OH)D in individuals were not available from each study, midpoints of the quantiles were used for pooling. As a result, estimates of risk for each quantile may have been less accurate than if data points on each individual had been used. This is unlikely to have affected the overall dose–response relationship, but it may have obscured some of the detail in the highest and lowest quantiles of the distribution, such as changes in the shape of the dose–response curve at the high and low extremes.

Previous studies have reported lower risk of colorectal cancer in association with intense physical activity.[18–22] It has been suggested that the association of physical activity with risk of colon cancer could be indirect,[23] and possibly a result of higher serum 25(OH)D levels in people who have high levels of physical activity, if the exercise is performed outdoors and is associated with greater UVB exposure. Alternatively, intensive physical activity may have a beneficial role on risk of colorectal cancer that is independent of serum 25(OH)D, through an as yet unidentified mechanism.[23] The study by Feskanich et al.[7] controlled for physical activity, and reported that there was no influence of physical activity on the association between serum 25(OH)D and risk of colorectal cancer, although physical activity was independently predictive of risk in this cohort.

Calcium intake also is associated with lower risk of colorectal cancer.[24–30] There is some correlation ($r=+0.33$) between total oral intake of vitamin D and calcium,[31] because certain foods in the United States that contain substantial amounts of calcium, such as milk, are fortified with vitamin D. However, because 90%–95% of circulating vitamin D and its metabolites in general result from exposure to solar UVB,[32–34] there is little correlation between intake of calcium and serum 25(OH)D levels. Feskanich et al.[7] controlled for calcium intake and this did not influence the results for 25(OH)D. Tangrea et al.[6] found that calcium intake was identical (1300 mg/day) in cases and controls, and therefore could not account for the inverse association of serum 25(OH)D with risk. Results of the other studies were not adjusted for calcium intake.

Women are four times more likely than men to take calcium supplements,[35] yet the associations of 25(OH)D with colorectal cancer were about the same in men[6] as in

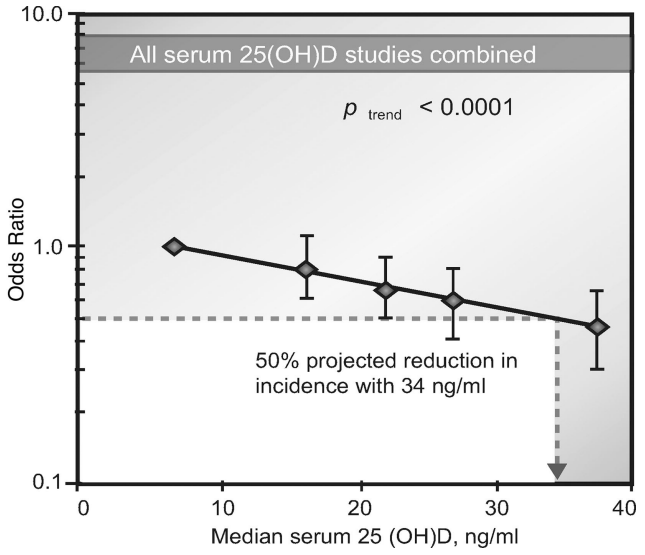

Figure 1. Dose–response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined.[1,4–7] The five points are the odds ratios for each quintile of 25(OH)D based on combined data from the five studies. (The anatomic site was the colon for studies by Garland et al.[4] and Braun et al.,[5] the distal colon and rectum for Tangrea et al.,[6] and the colon and rectum for Feskanich et al.[7] and Wactawski-Wende et al.[1])

women.[1,7] Therefore, the inverse association of 25(OH)D with risk of colorectal cancer could not have been accounted for solely by an effect of the calcium content of supplements that contain both calcium and vitamin D.

Evidence from oral intake studies of vitamin D is supportive of the serum results. A majority of observational studies have demonstrated an inverse association between intake of vitamin D and risk of colorectal cancer.[36] Many studies that found an association of oral intake of vitamin D with risk of colorectal cancer were conducted in populations that may have had a high prevalence of vitamin D inadequacy, such as populations living mainly at latitudes >40 degrees.[37–39] Studies of oral vitamin D intake that had equivocal findings had either adjusted for calcium[40–42] or had vitamin D intake mainly from fish products that may have contained nitrosoamines, which would tend to increase the risk of colorectal cancer.[43–45] Because vitamin D fortification is uncommon in Europe, these studies also had very low oral vitamin D intakes. One observational study[46] and a clinical trial using a low dose of vitamin D[1] found no association with colorectal cancer, probably because of the low dose.

Classical dose–response curves for micronutrients are either linear[47] or have a predominantly linear middle segment.[14,15] This appears to be true for most functions of vitamin D.[48,49] More studies of effects at higher vitamin D intakes are needed. In the meantime, our results suggest that a serum 25(OH)D level of ≥33 ng/mL could be associated with 50% lower incidence of colorectal cancer, compared to serum 25(OH)D <12 ng/mL.

Absence of Toxicity

According to an analysis of 30 studies reporting any adverse effect of high serum 25(OH)D in adults, no reproducible toxicity was reported below 100 ng/mL.[50] The median minimum threshold for toxicity in all studies was 197 ng/mL. Therefore, the projected serum 25(OH)D level of approximately 33 ng/mL would be below the threshold for minimal toxicity by a safety factor of 6.

A "No Adverse Effect Level" (NoAEL) level of 2000 IU/day of vitamin D has been established by the National Academy of Sciences (NAS).[51] The NAS reported that no illness from vitamin D intoxication has been described for intakes <3800 IU/day. One study reported that no cases of toxicity have ever been documented at doses <40,000 IU per day.[48]

A vitamin D3 intake of 1000–2000 IU/day, and a target of 33 ng/mL of serum 25(OH)D, are the most practical estimates now available for decision makers who wish to weigh the potential benefits compared to risks of actions that could reduce incidence of colon cancer. This translation of oral intake of vitamin D to serum 25(OH)D was computed from data on conversion of radiolabeled vitamin D_3 to 25(OH)D following its administration to volunteers.[33] Although the volunteers were White, it is likely that the findings would apply to those of other ethnicities, because the rate of conversion of vitamin D_3 to 25(OH)D is approximately the same in people of different ethnic groups.[52] Raising the current estimated median intake of 250–300 IU/day[53] of vitamin D to the current recommended daily intake of the National Academy of Sciences of 400 IU/day for mature adults[51] would increase median

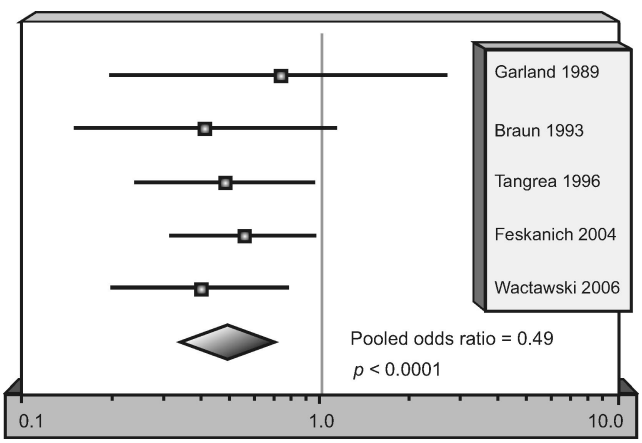

Figure 2. Forest plot of all studies of serum 25(OH)D and risk of colorectal cancer.[1,4–7] The upper and lower 95% confidence limits on the odds ratio are denoted by horizontal lines for each study, and the 95% confidence limits for the combined estimate for all studies are denoted by the points of the diamond. The odds ratios compare the highest quintile to the lowest.

serum 25(OH)D by only 5 ng/mL.[33] By contrast, an increase of the intake to 1000 IU/day of vitamin D3 would boost serum 25(OH)D by approximately 13 ng/mL, raising the estimated median level in the population to 33 ng/mL, which would keep virtually all of the population at levels below those associated with hypercalcemia or adverse health effects.[49–51,54,55]

Although a daily intake of 1000 IU would raise the median population serum levels to 33 ng/mL, this could be less than optimal because 50% of the population would still be below this median level. By contrast, an intake of 2000 IU/day, would raise the population median to 46 ng/mL. This is well below an intake level that would induce even mild hypervitaminosis.[51] Hypervitaminosis would be a concern, with intakes of 5000–10,000 IU per day and possibly higher, but not with 2000 IU per day.[49,50] Although every effort should be made to reduce the occurrence of mild hypervitaminosis, the consequences of vitamin D inadequacy are important enough that toleration of a small increase in the risk of mild hypervitaminosis may be needed.

The studies cited in this analysis are based on Whites. Intake of vitamin D should be greater for Black people and other individuals with more skin pigmentation than is typical in Whites, because such individuals have lower rates of photosynthesis of vitamin D3 in the skin.[56] However, the NAS has not provided separate guidelines for intake of vitamin D according to skin pigmentation, and therefore a recommendation for intake of >2000 IU per day cannot be made at this time.

Any effect of vitamin D on risk of colorectal cancer is not likely to occur in isolation. Other research has suggested that calcium and vitamin D tend to be somewhat synergistic in reducing incidence of colorectal cancer.[24,29,57,58] Low vitamin D status and low intake of calcium may contribute jointly to the high incidence of cancer of the colon and rectum in individuals who consume the typical Western diet in the United States and Europe.[30,59] In addition, the time period required to observe an effect on colorectal cancer risk following an increase in vitamin D intake is not known, but some evidence suggests that this could require ≥10 years.[60]

The findings of the study by Tangrea et al.[6] that the strongest association was for the distal colon and rectum suggest that the mechanism of vitamin D anticarcinogenesis may differ somewhat according to anatomic site in the large bowel. Cancers of the distal colon and rectum account for approximately two thirds of colorectal cancer,[61] and the high cancer incidence in these anatomic sites in individuals with low serum 25(OH)D may account for much of the overall association of vitamin D inadequacy with risk of colorectal cancer.

Overall, this meta-analysis supported the theory that there is an inverse association between serum 25(OH)D and risk of colorectal cancer. Although confounding is possible, there are three lines of epidemiologic evidence that support a causal basis for the association: the geographic gradient with latitude and solar UVB irradiance,[3,62–66] observational studies linking deficient serum 25(OH)D levels with increased risk,[1,4–7] and studies linking low oral intake of vitamin D with increased risk.[24,46,60,67–73] Also, vitamin D receptor polymorphisms that interfere with vitamin D utilization may increase risk of colorectal cancer, particularly in combination with low levels of serum 25(OH)D.[74,75] Finally, incidence of colorectal cancer is higher in African Americans,[76] who synthesize less vitamin D per minute spent in the sun.[56,77,78] It seems unlikely that a single confounder could account for all of these associations.

The epidemiologic findings regarding vitamin D and colon cancer are supported by numerous studies of the mechanisms in vivo and vitro.[79] For example, an experiment using human colon cancer cells (MC-26) grafted into Balb/C mice found that dietary vitamin D repletion reduced the volume of colon cancer-derived tumors by 40%.[80] Another experiment found that dietary vitamin D repletion reduced the volume of colon cancer xenografts in Balb/C mice by 60%.[81]

Vitamin D metabolites such as $1,25(OH)_2D$ are pleiotropic agents that induce cell cycle arrest and apoptosis in cancer cell lines vitro and to show antitumor activity against a variety of tumors in animal models.[82] Blinded experiments have revealed that increasing levels of serum $25(OH)_2D$ are associated with reduced epithelial cell proliferation and increased apoptosis in humans.[83,84] $1,25(OH)_2D$ is also effective in reducing the incidence of aberrant crypt foci induced by azoxymethane in rats.[85]

Based on overall consideration of results from observational and laboratory studies, the existing evidence is consistent with the hypothesis that increasing vitamin D_3 intake to 1000–2000 IU per day or raising the serum level of 25(OH)D to 33 ng/mL or higher would be associated with substantially lower incidence rates of colorectal cancer, with only minimal risks.

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