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Review

Could vitamin D sufficiency improve the survival of colorectal cancer patients?

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ABSTRACT

Purpose: To determine whether a higher serum 25-hydroxyvitamin D [25(OH)D] concentration at diagnosis is associated with longer survival of colorectal cancer patients.
Methods: A meta-analysis was performed of studies of the relationship between 25(OH)D and mortality of patients with colorectal cancer. A random-effects model was used to calculate a pooled hazards ratio. Homogeneity was evaluated through a DerSimonian–Laird test.
Results: Higher serum concentrations of 25(OH)D were associated with lower mortality in patients with colorectal cancer. Patients in the highest quintile of 25(OH)D had 37% lower mortality from colorectal cancer compared to those in the lowest quintile of 25(OH)D (pooled odds ratio = 0.63, $p < 0.0001$). Dose–response curves showed lower hazard ratios for mortality with higher serum 25(OH)D through at least 40 ng/ml. There were no exceptions.
Conclusions: Higher serum 25(OH)D was associated with lower mortality of patients with colorectal cancer. These results suggest that colorectal cancer patients with deficient levels of serum 25(OH)D should have their levels restored to a normal range (30–80 ng/ml). This could be done with regular testing of serum 25(OH)D to be confident that an adequate serum level is being maintained. Additional studies would be worthwhile to evaluate confounding or the possibility of reverse causation.

Contents

1. Introduction

There will be an estimated 50,310 deaths from colorectal cancer in the United States in 2014 [1], making it the third most common cause of death from cancer [1]. Previous ecological studies have shown an inverse relationship between exposure to ultraviolet B (UVB) irradiance and increased risk of colorectal cancer [2–11]. Colorectal cancer incidence and mortality rates

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tend to be higher in areas with low winter sunlight levels, and lower in sunny areas [12].

Over 80% of serum 25-hydroxyvitamin D [25(OH)D], the principal metabolite of vitamin D, is attained via dermal exposure to solar ultraviolet B [13]. Serum 25(OH)D increases in a dose-dependent relationship with UVB exposure and dietary vitamin D [14]. Once vitamin D is photosynthesized in the skin by contact with UVB radiation, it is converted in the liver to the main circulating vitamin D metabolite, 25(OH)D, which is thought to prevent cancer through up-regulation of e-cadherins, transmembrane proteins that help maintain cells in a well differentiated state by strengthening tight junctions between them [15].

Some of the circulating 25(OH)D is further metabolized by the enzyme 1-α-hydroxylase into 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$], the most biologically active vitamin D metabolite, although this metabolite is present in the circulation in approximately 1/1000th the concentration of 25(OH)D [16]. The principal site of $1,25(OH)_2D$ synthesis via 1-α-hydroxylase is the kidney, but production of the hormone occurs in a wide range of tissue including colonic epithelial tissue [17,18] which has vitamin D receptors that are highly sensitive to $1,25(OH)_2D$. A wide range of anti-carcinogenic properties are exhibited by $1,25(OH)_2D$ such as promotion of differentiation and induction of apoptosis in colon cancer cell lines. Moreover, Cross and colleagues found that expression of 1-α-hydroxylase is up-regulated in colon cancer cells [19], providing a strong basis for the role of high serum 25(OH)D concentrations in reducing mortality and improving survival in patients with colorectal cancer.

Ecological findings are useful for generating hypotheses; these studies led to the hypothesis that inadequate sunlight exposure and low serum vitamin D metabolite levels may substantially increase risk of colorectal cancer. While large numbers of modern ecological studies control for a number of confounders, it is worthwhile to note the challenge in exhaustive inclusion of confounders, especially for non-communicable chronic diseases like colorectal cancer. Furthermore, while ecological analyses are useful for identifying broad trends, individual areas may be chosen where the trend may not apply. For example, given the notably low rate of insurance coverage in the United States compared to other developed countries, it is plausible that this factor may confound the observed global trend with regard to colorectal cancer mortality. Other country-specific confounders may also confound this trend. For these reasons, it is important that laboratory studies and observational studies in individuals be assessed before drawing conclusions.

Fortunately, in the case for vitamin D's effect on colorectal cancer, evidence from epidemiological studies in individuals has been largely supportive. The majority of observational studies of serum 25(OH)D concentration or oral vitamin D intake [20–26] found significant, inverse relationships between vitamin D and risk colorectal cancer. While most studies have focused on the relationship between vitamin D and incidence of colorectal cancer, only a few studies have investigated the possible relationship between serum 25(OH)D status and colorectal cancer survival rates. To date, four studies have investigated the relationship between serum 25(OH)D and colorectal cancer mortality [27–30]. Two found a statistically significant inverse relationship between 25(OH)D concentrations and mortality from colorectal cancer [27,29]. The other two studies also found an inverse relationship that was not statistically significant [28,30].

Our hypothesis is that increased serum 25(OH)D concentrations substantially reduce mortality and improve survival in patients diagnosed with colorectal cancer. Therefore, the primary aim of this meta-analysis was to test our hypothesis by pooling results from all eligible studies published in medical journals on the association between 25(OH)D status and colorectal cancer survival.

2. Materials and methods

Several criteria were used to search for observational studies on the relationship between colorectal cancer risk and 25(OH)D. PubMed was used to select articles published between 1966 and 2014. The following search terms were used as medical subject headings (MeSH): ("Vitamin D" or "cholecalciferol" or "calcidiol" or "calcitriol" or "25-hydroxyvitamin D"), and ("case-control" or "epidemiology") and "human." These terms were used combined with the following subject terms: "colorectal neoplasms," "cancer," "survival," and "mortality."

Though biological and epidemiological evidence exists to suggest that increased exposure to solar UVB will increase levels of vitamin D, there would exist limitations if solar UVB measures were solely used to predict cancer survivability. For example, measures of solar UVB may function as proxy measures for physical activity, which likely has independent anticarcinogenic effects. Furthermore, the health effects from solar UVB exposure vary across levels of age, skin pigmentation, and clothing cover. For these reasons, it was decided that studies would be eligible for inclusion in this meta-analysis only if they directly analyzed serum 25(OH)D levels. Inclusion was also dependent upon reporting hazard ratios (HRs) by serum 25(OH)D quantiles, being a prospective or historical follow-up study, and being published in a medical journal. Search yields and subsequent exclusions are detailed in Fig. 1.

2.1. Statistical analysis

All HRs were plotted against serum 25(OH)D on a single graph. A pooled HR was computed by using individual HRs that compared the lowest category 25(OH)D to the highest, and by using the variance and O-E method for combining studies [31–32], an application of the Peto method [33]. An overall variance and O-E was determined through the individual HRs and their 95% confidence intervals (CIs) [34]. A *z*-score was calculated for the pooled HR by dividing its natural logarithm by its standard error, a method which has been used previously [35]. A forest plot was created to inspect the differences between HRs [36,37]. Homogeneity of studies was determined through a DerSimonian–

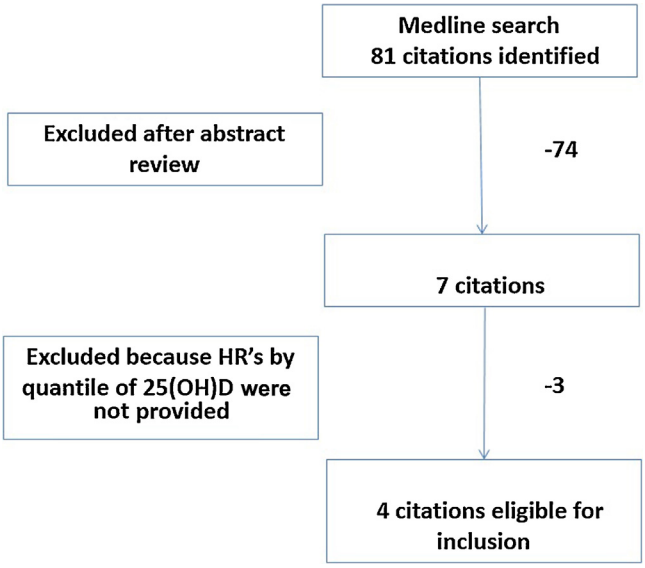

Fig. 1. Flow chart of literature review.

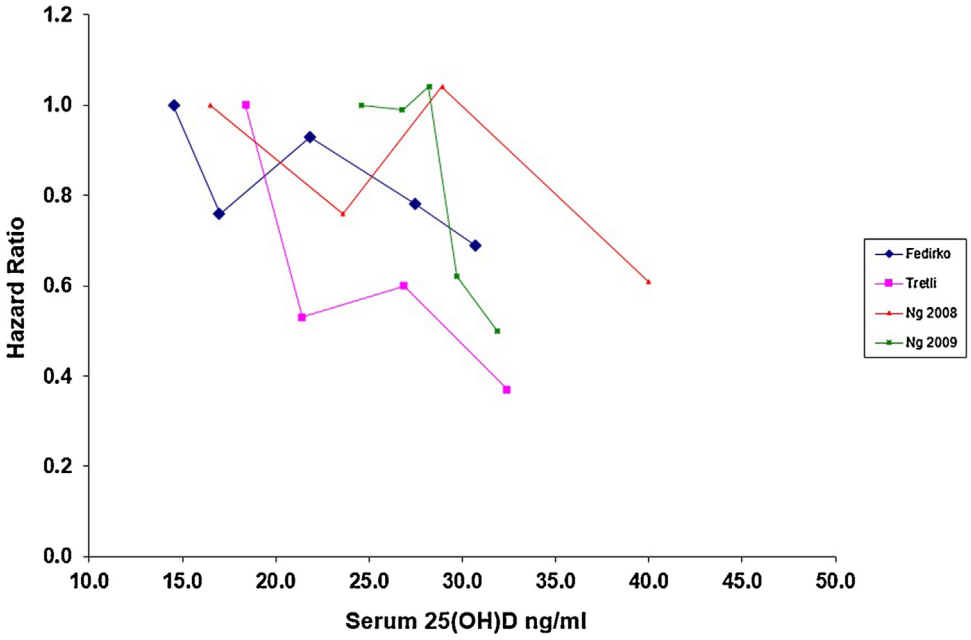

Fig. 2. Dose–response curves of 25-hydroxyvitamin D concentration at diagnosis with survival, patients with colorectal cancer, individual studies.

Laird test [38]. Rev Man 5 was used for these computations (Oxford, England: The Cochrane Collaboration).

2.2. Dose–response

A pooled estimate for dose–response between colon cancer mortality and serum 25(OH)D was calculated by obtaining the mean for each HR quantile and the mean midpoint or median for individual HR quantiles. We used the highest quantile as the reference group. If a study used the lowest quantile instead, we calculated the inverse HR. The mean upper and lower bounds for quantile HR 95% CIs was obtained in order to calculate 95% CIs for mean HRs. SAS version 9.2 was used for these calculations (Cary NC: SAS Institute).

3. Results

Four eligible studies were identified by the literature search (Fig. 1). Of the four studies performed on the relationship between serum 25(OH)D and colorectal cancer mortality, two [27–30] found a statistically significant reduction in mortality with increasing 25 (OH)D concentrations, while the other two studies found an inverse relationship between 25(OH)D and colorectal cancer mortality that did not reach statistical significance [28,30] (Fig. 2).

A total of 2575 colorectal cancer patients were included in this analysis (Table 1). The mean length of follow-up time for the three studies that reported follow-up time was 7.4 years. Individuals in the highest category of serum 25(OH)D concentration had a substantially lower risk of mortality from colorectal cancer. The overall pooled HR summarizing the estimated risk in the highest

Table 1
Characteristics of studies of serum 25-hydroxyvitamin D and colorectal cancer prognosis, according to PubMed search, 1966–2014.

First author	Year	Study design	Length of follow-up (years)	Adjustment	Number of events/patients	25(OH)D Quantile (ng/ml)	Hazard ratio	95% Confidence Interval	
								Lower	Upper
Ng [27]	2008	PC[a]	6.5	Age, sex, tumor stage, tumor grade, BMI, season of blood draw, vitamin D intake, race, physical activity, location of tumor	123/304	16.4	1	–	–
						23.6	0.76	0.41	1.42
						28.8	1.04	0.58	1.89
						40	0.61	0.31	1.19
Ng [28]	2009	PC	9.7	Age, sex, tumor stage, tumor grade, tumor location, year of diagnosis	119/1017	24.6	1	–	–
						26.8	0.99	0.58	1.68
						28.2	1.04	0.61	1.78
						29.7	0.62	0.34	1.11
						31.9	0.5	0.26	0.95
Fedirko [29]	2012	PC	6.1	Age, sex, tumor stage, tumor location, BMI, season of blood draw, race, physical activity, location of tumor, smoking, calcium intake	541/1202	11.6	1	–	–
						17.2	0.76	0.56	1.02
						22	0.93	0.69	1.24
						27.2	0.78	0.58	1.06
						39.6	0.69	0.5	0.93
Tretli [30]	2012	PC	Not provided	Age, season of blood draw, sex, tumor stage, time between sampling and 25(OH)D measurement	26/36	<17.6	1	–	–
						17.6-22.4	0.46	0.15	1.48
						22.5-30.4	0.73	0.25	2.15
						>30.4	0.2	0.04	1.1

[a] PC: Prospective cohort.

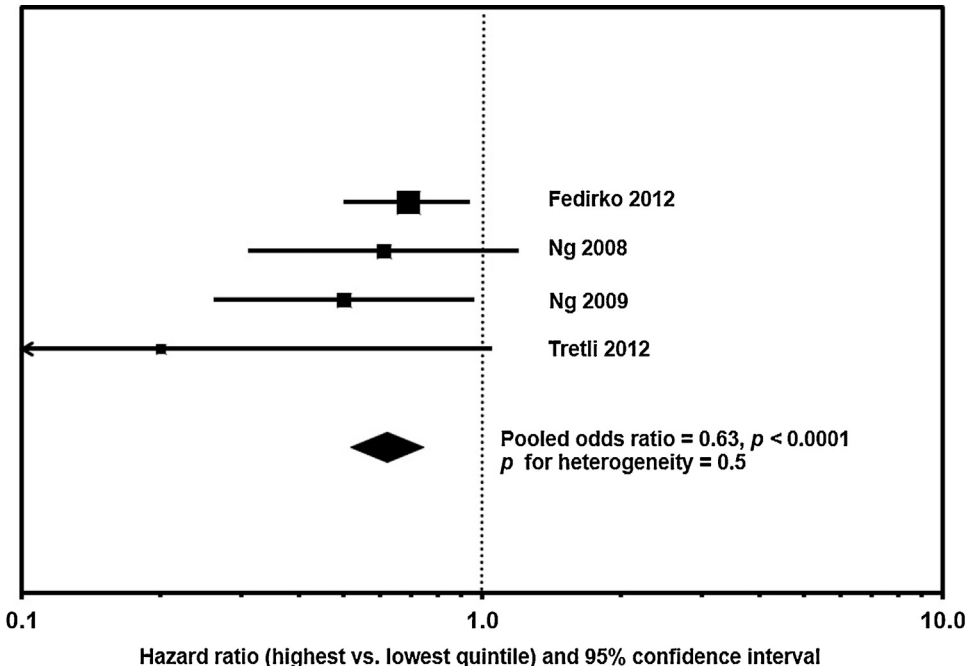

Fig. 3. Association of serum 25-hydroxyvitamin D concentration at diagnosis with hazard ratios for mortality, patients with colorectal cancer, comparing highest with lowest quintiles.

compared to the lowest category of 25(OH)D across all studies was 0.63 (HR 95% CI 0.5–0.8, $p < 0.0001$) (Fig. 3). The DerSeimonian–Laird test indicated homogeneity in all studies (chi-square = 2.67, $p = 0.5$). A fixed-effects model produced similar results. Furthermore, the combined dose–response curve revealed a strong inverse association between serum 25(OH)D concentrations and colorectal cancer mortality ($R^2 = 0.65$; $p < 0.001$) (Fig. 4). A funnel plot revealed no strong indication of publication bias (Appendix Fig. A1).

4. Discussion

In this meta-analysis, higher serum 25(OH)D concentrations were associated with lower risk of mortality in patients with colorectal cancer. Patients with the highest concentration of 25 (OH)D experienced a 47% reduction in mortality when compared to patients with the lowest concentrations of 25(OH)D. A meta-analysis has the advantage of larger numbers and, therefore, higher precision than any individual study. Nevertheless, associations

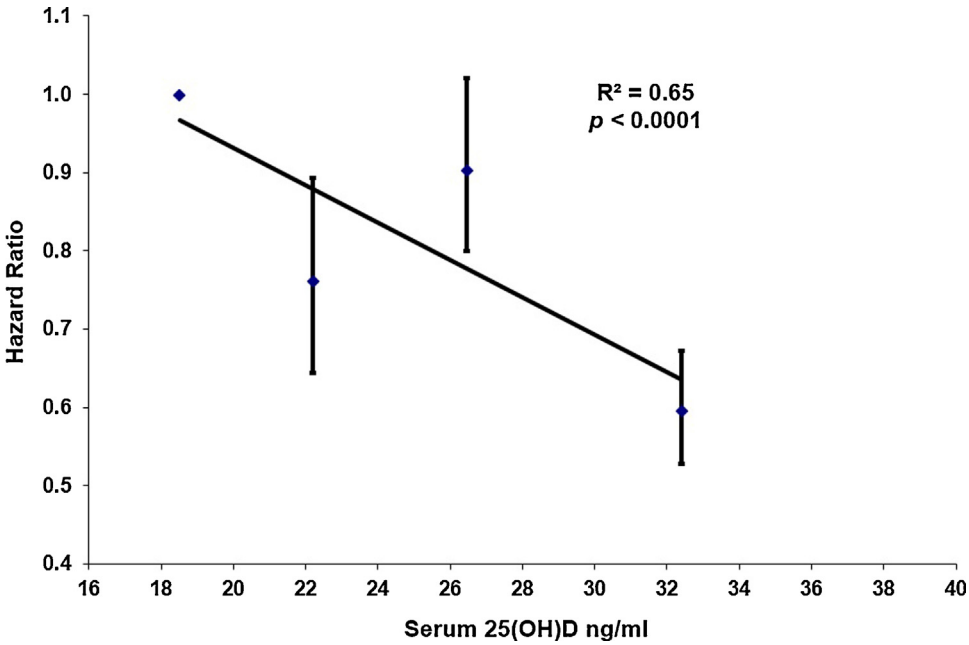

Fig. 4. Pooled dose–response relationship of serum 25-hydroxyvitamin D concentration with hazard ratios for mortality, patients with colorectal cancer.

from a meta-analyses are subject to validity challenges that are common among the studies it analyzes. In this case, the studies analyzed do not comprehensively assess for confounding anticarcinogenic and carcinogenic effects from biological and behavioral factors unrelated to serum 25(OH)D. Therefore, while these results are encouraging for a protective role of vitamin D sufficiency, their interpretation warrants caution.

Furthermore, laboratory studies have demonstrated anticancer effects of vitamin D metabolites, especially $1,25(OH)_2D$, on three critical phases in the development of colorectal tumors: differentiation, apoptosis, and angiogenesis [39–42]. Cross et al. demonstrated that the enzyme responsible for conversion of 25(OH)D to $1,25(OH)_2D$, 1-α-hydroxylase, is upregulated in colon cancer cells [19].

On the other hand, the results of this study could have resulted from reverse causation. It is possible that the serum 25(OH)D concentration in more serious cases were lowered as a result of the tumor itself resulting in death early in the natural history of the disease. If that were so, the serum 25(OH)D could be a biomarker for severity of the cancer, rather than a factor that caused the longer survival. However, this is unlikely and there is no biological basis for such a phenomenon. A clinical trial showed that 1000 IU of vitamin D, along with calcium, resulted in a 77% reduced incidence of all invasive cancers, including colon cancer [43]. Although this study points to a general anticarcinogenic effect of vitamin D, it does not necessarily lend itself to suggest that vitamin D improves colorectal cancer survival, especially as the outcome of the trial was incidence rather than survivability. As the National Academy of Sciences suggests an upper-level dose of 10,000 IU per day of vitamin D, it may be prudent to conduct a similar clinical trial at this dose [44]. In addition, no laboratory study has proven reverse causation, showing that tumor presence reduces 25(OH)D concentration. Furthermore, cancer mortality is lower in areas of the US with higher levels of UVB [2], which is not explained by reverse causation. A similar association exists globally [11].

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Appendix.

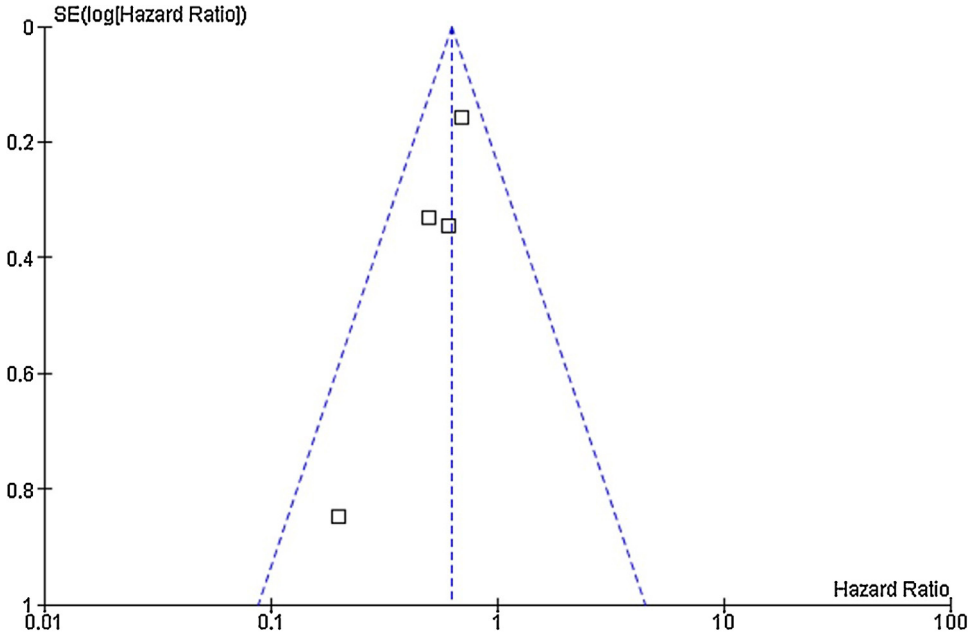

Fig. A1. Funnel plot of studies included in the meta-analysis.

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