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Vitamin D and Colorectal Cancer Prevention: A Review of Epidemiologic Studies

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Abstract Vitamin D is hypothesized to prevent cancer development, and its potential anticarcinogenic effect against colorectal cancer has been explored in epidemiologic studies. Epidemiologic studies found that a low circulating level of 25-hydroxyvitamin D was associated with higher risk of colorectal cancer, whereas the association for vitamin D intake has not been as clear as for circulating vitamin D levels. A large intervention study on vitamin D supplementation and colorectal cancer did not show a protective benefit against colorectal cancer development, but several possible explanations remain open. Genetic polymorphisms in the pathway of vitamin D metabolism also have drawn attention, and single polymorphism studies and Genome Wide Association Studies (GWAS) have been conducted. Given a relatively high prevalence of vitamin D insufficiency among industrialized populations, further research on the optimal dose and duration of vitamin D supplementation, interaction with other nutrients or genes, and the appropriate timing of vitamin D interventions is warranted.

Keywords Vitamin D · 25-hydroxyvitamin D · Colorectal cancer · Colorectal adenoma · Epidemiology

Introduction

Colorectal cancer is the third most common cancer in men and the second most common in women [1•]. A more than tenfold variation in colorectal cancer incidence rates across countries and the rapid increase in incidence rates in countries experiencing industrialization suggest a strong link with lifestyle factors.

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Vitamin D is hypothesized to prevent colorectal cancer development, and its potential anticarcinogenic effect against colorectal cancer has been explored in epidemiologic studies. Vitamin D is produced by exposing the skin to ultraviolet radiation, which is required for conversion of 7-dehydrocholesterol into cholecalciferol in the skin. Cholecalciferol is hydroxylated to 25-hydroxyvitamin D, and subsequently to 1,25-dihydroxyvitamin D. The vitamin D receptor binds to 1,25-dihydroxyvitamin D and interacts with target-cell nuclei and mediates the biological actions of vitamin D. Vitamin D may reduce the risk of colorectal cancer through regulation of progression and differentiation [2] and inhibition of angiogenesis [3]. In animal studies, vitamin D (the vitamin D3 analogue; EB 1089) improved tumor control by radiation treatment, possibly by promoting apoptosis [4].

Sources of vitamin D include food, supplements, and ultraviolet radiation. Vitamin D intake from natural foods is somewhat limited, because only a few food items contain vitamin D, such as fatty fish, mushrooms, egg yolks, and liver. Vitamin D-fortified foods or supplements contribute to vitamin D intake in countries where fortification and supplemental use are common. Sunlight is the major determinant of vitamin D status, and therefore, skin pigmentation, season, geographic latitude, and sunscreen use are important determinants of circulating vitamin D levels. Serum or plasma levels of 25-hydroxyvitamin D are regarded as a useful biomarker of vitamin D status integrating intake through foods, supplements, and exposure to ultraviolet light.

Because of shaded environments, sedentary lifestyle, and high indoor activity, growing concerns about the prevalence of vitamin D insufficiency and deficiency have recently surfaced. Along with this issue, accumulating epidemiologic evidence suggests elevated risks of cancers of several sites among individuals with low levels of vitamin D. In particular, a well-maintained vitamin D status has been most consistently found to be associated with lower risk of colorectal neoplasia

compared with other cancer sites, and systematic reviews have documented the possibility that this hypothesis could be true. The hypothesis of a potential role of vitamin D has been extended to research on genetic polymorphisms in the pathway of vitamin D metabolism and colorectal cancer.

Vitamin D Levels

The Institute of Medicine (IOM) recently issued a new recommended daily allowance of vitamin D and determined a sufficiency threshold at 20 ng/ml (50 nmol/l) of serum 25-hydroxyvitamin D [5••, 6]. The IOM recommended 600 IU of vitamin D daily for all ages up to age 70 years and 800 IU after age 70 years. The Centers for Disease Control and Prevention issued its Second National Report on Biochemical Indicators of Diet and Nutrition and reported that the national mean 25-hydroxyvitamin D level of the U.S. population aged 1 year or older, estimated from the U.S. National Health and Nutrition Examination Survey 2003–2006, was 22 ng/ml and that the prevalences of <12 g/ml and 12 to <20 ng/ml of 25-hydroxyvitamin D were 8.1 % and 23.6 %, respectively [7]. Low vitamin D status also was observed in several Asian countries. The Korean National Health and Nutrition Examination Survey showed that 47 % of men and 65 % of women aged 10 years or older had lower than 20 ng/ml of 25-hydroxyvitamin D [8]. A Chinese study in Shanghai observed that 30 % of men and 46 % of women had <20 ng/ml of 25-hydroxyvitamin D [9]. Vitamin D insufficiency also was prevalent in Japan [10] and the Middle East [11].

Ecological Studies

Ecological studies provided basic insight on sunlight and colorectal cancer, facilitating further analytic studies. In 1980, Garland and Garland showed higher mortality rates of colon cancer in U.S. regions with low solar radiation [12]. In addition, deaths from colon cancer were higher in industrialized areas than rural areas. Recent work incorporated ultraviolet radiation data and examined ultraviolet exposure and cancer mortality in the United States [13]. The author obtained ultraviolet radiation data for July 1992 from the Total Ozone Mapping Spectrometer (TOMS) of the National Aeronautics and Space Administration (NASA) and the U.S. Department of Agriculture (USDA) and calculated correlations with colon or rectal cancer mortality between 1970 and 1994, showing inverse correlations. Ecological studies in Japan [14] and China [15] also showed an inverse correlation between ambient ultraviolet radiation intensity and colon cancer mortality. Notably, in the Chinese study, the inverse correlation was observed only among rural residents and not urban residents [15], suggesting a lack of sun exposure linked to industrialization. Existence of confounding factors and misclassification of exposures due to nonindividual ultraviolet levels are major limitations in ecologic studies.

Observational Studies

Vitamin D Intake and Colorectal Adenoma and Cancer

The majority of colorectal cancers evolve from colorectal adenoma and screening and subsequent removal of colorectal adenoma prevents colorectal cancer. Prospective research on colorectal adenoma is more difficult than colorectal cancer because of its asymptomatic nature and the absence of linkage to national statistical data. Many observational studies examined the presence of colorectal adenoma rather than the development of adenoma among participants who underwent colonoscopy or sigmoidoscopy.

Case–control and cohort studies examined vitamin D intake from food or supplements in relation to colorectal adenoma and cancer. Relatively fewer studies examined colorectal adenoma compared with colorectal cancer. Several studies obtained vitamin D intake from participants at the time when they underwent endoscopy [16, 17] or after diagnosis [18]. Other studies assessed vitamin D intake from questionnaires or interviews 12 months or more before diagnosis of adenoma [19–23]. A few studies prospectively examined recurrent adenoma among participants diagnosed with adenoma and found mixed results [24–27]. A summary relative risk (RR) of 0.89 (95 % confidence interval (CI)=0.78-1.02) for total vitamin D intake in relation to colorectal adenoma was observed in a meta-analysis of 12 observational studies [28].

Dietary vitamin D from food was inversely associated with colorectal cancer, whereas the associations for total vitamin D from food and supplements or vitamin D from supplements were not conclusive. A systematic review of cohort studies found that dietary vitamin D from food was inversely associated with colorectal cancer; however, statistical significance was not reached for total vitamin D intake from foods and supplements [29]; the RRs (95 % CIs) for an increase of 100 IU/d were 0.95 (0.93-0.98) for dietary vitamin D from food and 0.98 (0.95-1.01) for total vitamin D from food and supplements. In this meta-analysis of total vitamin D and colorectal cancer, when one study was excluded from the analysis, heterogeneity across studies was reduced and the summary RR became statistically significant (RR=0.97; 95 % CI=0.95-0.99). For vitamin D supplement use, findings have been inconsistent [30–37]. Lack of an association for vitamin D supplements could be related to the possibility of confounding factors if a certain medical condition or behavior could motivate individuals' supplemental use. Also, there is a possibility that vitamin D intake from food or supplements could be limited in reflecting individuals' vitamin D status.

Circulating Vitamin D Levels and Colorectal Adenoma and Cancer

For colorectal adenoma research, circulating levels of vitamin D often are measured when individuals undergo endoscopy. Blood collection at endoscopy does not necessarily indicate vitamin D status before development of adenoma. Most observational studies except the Nurses' Health Study [38], and the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial [39] investigated the association in a cross-sectional manner. Table 1 shows studies on circulating vitamin D levels and colorectal adenoma. Most studies were conducted in multiple regions in the United States and one study was performed in Japan. Four investigations were prospective studies and five were case–control studies. Among the four prospective studies, two studies were trials of adenoma recurrence (treatment reagents were ursodeoxycholic acid in one study [27] and calcium carbonate in the other study [40]), and the other two studies [38, 39] were prospective studies that followed participants with updated information on sigmoidoscopy or colonoscopy. In the Nurses' Health Study that analyzed 25-hydroxyvitamin D levels in blood specimens stored and subsequently followed adenoma development [38], the RRs (95 % CIs) for each subsequent quartile compared to the lowest quartile were 0.64 (0.41-1.0), 0.58 (0.36-0.95), and 1.04 (0.66-1.66). The PLCO study found a decreasing risk of advanced distal colorectal adenoma with increasing serum 25-hydroxyvitamin D levels in women (OR=0.27; 95 % CI=0.11-0.69; p for trend=0.0002). In five case–control studies, blood samples of participants were collected at or after diagnosis of colorectal adenoma. A recent meta-analysis of studies on circulating levels of 25-hydroxyvitamin D and colorectal adenoma found a significant inverse association with colorectal adenoma [28, 41].

Several nested case–control studies that collected blood samples before diagnosis of colorectal cancer examined whether high circulating 25-hydroxyvitamin D levels before development of colorectal cancer prevented risk of colorectal cancer (Table 2). The majority of study populations was Caucasian [42–48], one was a multiethnic population [49], and the other was Japanese [50]. In the Japanese study, the odds ratio (OR (95 % CI)) was 0.73 (0.35-1.5) in men and 1.1 (0.50-2.3) in women, comparing the top with the bottom quartiles. Further prospective study is warranted for other ethnic groups. Summary evidence showed an inverse association for colorectal cancer, with a stronger association for rectal cancer [51]; inclusion of prospective studies with 1,822 colon and 868 rectal cancers showed that increasing circulating 25(OH)D levels were associated with a significant reduction in colorectal cancer (OR=0.66, 95 % CI=0.54–0.81 for top vs. bottom categories) [51]. The inverse association was stronger for rectal cancer (OR=0.5; 95 % CI=0.28–0.88 for top vs. bottom categories) than colon cancer (OR=0.77; 95 % CI=0.56–1.07 for top vs. bottom categories). Given insufficient statistical power to detect interactions in individual studies, the joint effects of vitamin D status with insulin-like growth factor, retinol, calcium, and genetic polymorphisms merit further investigation. A pooled analysis of existing cohort studies may provide etiologic insight into potential interactions with other relevant factors.

Intervention Studies

A large, randomized, double-blind, intervention trial of 36,282 postmenopausal women did not support the hypothesis of reduction in colorectal cancer with vitamin D supplementation [47]. Specifically, a daily dose of 1000 mg of calcium plus 400 IU of vitamin D for an average of 7 years did not lower colorectal cancer development compared to the placebo group. However, the same data analyzed in a nested case–control design showed a 2.5 times higher risk of colorectal cancer among postmenopausal women with low baseline serum 25-hydroxyvitamin D levels (<31 nmol/l) compared with those with high levels (58.4 nmol/l or more) [47], suggesting the possibility that a duration of 7 years was not sufficient to reduce risk in a trial. Several other explanations of a lack of effect in this trial are possible; 400 IU of vitamin D may not be adequate to create a contrast in the likelihood of colorectal cancer development between intervention and control arms. Furthermore, additional benefit above a certain level of vitamin D could be minimal if postmenopausal women participating in this trial had already kept vitamin D replete. Low benefit of vitamin D among those who used estrogen therapy also has been suggested [52]. A reanalysis of the Women's Health Initiative trial of vitamin D and calcium supplementation showed a nonsignificant higher risk of colorectal cancer among those who received vitamin D and calcium supplementation and were concurrently assigned to estrogen therapy, but a nonsignificant lower risk of colorectal cancer among those who received vitamin D and calcium supplementation and were concurrently assigned to the placebo group of the estrogen trial [52]. This apparent interaction of estrogen therapy with calcium and vitamin D supplementation warrants further investigation.

Studies of Genetic Polymorphisms

Genetic polymorphisms related to vitamin D production pathways or vitamin D metabolites have been examined. Of the vitamin D receptor polymorphisms studied, inconsistent findings were observed for FokI, PolyA, TaqI, Cdx2, and ApaI, and colorectal adenoma or cancer [39, 53–56]. Summary evidence indicated that the BsmI vitamin D

Table 1 Studies of circulating levels of 25(OH)D and risk of colorectal adenoma

First author, year [ref no.]	Country (Sex)	Study design	Endpoint	Type of endoscopy	Age at blood donation in controls (yr)	No. of cases / controls	25(OH)D, mean or median	RR (95 % CI)
Platz 2000 [38]	USA (W)	Prospective	First adenoma	Sigmoidoscopy or colonoscopy	58.5 in 1990, mean	326 / 326	26.4 in cases and 26.8 ng/mL in controls, mean	Quartile Q1: 1.00 Q2: 0.64 (0.41-1.00) Q3: 0.58 (0.36-0.95) Q4: 1.04 (0.66-1.66)
Levine 2001 [19]	USA (M, W)	Case–control	First adenoma	Sigmoidoscopy	61.8, mean	473 / 506	25.6 in cases and 26.9 ng/mL in controls, mean	Quartile Q1: 1.00 Q2: 0.99 (0.68-1.44) Q3: 0.86 (0.59-1.26) Q4: 0.74 (0.51-1.09)
Peters 2001 [20]	USA (M, W)	Case–control	First (61 %) or recurrent adenoma	Colonoscopy (86.2 %) or sigmoidoscopy	57, median	236 / 218	24.7 in cases and 26.5 ng/mL in controls, median	Quintile Q1: 1.00 Q2: 0.40 (0.22-0.74) Q3: 0.67 (0.38-1.19) Q4: 0.47 (0.26-0.85) Q5: 0.43 (0.23-0.81)
Grau 2003 [40]	USA (M, W)	Prospective	Recurrent adenoma	Colonoscopy	61, mean	376 / 422	29.1 ng/mL, median	Median <Med: 1.05 (0.85-1.29) >Med: 0.71 (0.57-0.89)
Peters 2004 [39]	USA (M, W)	Prospective	First adenoma	Sigmoidoscopy	62.3, mean	394 / 397	27.0 in cases and 28.3 ng/mL in controls, mean	Quintile Men Q1:1.00 Q2:0.73 (0.41-1.32) Q3:1.08 (0.61-1.90) Q4:0.89 (0.49-1.64) Q5:1.10 (0.6-2.05) Women Q1:1.00 Q2:0.93 (0.39-2.22) Q3:0.56 (0.22-1.44) Q4:0.28 (0.11-0.75) Q5:0.27 (0.11-0.69)
Jacobs 2007 [27]	USA (M, W)	Prospective	Recurrent adenoma	Colonoscopy (97.7 %) and sigmoidoscopy[a]	66.0, mean	210 / 358		Tertile T1: 1.00

Table 1 (continued)

First author, year [ref no.]	Country (Sex)	Study design	Endpoint	Type of endoscopy	Age at blood donation in controls (yr)	No. of cases / controls	25(OH)D, mean or median	RR (95% CI)
							26.9 ng/mL in men, and 25.1 ng/mL in women, mean	T2: 0.74 (0.47-1.16) T3: 0.74 (0.46-1.17)
Miller 2007 [61]	USA (M, W)	Case–control	First adenoma	Colonoscopy	54.4, mean	111 / 238	27.5 in cases and 31.4 ng/mL in controls, mean	Tertile T1: 1.00 T2: 0.74 (0.4-1.38) T3: 0.51 (0.27-0.98)
Takahashi 2010 [62]	Japan (M, W)	Case–control	First adenoma	Colonoscopy	51.8, mean	656 / 648	26.2 in cases and 26.1 ng/mL in controls, mean	Quartile Q1: 1.00 Q2: 1.21 (0.86-1.70) Q3: 1.21 (0.87-1.69) Q4: 1.25 (0.85-1.84)
Fedirko 2010 [63]	USA (M, W)	Case–control	First adenoma	Colonoscopy	53.6, mean	616 / 770	24.5 in cases and 25.5 ng/mL in controls, mean	Quartile Q1: 1.00 Q2: 0.77 (0.55-1.09) Q3: 0.85 (0.6-1.2) Q4: 0.59 (0.41-0.84)

M, men; W, women

[a] Information was obtained from Alberts et al. [64]

Table 2 Prospective studies of circulating levels of 25-hydroxyvitamin D and risk of colorectal cancer

Study name[a]	First author, year [ref no.]	Country (Sex)	Age at blood donation in controls (yr)	Study dates (follow-up)	No. of cases and controls	25(OH)D, mean or median	RR (95 % CI)
CLUE A[b]	Garland, 1989 [42]	USA (M, W)	74.7 % in 45–74 yr	1975-1983	34 / 67	30.5 in cases and 33.3 ng/mL in controls, mean	Quintile Q1: 1.00 Q2: 0.48 Q3: 0.25 Q4: 0.21 Q5: 0.73
CLUE B[b]	Braun, 1995 [43]	USA (M, W)	55, median	1984-1991	57 / 114	23.6 in cases and 23.2 ng/mL in controls, mean	Quintile Q1: 1.0 Q2: 0.3 (0.1-1.0) Q3: 0.5 (0.2-1.5) Q4: 0.7 (0.2-2.0) Q5: 0.4 (0.1-1.4)
ATBC[b]	Tangrea, 1997 [44]	Finland (M)	60, median	1985-1993	146 / 290	12.1 in cases and 13.8 ng/mL in controls, mean	Quartile Q1: 1.0 Q2: 1.3 (0.8-2.4) Q3: 1.2 (0.7-2.2) Q4: 0.9 (0.5-1.7)
NHS[c]	Feskanich, 2004 [45][d]	USA (W)	60.0, mean	1989-2000	193 / 383	23.6 in cases and 24.3 ng/mL in controls in lab1, 27.0 in cases and 30.3 ng/mL in controls in lab2, mean	Quintile Q1: 1.00 Q2: 0.93 (0.53-1.63) Q3: 0.79 (0.44-1.4) Q4: 0.58 (0.31-1.07) Q5: 0.53 (0.27-1.04)
HPFS[c]	Wu, 2007 [46]	USA (M)	66.1, mean	1993-2002	179 / 356	28.7 in cases and 29.4 ng/mL in controls, mean	Quintile Q1: 1.00 Q2: 0.97 (0.55-1.7) Q3: 0.66 (0.35-1.24) Q4: 0.51 (0.27-0.97) Q5: 0.83 (0.45-1.52)
WHI[b]	Wactawski-Wende, 2006 [47][e]	USA (W)	50-79, range	1993-2005	306 / 306	N/A	Quartile Q1: 2.53 (1.49-4.32) Q2: 1.95 (1.18-3.24) Q3: 1.96 (1.18-3.24) Q4: 1.00
JPHS[c]	Otani, 2007 [50]	Japan (M)	56.9, mean	1990-2003	196 / 392	27.3 in cases and 27.6 ng/mL in controls, median	Quartile Q1: 1.00

Table 2 (continued)

Study name[a]	First author, year [ref no.]	Country (Sex)	Age at blood donation in controls (yr)	Study dates (follow-up)	No. of cases and controls	25(OH)D, mean or median	RR (95% CI)
							Q2: 0.76 (0.42-1.4)
							Q3: 0.76 (0.39-1.5)
							Q4: 0.73 (0.35-1.5)
		Japan (W)	56.4, mean	1990-2003	179 / 358	22.5 in cases and 22.3 ng/mL in controls, median	Quartile
							Q1: 1.00
							Q2: 1.00 (0.55-1.9)
							Q3: 1.20 (0.65-2.3)
							Q4: 1.10 (0.5-2.3)
EPIC[b,c]	Jenab, 2010 [48][e]	Europe (M, W)	58.7 for colon, 58.0 for rectum, mean	1992-2003	1248 / 1248	20.7 in cases and 22.9 ng/mL in controls for colon, 22.0 in cases and 22.0 ng/mL in controls for rectum, geometric mean	Quintile
							Q1: 1.32 (0.87-2.01)
							Q2: 1.28 (1.05-1.56)
							Q3: 1.00
							Q4: 0.88 (0.68-1.13)
							Q5: 0.77 (0.56-1.06)
MEC[c]	Woolcott, 2010 [49]	USA (M,W)	69.2, mean	2001-2006	229 / 434	23.2 in cases and 25.0 ng/mL in controls, mean	Quintile
							Q1: 1.00
							Q2: 0.63 (0.37-1.08)
							Q3: 0.54 (0.32-0.93)
							Q4: 0.62 (0.36-1.07)
							Q5: 0.6 (0.33-1.07)
PHS[c]	Lee [51]	USA (M)	56.6, mean	1982-2000	229 / 389	26.6 in cases and 25.6 ng/mL in controls, mean	Quartile
							Q1: 1.00
							Q2: 0.71 (0.42–1.21)
							Q3: 1.24 (0.76–2.04)
							Q4: 1.08 (0.62-1.87)

[a] ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CLUE, from the campaign slogan, "Give us a CLUE to cancer"; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JPHC, Japan Public Health Center Study; MEC, Multiethnic Cohort Study; NHS, Nurses' Health Study; PHS, Physicians' Health study; WHI, Women's Health Initiative

M, men; W, women

[b] Serum specimen was used

[c] Plasma specimen was used

[d] Estimates of quantile cutoff were obtained from the investigator of the Nurses' Health Study

[e] The conversion factor for 25(OH)D from nmol/L to ng/mL is 0.401

receptor polymorphism was associated with colorectal cancer risk [29]; the summary OR for the BB versus bb genotype of eight studies was 0.57 (95 % CI=0.36-0.89). A few attempts were made to determine genetic polymorphisms to predict circulating vitamin D metabolites. Recent genome-wide association studies (GWAS) of circulating vitamin D found several genetic variants in group-specific component (vitamin D binding) protein (GC), NADSYN1/DHCR7, and CYP2R1 predicting circulating vitamin D levels [57, 58]. Several candidate gene approaches also reported a potential link between variants of the GC gene and cytochrome P450 genes [59, 60] and vitamin D levels. However, further studies need to elucidate whether a combined benefit of vitamin D status with those variants exists for colorectal cancer prevention.

Conclusions

The role of vitamin D as a chemopreventive agent has drawn great attention these days and evidence about its relationship to colorectal cancer has accumulated. Although vitamin D intake from food in prospective studies, or the effect of vitamin D supplementation in intervention trials did not provide clear evidence that vitamin D lowers colorectal cancer development, individuals with low circulating levels of vitamin D have shown to be at higher risk of colorectal cancer compared with those with high levels of vitamin D.

Overall, inverse associations of circulating levels of vitamin D and dietary vitamin D intake with both colorectal adenoma and cancer support the hypothesis that low vitamin D status increases the risk of colorectal cancer. However, several questions remained unresolved, including the optimal dose and duration of vitamin D supplementation, interactions with female hormones, calcium, and retinol, the appropriate timing of vitamin D intervention on colorectal carcinogenesis, and the association among non-Caucasian ethnic groups. Although evidence from high-quality observational studies and one large-scale, randomized trial is available regarding vitamin D and colorectal cancer prevention, when considering that colorectal cancer is one of the most common cancer sites and the questions that still remain, further large prospective and intervention studies are warranted to clarify the causal link and to find an effective way to use vitamin D for colorectal cancer prevention.

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