Circulating levels of vitamin D, vitamin D receptor polymorphisms, and colorectal adenoma: a meta-analysis

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Abstract

Growing evidence suggests an elevated risk for colorectal neoplasia among individuals with low levels of vitamin D, the biological actions of which are mediated by the vitamin D receptor (VDR). To investigate the association among vitamin D status, VDR polymorphisms (FokI, and BsmI), and colorectal adenoma, we conducted a meta-analysis of nine studies of circulating levels of 25-hydroxyvitamin D (25(OH)D) and five studies of FokI or BsmI polymorphisms in relation to colorectal adenomas. Study-specific relative risks (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model. A total of 3398 colorectal adenomas for 25(OH)D and 1754 colorectal adenomas for VDR were included in the meta-analysis. We identified a significant inverse association between colorectal adenoma (combined RR, 0.93; 95% CI, 0.87-0.98 per 10 ng/mL increase in 25(OH)D levels). When we examined FokI and BsmI polymorphisms in the meta-analysis, we found no association for either FokI (combined RR, 1.00; 95% CI, 0.95-1.06) or BsmI (combined RR, 0.99; 95% CI, 0.93-1.05) in the additive model. These data suggest an inverse association between circulating 25(OH)D levels and colorectal adenoma risk.

Key Words: Colorectal adenoma, 25-hydroxyvitamin D, vitamin D receptor, meta-analysis

Introduction

Vitamin D decreases cancer risk by improving differentiation and apoptosis and decreasing proliferation, invasiveness, metastatic potential, and angiogenesis [1]. Vitamin D is produced by exposing the skin to ultraviolet radiation, which is required for conversion of 7-dehydrocholesterol into vitamin D (cholecalciferol), which is then hydroxylated to 25-hydroxylvitamin D (25(OH)D) in the liver. This 25(OH)D is converted to 1,25-dihydroxyvitamin D (1,25(OH)2D) by 1-α-hydroxylase in the kidney [2] and other sites, including the colon [3].

The vitamin D receptor (VDR) binds to 1,25(OH)2D and interacts with target-cell nuclei; thus, mediating the biological actions of vitamin D [4]. Because of the potential importance of VDR in cancer etiology, the associations between variants of the VDR gene and colorectal cancer have been examined in several studies [5,6]. The most frequently studied single nucleotide polymorphisms are FokI (rs2228570) and BsmI (rs1544410). The FokI restriction fragment length polymorphism exhibits two isoform VDR proteins that may have different transcription efficiencies [7]; the presence of the restriction site produces the 427-residue isoform (f-allele) of the VDR, whereas the absence of the restriction site results in the 424-residue isoform (F-allele), which may have higher transcriptional activity. The BsmI restriction site in the intron at the 3´-untranslated region of the VDR gene, which is strongly linked with polymorphisms in ApaI, TaqI, and poly(A) and does not change the encoded VDR protein, is associated with bone mineral density [8] and prostate cancer [9]. The B of BsmI denotes the absence of a restriction site, and b denotes the presence of a restriction site.

Given the possible favorable effect of vitamin D against cancer, several epidemiological studies have suggested a possible increased risk for colorectal neoplasia with low vitamin D status [10] or with certain VDR gene alleles [5,6]. Several case-control and prospective studies found inverse or no associations between circulating vitamin D levels and colorectal adenoma [11-19]. We performed a meta-analysis of nine studies, including 3,398 cases and 3,883 controls, to examine whether circulating blood 25(OH) levels were inversely associated with colorectal adenoma, a precursor colorectal cancer lesion. We also examined the associations between common FokI and BsmI polymorphisms and colorectal adenoma in a meta-analysis of five studies for each polymorphism.

Subjects and Methods

Identification and selection of studies

We searched the PUBMED database for the period before January 2011 using the terms [(vitamin D [MeSH] and "vitamin D" or "25-hydroxyvitamin D") and ("adenoma")] and the EMBASE and MEDLINE databases using the terms [("vitamin D" or "25-hydroxyvitamin D") and ("adenoma")] for circulating vitamin D levels and colorectal adenoma. The search was restricted to human studies reported in English-language articles. In total, 147 abstracts were identified in the PUBMED database and 48 from EMBASE and MEDLINE. We also examined references from these publications to identify further studies. For VDR, we searched the PUBMED, EMBASE, and MEDLINE databases for the period up to January 2011 using the terms [(("vitamin D receptor" or "Fok" or "Bsm") and ("adenoma")) or ("rs2228570" or "rs1544410")]. The search was restricted to human studies reported in English-language articles. In total, 68 abstracts were identified from the PUBMED database and 35 from EMBASE and MEDLINE. We identified nine studies [11-19] that examined serum or plasma 25(OH)D and first colorectal adenoma or adenoma recurrence, and five studies for each polymorphism [15,16,20-24] that reported the associations between the FokI or BsmI polymorphisms and colorectal adenoma or adenoma recurrence and met the following criteria; 1) serum or plasma 25(OH)D or VDR FokI or BsmI polymorphisms were assayed as the exposure of interest; 2) the outcome of interest was colorectal adenoma or adenoma recurrence; and 3) the relative risk (RR) and 95% confidence intervals (CIs) were reported.

Statistical analysis

We extracted the RRs for a standard unit of increase in 25(OH)D levels and the RRs comparing the top 25(OH)D categories with the bottom categories. To construct dose-response models if the RR per standard unit of increase was not reported, we fit a linear model to estimate the RRs per 10 ng/mL increase in circulating vitamin D levels using the method proposed by Greenland and Longnecker [25] and Orsini et al. [26]. For the common VDR polymorphisms FokI and BsmI, we considered the homozygous genotype of the more prevalent allele as the reference group (F for FokI and b for BsmI). We extracted the number of cases and controls for the crude combined RR to combine all studies and present the combined RRs in additive, dominant, and recessive models. We contacted the author of one study to obtain the RRs for FokI polymorphisms in dominant and recessive models, but were unable to obtain the data. For one study [16], which did not report the number of cases or controls by FokI polymorphism but did report the RRs with the reference group of the FF genotype, we used the RRs presented for the additive model but did not include that study for dominant

and recessive models because of a lack of information. The results were similar when we compared the combined RRs of the adjusted estimates with the crude combined RR in four studies that reported the adjusted RRs comparing the homozygous genotype of variant type with the homozygous genotype of the wild type (data not shown).

The summary RRs were estimated using a random effects model developed by DerSimonian and Laird [27]. The individual study estimates were weighted by the inverse of their variance. We tested for heterogeneity among studies using the Q statistic [27] and examined heterogeneity by type of study, country, or adjustment for season, body mass index (BMI), and physical activity across studies. Publication bias was assessed using the Egger regression asymmetry test [28]. All statistical analyses were performed with STATA 11 statistical software (StataCorp, College Station, TX, USA). A $P < 0.05$ (two sided) was considered statistically significant.

Results

Circulating 25(OH)D levels and colorectal adenoma

Nine studies met the inclusion criteria for circulating vitamin D levels and colorectal adenoma (Table 1), including four prospective studies and five case-control studies. Among the four prospective studies, two were trials of adenoma recurrence (treatment reagents were ursodeoxycholic acid in one study [12] and calcium carbonate in the other study [16]), and the other two studies were prospective, which followed participants with updated information on sigmoidoscopy or colonoscopy. In the five case-control studies, blood samples of participants were collected at or after diagnosis of colorectal adenoma. Eight studies were conducted in multiple regions in the US, and one study was conducted in Japan. In total, 3,398 cases and 3,883 controls were included in the meta-analysis of circulating 25(OH)D levels and colorectal adenoma. Of the nine studies, time of blood draw (season, month, or date) was matched or adjusted in six studies [12-15,18,19], and BMI or physical activity was considered a confounding factor in seven studies [11-15,17,18]. Colorectal adenoma cases were ascertained mostly through colonoscopies in six studies. Five studies [11,15-17,19] reported estimates by calcium intake strata.

We observed a significant inverse association between 25(OH)D levels and colorectal adenoma (combined RR, 0.93; 95% CI, 0.87-0.98 per 10 ng/mL increase in 25(OH)D levels (Fig. 1). For a 20 ng/mL increase in 25(OH)D levels, the combined RR was 0.84 (95% CI, 0.73-0.96). When we compared top with bottom categories of 25(OH)D levels, the combined RR (95% CI) was 0.73 (0.54-0.92). To examine whether there was a tendency for investigators to publish positive findings, we explored asymmetry of a funnel plot. There was no evidence of publication bias at the 0.05 level (Egger's test $P = 0.07$ for RRs per 10 ng/mL

Table 1. Included studies of circulating levels of 25(OH)D and risk of colorectal adenoma

First author, year [Ref no.]	Country (Sex[1])	Study design	Endpoint	Type of endoscopy	Age at blood donation in controls (years)	No. of cases / controls	25(OH)D, mean or median
Platz, 2000 [13]	US (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
Levine, 2001 [17]	US (M, W)	Case-control	First adenoma	Sigmoidoscopy	61.8, mean	473 / 506	25.6 in cases and 26.9 ng/mL in controls, mean
Peters, 2001 [15]	US (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
Grau, 2003 [16]	US (M, W)	Prospective	Recurrent adenoma	Colonoscopy	61, mean	376 / 422	29.1 ng/mL, median
Peters, 2004 [14]	US (M, W)	Prospective	First adenoma	Sigmoidoscopy	62.3, mean	394 / 397	27.0 in cases and 28.3 ng/mL in controls, mean
Jacobs, 2007 [12]	US (M, W)	Prospective	Recurrent adenoma	Colonoscopy (97.7%) and sigmoidoscopy[2]	66.0, mean	210 / 358	26.9 ng/mL in men, and 25.1 ng/mL in women, mean
Miller, 2007 [19]	US (M, W)	Case-control	First adenoma	Colonoscopy	54.4, mean	111 / 238	27.5 in cases and 31.4 ng/mL in controls, mean
Takahashi, 2010 [18]	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
Fedirko, 2010 [11]	US (M,W)	Case-control	First adenoma	Colonoscopy	53.6, mean	616 / 770	24.5 in cases and 25.5 ng/mL in controls, mean

[1] M, men; W, women
[2] Information was obtained from Alberts *et al*, [48].
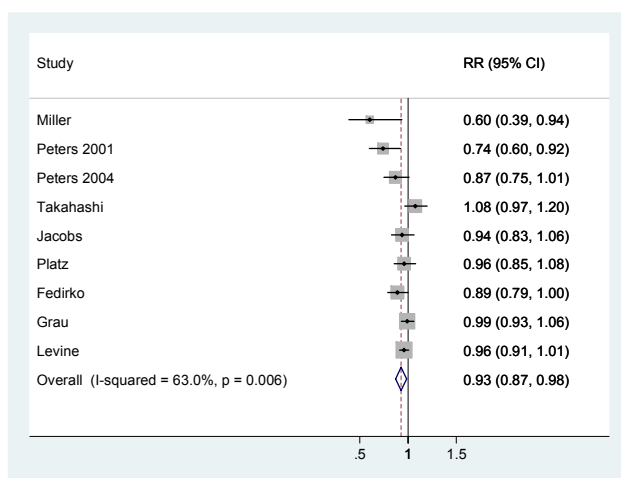
Fig. 1. Study-specific and combined relative risks (RRs) and 95% confidence intervals (CIs) of colorectal adenoma per 10 ng/mL increase in blood 25(OH)D levels. Black circles indicate the study-specific relative risks; horizontal lines represent the 95% CIs. The area of the gray squares reflects the study-specific weights (inverse of the variance). The dashed line represents the combined RR and the diamond represents the 95% CI for the combined RR.

increase in 25(OH)D levels). We explored the heterogeneity in 25(OH)D levels across colorectal adenoma studies using sensitivity analyses. After excluding the study conducted in Japan [18], the combined RR (95% CI) per 10 ng/mL increase in 25(OH)D levels was 0.91 (0.86-0.97; *P* heterogeneity = 0.02). When we excluded one study [19], which did not consider the covariance estimate across exposure levels because it did not report the number of subjects [25,26], we found a combined RR of 0.94 (95% CI, 0.89-0.99) per 10 ng/mL increase in 25(OH)D levels. We pooled estimates only among studies that considered season and BMI or physical activity; combined RRs (95% CI) per 10 ng/mL increase in 25(OH)D levels were 0.89 (95% CI,

0.79-1.00) and 0.93 (95% CI, 0.87-0.99), respectively. When we excluded two clinical trials of colorectal adenoma recurrence, the results were similar; the combined RR was 0.92 (95% CI, 0.86-0.99) per 10 ng/mL increase in 25(OH)D levels. The combined RRs (95% CIs) were 0.96 (0.91-1.01) in a meta-analysis of four prospective studies and 0.89 (0.78-1.00) in a meta-analysis of five case-control studies.

We also examined whether the association varied by calcium status in five studies [11,15-17,19]. When we pooled estimates by calcium status (high vs. low), we observed combined RRs of 0.71 (95% CI, 0.50-0.92) for high calcium status and 0.91 (95% CI, 0.75-1.06) for low calcium status.

VDR polymorphisms (FokI and BsmI) and colorectal adenoma

We found five studies for each polymorphism (1754 cases for FokI and 1740 cases for BsmI) that met the inclusion criteria for common polymorphisms of FokI or BsmI in relation to colorectal adenoma occurrence or adenoma recurrence (Table 2). For FokI polymorphisms, the endpoints were colorectal adenoma recurrence in three studies and adenoma occurrence in two studies. For BsmI polymorphisms, one study [23] examined colorectal adenoma recurrences in a randomized clinical trial of calcium carbonate.

We detected no association for the FokI polymorphisms; combined RRs (95% CIs) were 1.00 (0.95-1.06) in the additive model (five studies; Fig. 2), 1.04 (0.82-1.25) in the dominant model (three studies), and 0.86 (0.60-1.12) in the recessive model (three studies). For BsmI polymorphisms, combined RRs (95% CIs) were 0.99 (0.93-1.05) in the additive model (five studies), 0.96 (0.84-1.09) in the dominant model (five studies), and 1.00 (0.82-1.17) in the recessive model (five studies). Egger's test showed no significant evidence of publication bias (*P* = 0.95 for

Table 2. Included studies of vitamin D receptor polymorphisms (FokI and BsmI) and risk of colorectal adenoma

| First author, year (Ref no.)	Country (Sex[1])	Ethnicity	MAF[2] in controls	Endpoint	Type of endoscopy	No. of cases / non-cases	FokI RR (95% CI)	BsmI RR (95% CI)
Kim, 2001 [20]	US (M, W)	97% of Caucasian[3]	0.43 for BsmI	First adenoma	Colonoscopy	393 / 406	-	0.71 (0.46-1.11) for BB vs. bb
Ingles, 2001 [21]	US (M, W)	57% of non-Hispanic white in controls	0.40 for FokI 0.37 for BsmI	First adenoma	Sigmoidoscopy	373 / 394	0.94 (0.60-1.5) for ff vs. FF	1.1 (0.73-1.8) for BB vs. bb
Peters, 2001 [15]	US (M, W)	89% of non-Hispanic white in controls	0.35 for FokI	First or recurrent adenoma	Colonoscopy (86.2%) or sigmoidoscopy	208 / 184	0.75 (0.36-1.58) for FF vs. ff	-
Boyapati, 2003 [22]	US (M, W)	90.2% of Caucasian in controls	0.45 for BsmI	First adenoma	Colonoscopy	177 / 228	-	0.87 (0.53-1.45) for bb vs. BB
Grau, 2003 [16]	US (M, W)	84% of Caucasian	0.36 for FokI[4]	Recurrent adenoma	Colonoscopy	376 / 422	1.06 (0.86-1.32) for ff vs. FF	-
Hubner, 2008 [23]	UK (M, W)	100% Caucasian	0.38 for FokI 0.40 for BsmI	Recurrent adenoma	Colonoscopy	137 / 409	0.92 (0.58-1.46) for ff vs. FF	1.07 (0.73-1.57) for BB vs bb
Egan, 2010 [24]	US (M, W)	95% of Caucasian	N/A	Recurrent adenoma	Colonoscopy[5]	660 / 779	0.93 (0.80-1.09) in additive model	1.01 (0.87-1.18) in additive model

[1] M, men; W, women
[2] Minor allele frequency
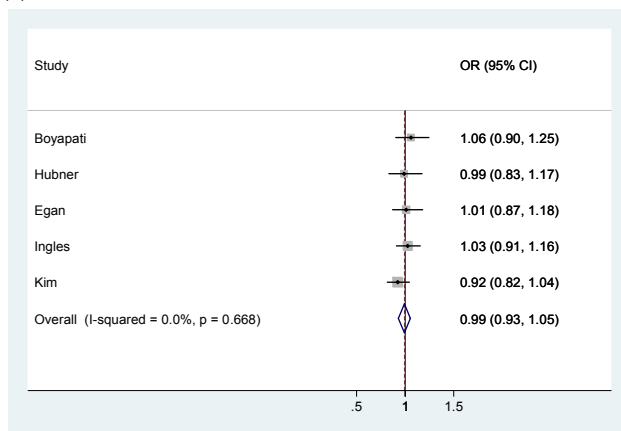[3] We obtained information on ethnicity from Smith-Warner *et al*. [49].
[4] Among all participants
[5] We obtained information on type of endoscopy from Alberts *et al*. [50] and Alberts *et al*. [48].

(A) FokI and colorectal adenoma
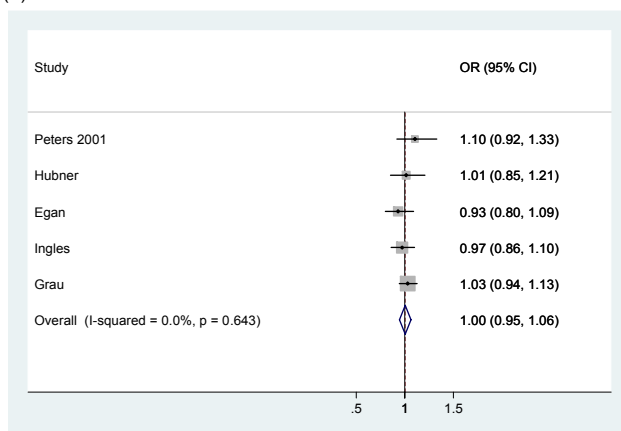
(B) BsmI and colorectal adenoma

Fig. 2. Study-specific and combined relative risks (RRs) and 95% confidence intervals (CIs) for colorectal adenoma according to FokI and BsmI polymorphisms in the additive model. Black circles indicate study-specific odds ratios; horizontal lines represent the 95% CIs. The area of the gray squares reflects the study-specific weights (inverse of the variance). The dashed line represents the combined RR and the diamond represents the 95% CI for the combined RR.

FokI and *P* = 0.53 for BsmI in the additive model). We also pooled adjusted RRs shown in the articles; the combined RR (95% CI) was 1.02 (0.84-1.21) for ff vs. FF genotype of FokI and 0.93 (0.71-1.15) for BB vs. bb of BsmI in four studies.

Discussion

We found an inverse association between circulating vitamin D levels and the risk for colorectal adenoma. However, we did not observe any associations between common FokI and BsmI polymorphisms and colorectal adenoma in this meta-analysis.

The hypothesis that vitamin D may prevent colorectal neoplasia has been supported by both experimental evidence and summaries of epidemiological studies on circulating vitamin D levels. Vitamin D may reduce the risk of colorectal neoplasia by regulating progression and differentiation [1] and inhibiting angiogenesis [29]. This hypothesis is supported by animal studies showing that vitamin D (the vitamin D3 analogue EB 1,089) improves tumor control following radiation treatment, possibly by promoting apoptosis [30]. Based on the geographic distribution of colon cancer mortality rates in the US, with the highest rates in regions with the least amount of sunlight, Garland and Garland hypothesized that vitamin D protects against colon cancer [31]. A recent systematic review of serum or plasma 25(OH)D levels and colorectal cancer incidence reported a 34% lower risk of colorectal cancer among individuals in the top quintiles compared to those in the bottom quintiles [32], which agrees with our meta-analysis results for colorectal adenoma. A previous meta-analysis of seven circulating vitamin D level and colorectal adenoma studies showed a RR of 0.70 (95% CI, 0.56-0.87) by comparing the highest with lowest quintile of 25(OH)D levels [33]. When we included two more studies [11,18], we found a 7% decreased risk for colorectal adenoma per 10 ng/mL increase

in 25(OH)D levels, and our results were robust in multiple sensitivity analyses. Our meta-analysis results of five calcium status studies suggested that calcium and vitamin D may interact in the development of colorectal adenoma, which has been the subject of several previous studies with inconsistent findings [34-37]. This warrants further study. Given the high prevalence of vitamin D insufficiency in Korea [38], US, and Canada [39], the role of vitamin D in chronic disease development may merit priority for future research.

The cellular effects of 1,25(OH)2D are mediated primarily through binding to the nuclear VDR, which regulates the transcription of numerous genes, including protooncogenes and tumor suppressor genes [40]. Normal epithelial colon cells and cancer cells express VDR [41]. Epidemiological studies have examined the association between VDR polymorphisms and colorectal cancer, because of great interest in the preventive effect of vitamin D in relation to cancer at several sites [10]. The most frequently assessed genotypes are FokI and BsmI. However, a meta-analysis of FokI and BsmI and colorectal cancer incidence yielded no significant associations [6]. Our meta-analysis of colorectal adenoma also showed no association with FokI or BsmI polymorphisms. Previous studies have reported inconsistent findings for other VDR polymorphisms in relation to colorectal adenoma or cancer [14,23,24,42-45].

Each study relied upon a single measure of plasma vitamin D metabolite levels, which did not allow us to examine changes across time. However, a single measure of vitamin D metabolites is a useful marker for long-term vitamin D status [46,47]. Although we cannot rule out residual or unmeasured confounding factors, the combined estimates from studies that controlled for season, BMI, or physical activity still showed significant or marginally significant inverse associations, suggesting that our results may not be entirely explained by bias due to confounding factors. The combined adjusted RRs (when available) also showed no association for FokI or BsmI polymorphisms, which is in agreement with the combined crude RRs. The heterogeneity we found across studies in the meta-analysis may be due to differences in laboratory measurement methods, follow-up periods, seasons of blood draw, exposure to sunlight, ethnicity, or the prevalence of interaction factors and unknown/unmeasured confounding factors. The majority of our population was Caucasian for the combined estimates of VDR polymorphisms; thus this result is not generalizable to other populations.

In summary, our meta-analysis found a significant inverse association between 25(OH)D levels and colorectal adenoma. No significant association between FokI or BsmI polymorphisms and colorectal adenoma was detected. Further prospective studies or randomized clinical trials of vitamin D in relation to colorectal neoplasia and other VDR gene polymorphisms may be necessary.

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