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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Meta-Analyses of Vitamin D Intake, 25-Hydroxyvitamin D Status, Vitamin D Receptor Polymorphisms, and Colorectal Cancer Risk

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Abstract

Background: Our objective was to conduct a systematic review and meta-analysis of prospective studies on colorectal cancer (CRC) and vitamin D intake and 25-hydroxyvitamin D status, as part of the World Cancer Research Fund Continuous Update Project. We also aimed at conducting meta-analysis of all studies on CRC and vitamin D receptor (*VDR*) single-nucleotide polymorphisms.

Methods: Relevant studies were identified in PubMed (up to June 2010). Inclusion criteria were original and peer-reviewed publications with a prospective design (for studies on vitamin D intake or status). Random effects of dose-response meta-analyses were performed on cancer incidence.

Results: We observed inverse associations of CRC risk with dietary vitamin D [summary relative risk (RR) per 100 IU/day = 0.95, 95% CI: 0.93–0.98; 10 studies; range of intake (midpoints) = 39–719 IU/day] and serum/plasma 25-hydroxyvitamin D (RR per 100 IU/L = 0.96, 0.94–0.97; 6 studies; range = 200–1,800 IU/L), but not with total vitamin D (5 studies). Supplemental (2 studies; range = 0–600 IU/day) and total (4 studies; range = 79–732 IU/day) vitamin D intake and 25-hydroxyvitamin D status (6 studies; range = 200–1,800 IU/L) were inversely associated with colon cancer risk. We did not observe statistically significant associations between *FokI*, *PolyA*, *TaqI*, *Cdx2*, and *ApaI VDR* polymorphisms and CRC risk. The *BsmI* polymorphism was associated with a lower CRC risk (RR = 0.57, 0.36–0.89 for BB versus bb, 8 studies).

Conclusions: These meta-analyses support the evidence of an inverse association between vitamin D intake, 25-hydroxyvitamin D status, and the *BsmI VDR* polymorphism and CRC risk.

Impact: Improving vitamin D status could be potentially beneficial against CRC incidence. *Cancer Epidemiol Biomarkers Prev; 20(5); 1003–16. ©2011 AACR.*

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide, accounting for more than one million cases and 600,000 deaths every year (1). Understanding the role of diet—a modifiable risk factor—in colorectal carcinogenesis might inform primary prevention strategies. A substantial body of literature has addressed the relationship between vitamin D and CRC risk. This relationship has been studied by estimates of dietary, supplemental and total vitamin D intakes, and circulating 25-hydroxyvitamin D level, a biomarker of vitamin D status reflecting both intake and synthesis related to sunlight exposure.

Regarding dietary vitamin D intake, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) report in 2007 concluded that the evidence of a protective effect of vitamin D on the risk of CRC was limited suggestive [relative risk (RR) for 100 IU/day = 0.99, 95% CI = 0.97–1.00; ref. 2]. Since then, 5 new prospective cohort studies on vitamin D intake and CRC have been published (3–7), substantially increasing the evidence base available, but no updated dose-response meta-analyses have been published on vitamin D intake. In 2009, Huncharek and colleagues performed the highest versus lowest meta-analysis of vitamin D intake and CRC and observed no statistically significant results (8).

Regarding serum/plasma 25-hydroxyvitamin D status and CRC risk, 3 dose-response meta-analyses have been

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published (9–11), suggesting an inverse association. Since the most recent meta-analysis, conducted by International Agency for Research on Cancer in 2010 (9), new results from the multiethnic cohort (12) have been published. None of these published meta-analyses provided information on proximal and distal colon cancer subtypes. In addition, these articles did not investigate a potential nonlinear dose-response relationship between 25-hydroxyvitamin D and CRC risk. This could be useful for determining whether an optimal value for vitamin D status can be retained about CRC prevention, and/or for validating optimal levels proposed by some authors (13, 14).

The vitamin D receptor (*VDR*) is an intracellular hormone receptor that specifically binds the biologically active form of vitamin D (1,25-dihydroxyvitamin D) and interacts with specific nucleotide sequences of target genes to produce a variety of biologic effects (15). It has been hypothesized that for individuals with similar vitamin D intake or status, those having a less active *VDR* could present an increased susceptibility to CRC risk. However, the evidence to date has been inconclusive. Two reviews (16, 17) and 2 meta-analyses (18, 19) have been published on the topic. Since the publication of the most recent meta-analysis (18), several new studies have been published (20–22), including results from the EPIC (European Prospective Investigation into Cancer and Nutrition) study, based on more than 1,200 CRC cases. In addition, this meta-analysis focused on *BsmI* and *FokI* polymorphisms only; it did not observe overall statistically significant associations (18).

Our objective was to conduct a systematic review and meta-analysis of prospective studies on CRC and vitamin D intake published up to June 2010, as part of the WCRF Continuous Update Project. We also conducted meta-analyses of prospective studies on CRC and 25-hydroxyvitamin D level and studies on *VDR* single-nucleotide polymorphisms. This article provides a complete and updated state of the art about vitamin D and CRC risk, including substantially increased evidence base since previous reviews, and complementary types of exposures (intake/biomarker/*VDR* polymorphisms). It includes a linear dose-response approach (key feature in the discussion of causality) and an investigation of a potential nonlinear dose-response trend for vitamin D status that has never been meta-analyzed before.

Materials and Methods

Search strategy and selection criteria

The present review is part of the Continuous Update Project implemented by the WCRF/AICR and conducted at Imperial College London, London, UK, on the associations between food, nutrition, physical activity, and the prevention of cancer. The complete protocol for the review is available on the WCRF Website (23). Briefly, we updated the systematic literature review (24) with study results published through June 2010. We searched PubMed without any language restriction by using the same search strategy that was used to retrieve papers for the WCRF/AICR report (2). The search terms (MeSH terms and text words) identified a broad range of factors on diet and nutrition. The full search strategy is available online (23). We also hand-searched reference lists from retrieved articles, reviews, and meta-analysis papers on the related topic. The search and data extraction of articles published up to June 2006 was conducted by several reviewers at Wageningen University, Wageningen, The Netherlands, during the systematic literature review for the WCRF/AICR report (2). The search, data selection, and extraction from June 2006 to June 2010 were done by 2 reviewers at Imperial College London.

Studies were included in this review whether they reported original data on the association of colorectal, colon, or rectal cancer incidence with vitamin D intake (dietary, supplemental, and total), 25-hydroxyvitamin D status, and *VDR* single-nucleotide polymorphisms and whether they were based on a prospective design (cohort or nested case control) for studies on vitamin D intake and status. For *VDR* polymorphisms, all nested case-control and case-control studies were included. Only published peer-reviewed studies were included. To include the studies in the meta-analyses, estimates of the RRs with the 95% CIs had to be available in the publication. For the dose-response analysis, a quantitative measure of exposure and the number of cases and person-years were also needed. When multiple papers on the same study were identified, the inclusion of results in the meta-analysis was based on longer follow-up, more cases recruited, and completeness of the information required to do the meta-analyses.

Data extraction

For each relevant study, information on study characteristics, cancer site, description of exposure, results, and details of the adjustment for confounders were extracted and stored in a database. The search, data selection, and extraction were done by 2 reviewers. Ten percent of the work was double checked by an independent reviewer.

Statistical analyses

Random effects models that consider both within-study and between-study variation (25) were used to calculate summary RRs and 95% CIs for the associations of colorectal, colon, or rectal cancer incidence with vitamin D intake, 25-hydroxyvitamin D level, and *VDR* single-nucleotide polymorphisms: *FokI* (rs2228570), *BsmI* (rs1544410), *PolyA* (rs17878969), *TaqI* (rs731236), *Cdx2* (rs11568820), and *ApaI* (rs7975232). We used the most fully adjusted RR in the article, provided that they were not adjusted for factors potentially in the causal pathway.

For vitamin D intake and biomarkers, linear dose-response and highest versus lowest meta-analyses were conducted (25). We used the method described by Greenland and Longnecker (26) for the dose-response analysis to compute the trend from the correlated RRs and CIs

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across categories of exposure. We estimated, using standard methods (27), the distribution of cases or person-years in studies that did not report these and reported results by quantiles. In 2 studies (7, 28) in which the results were reported by functional categories and person-years by category were not reported, we used variance-weighted least-squares regression to estimate the trends.

The median level of exposure in each category was assigned to the corresponding RR when reported in the study. If not reported, the value assigned was the midpoint of the lower and upper bound in each category. For extreme open-ended categories, half the width of the adjacent exposure category was subtracted (for the lowest category) or added (for the uppermost category) to obtain the midpoint. For studies that reported results separately for colon and rectal cancer, but not combined (29–32), we combined the results by the Hamling procedure (33) to obtain an overall estimate for CRC; the same method was applied for distal and proximal colon cancer to obtain an overall estimate for colon cancer (4).

Statistical heterogeneity between studies was assessed by the Cochran Q test and the I^2 statistic (34). I^2 values of approximately 25%, 50%, and 75% are considered to indicate low, moderate, and high heterogeneity, respectively. We also conducted linear metaregression and stratified analyses by gender, number of cases, geographic location, ethnicity, range of exposure, adjustment for confounding factors such as calcium intake and sunlight exposure/season, and deviation from Hardy–Weinberg equilibrium (for studies on *VDR* polymorphisms) to investigate the potential sources of heterogeneity. Small study bias such as publication bias was examined in funnel plots and by Egger's test (35). The influence of each individual study on the summary RR was examined by excluding each, in turn, and pooling the rest.

A potential nonlinear dose-response relationship between dietary vitamin D intake and 25-hydroxyvitamin D status and CRC was examined by using fractional polynomial models (36).

A 2-sided $P < 0.05$ value was considered statistically significant. All analyses were conducted by STATA version 9.2.

Results

Figure 1 presents the flowchart for study selection. We identified a total of 50 publications that examined the relationship between vitamin D intake and/or status (prospective studies) or *VDR* polymorphisms and CRC. Among these, 8 publications were excluded from the meta-analyses: one was a component study of a multicenter cohort (37), 2 were superseded by more recent publications (38, 39), one restricted to cancer mortality as only outcome (40), one focused on *VDR* single-nucleotide polymorphisms that were not found in other publications on CRC risk (41), and 3 publications did not provide sufficient data to be included in the meta-analyses (22, 42, 43). Regarding the later 3 publications, only mean exposure data were provided in 2 of them: mean dietary vitamin D intake was either higher in noncases than in CRC cases (42) or similar in both groups (43). The third publication provided ORs of associations between CRC risk and heterozygous or homozygous mutant (grouped, but not separated) versus wild type for several *VDR* single-nucleotide polymorphisms. No association was observed for the main *VDR* polymorphisms studied (i.e., *BsmI*, TakI, and *Cdx2*; ref. 22). Finally, 42 publications have been included in the present meta-analyses on CRC incidence. Online Supplementary Appendix 1 provides descriptive information on these studies.

Otherwise mentioned next, there was no indication of publication bias with Egger's test and sensitivity analyses excluding 1 study at a time did not substantially modify the findings. For vitamin D intake and status, results of dose-response meta-analyses are presented next, whereas results of the highest versus lowest meta-analyses are presented in online Supplementary Appendix 2.

Vitamin D intake

We observed a statistically significant inverse association between dietary vitamin D and CRC risk (Table 1, Fig. 2A; summary RR = 0.95, 95% CI: 0.93–0.98) for an increase of 100 IU/day (10 studies included). Associations did not reach statistical significance for colon and rectum cancers separately (Table 1), nor for proximal and distal colon (data not shown). No statistical heterogeneity was detected except for rectal cancer, which was partly related to gender, as shown by metaregression analysis ($P = 0.002$). In stratified analyses, studies including more than 50% of women (5, 44, 45) showed a statistically significant inverse association between dietary vitamin D intake and rectal cancer (RR = 0.78, 0.67–0.90), whereas studies including more than 50% of men (4, 28, 46) showed no association (RR = 1.09, 0.84–1.40; data not tabulated). Available data were insufficient to conduct the separate meta-analyses by gender. Main sources of dietary vitamin D (i.e., dairy products, refs. 28, 44; fish, refs. 4, 46; or both, refs.5, 45) varied across studies. In the rectal cancer analysis, a higher RR (2.22, 0.99–4.97) was observed for the Finnish Social Insurance Institution's Mobile Clinic (46) compared with other studies. In the corresponding publication (46), the authors stated that fish was the main contributor to dietary vitamin D intake, and an increased CRC risk was associated with high consumption of salted and smoked fish in this study. When this study was excluded from the analysis, the summary RR became 0.88 (0.77–1.02) and heterogeneity was reduced, but remained moderate ($I^2 = 45.7\%$, $P = 0.12$). Restriction of the analyses to studies that investigated both colon and rectum cancer sites did not modify the results (summary RR for colon became 0.97, 0.91–1.03 and was unchanged for rectum). There was no strong evidence of nonlinearity of the association between dietary vitamin D intake and CRC risk (for nonlinearity, $P = 0.4$) within the studied range of intake (midpoints of the lowest and highest categories: 40–720 IU/day).

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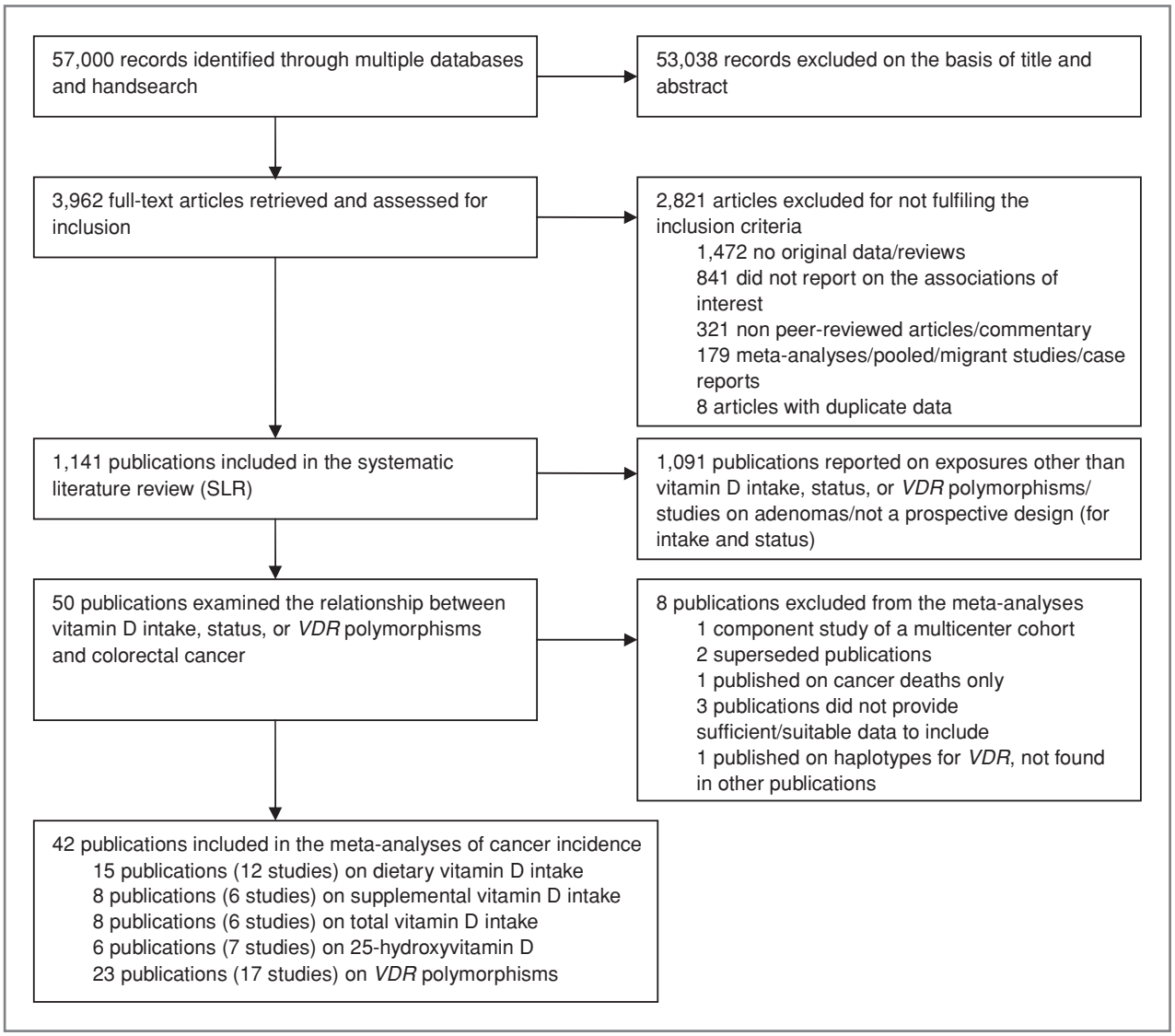

Figure 1. Flowchart of study selection for the association of vitamin D intake and status (prospective studies) and *VDR* polymorphisms with CRC (up to June 2010).

No dose-response analysis could be done for supplemental vitamin D and overall CRC due to insufficient data. However, 2 studies were available for dose-response meta-analysis of supplemental vitamin D and colon cancer specifically (29, 30), leading to a statistically significant inverse association (summary RR per 100 IU/day = 0.93, 0.88–0.98).

The association between total vitamin D and CRC (Table 1, Fig. 2B) was not statistically significant with high heterogeneity and lower number of available studies compared with dietary vitamin D (5 vs. 10). In sensitivity analyses excluding each study, in turn, the summary RR for total vitamin D and CRC became statistically significant (0.97, 0.95–0.99) and heterogeneity was substantially reduced ($I^2 = 36.5\%$, $P = 0.2$) when the Women's Health Study (47) was excluded from the analysis (data not tabulated). In sensitivity analyses restricted to the publications presenting results on both dietary and total vitamin D and CRC (7, 28, 44, 47), summary RRs were 0.93 (0.89–0.98) for dietary vitamin D and 0.99 (0.95–1.02) for total vitamin D. We observed an inverse association between total vitamin D and colon cancer risk (RR per 100 IU/day = 0.93, 0.90–0.98), but no association for rectal cancer (Table 1, Fig. 2B). In the highest versus lowest meta-analyses, total vitamin D was inversely associated with both CRC 0.84 (0.72–0.97) and colon cancer 0.71 (0.58–0.87) risk (Supplementary Appendix 2).

25-hydroxyvitamin D level (biomarker of vitamin D status)

We observed an inverse association between circulating 25-hydroxyvitamin D level and CRC risk (Table 1,

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Table 1. Summary RRs of meta-analyses for the associations of colorectal, colon, and rectum cancer with vitamin D intake and status (dose-response analyses) and *VDR* polymorphisms

	CRC			Colon cancer			Rectum cancer		
	Summary RR (95% CI)	***n***	**I^2, $P_{heterogeneity}$**	**Summary RR (95% CI)**	***n***	**I^2, $P_{heterogeneity}$**	**Summary RR (95% CI)**	***n***	**I^2, $P_{heterogeneity}$**
Vitamin D Intake (for an increase of 100 IU/d)									
Dietary vitamin D	0.95 (0.93–0.98)	10	11.0%, $P = 0.34$	0.97 (0.92–1.02)	8	0.0%, $P = 0.66$	0.91 (0.77–1.08)	6	58.9%, $P = 0.03$
Included studies			*(4–7, 28, 44–47, 90)*			*(4, 5, 28–30, 44–46)*			*(4, 5, 28, 44–46)*
Supplemental vitamin D				0.93 (0.88–0.98)	2	0.0%, $P = 0.98$			
Included studies						*(29, 30)*			
Total vitamin D	0.98 (0.95–1.01)	5	61.7%, $P = 0.034$	0.93 (0.90–0.98)	4	49.5%, $P = 0.12$	0.99 (0.94–1.04)	3	5.6%, $P = 0.35$
Included studies			*(7, 28, 29, 32, 44, 47)*			*(28–30, 44)*			*(28, 32, 44)*
Biomarker of vitamin D status (for an increase of 100 IU/L)									
25-hydroxyvitamin D	0.96 (0.94–0.97)	6	0.0%, $P = 0.81$	0.95 (0.92–0.995)	6	47.9%, $P = 0.09$	0.95 (0.86–1.05)	5	66.7%, $P = 0.02$
Included studies			*(5, 12, 48, 49, 91)*			*(5, 48, 49, 91, 92)*			*(5, 48, 49, 91)*
VDR polymorphisms									
FokI: fF vs. FF	1.03 (0.87–1.22)	10	71.3%, $P < 0.0001$	1.04 (0.79–1.36)	4	70.9%, $P = 0.02$	1.01 (0.82–1.23)	3	15.5%, $P = 0.31$
Included studies			*(19, 21, 50–57)*			*(21, 52, 58, 59)*			*(21, 52, 53)*
ff vs. FF	0.98 (0.74–1.30)	10	80.8%, $P < 0.0001$	1.26 (0.76–2.11)	4	85.7%, $P < 0.0001$	1.03 (0.80–1.34)	3	13.0%, $P = 0.32$
Included studies			*(19, 21, 50–57)*			*(21, 52, 58, 59)*			*(21, 52, 53)*
BsmI: Bb vs. bb	0.81 (0.64–1.02)	9	86.8%, $P < 0.0001$	1.01 (0.89–1.14)	2	0.0%, $P = 0.96$	0.97 (0.70–1.33)	3	55.8%, $P = 0.10$
Included studies			*(19–21, 50, 51, 53, 54, 93, 94)*			*(21, 53)*			*(21, 53, 95)*
BB vs. bb	0.57 (0.36—0.89)	8	94.0%, $P < 0.0001$	0.82 (0.66–1.02)	2	22.4%, $P = 0.26$	0.95 (0.76–1.20)	3	0.0%, $P = 0.97$
Included studies			*(19–21, 50, 53, 54, 93, 94)*			*(21, 53)*			*(21, 53, 95)*
TaqI: Tt vs. TT	1.00 (0.74–1.35)	5	45.9%, $P = 0.12$	1.04 (0.78–1.39)	2	0.0%, $P = 0.75$			
Included studies			*(20, 51, 54, 57, 60)*			*(59, 96)*			
tt vs. TT	1.34 (0.80–2.24)	4	64.7%, $P = 0.04$	0.98 (0.36–2.66)	2	86.1%, $P = 0.007$			
Included studies			*(20, 54, 57, 60)*			*(59, 96)*			
Cdx2: Cc vs. cc	1.09 (1.001–1.18)	4	0.0%, $P = 0.80$	1.04 (0.91–1.20)	2	0.0%, $P = 0.90$			
Included studies			*(19, 20, 54, 97)*			*(59, 97)*			
CC vs. cc	1.11 (0.94–1.32)	4	0.0%, $P = 0.98$	1.43 (0.76–2.68)	2	52.1%, $P = 0.15$			
Included studies			*(19, 20, 54, 97)*			*(59, 97)*			
PolyA: LS vs. LL	0.93 (0.82–1.06)	2	0.0%, $P = 0.62$						
Included studies			*(72, 98, 99)*						
SS vs. LL	0.84 (0.66–1.06)	2	0.0%, $P = 0.35$						
Included studies			*(72, 98, 99)*						
ApaI: Aa vs. aa	0.95 (0.80–1.13)	5	32.2%, $P = 0.21$						
Included studies			*(19, 20, 51, 54, 60)*						
AA vs. aa	0.91 (0.67–1.23)	5	65.0%, $P = 0.02$						
Included studies			*(19, 20, 51, 54, 60)*						

Note: *n* denotes the number of studies included.

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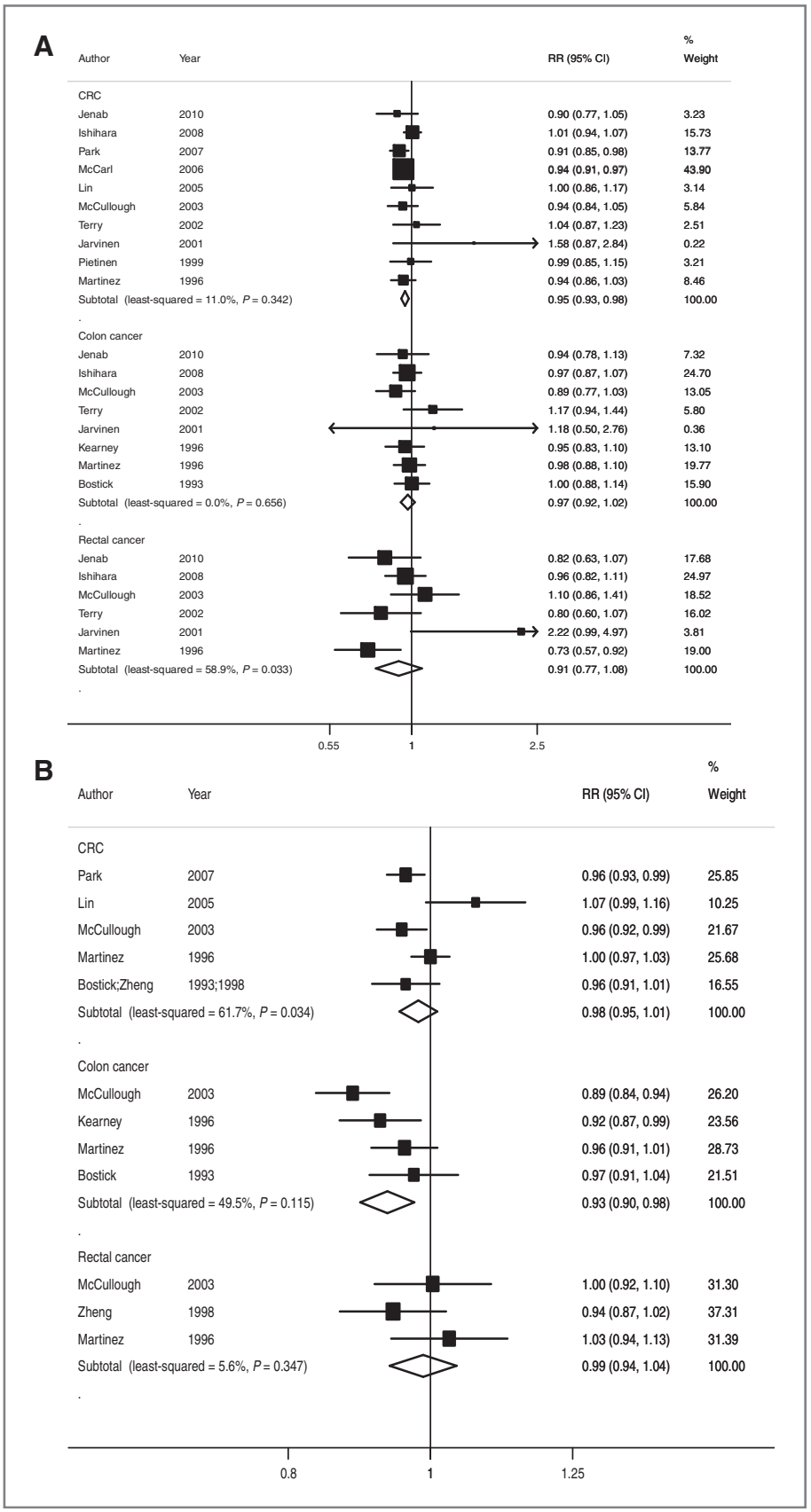

Figure 2. Dose-response meta-analyses on dietary and total (dietary + supplemental) vitamin D intake, circulating 25-hydroxyvitamin D, and risk of colorectal, colon, and rectal cancer. A, dietary vitamin D (for an increase of 100 IU/d). B, total vitamin D (for an increase of 100 IU/d).

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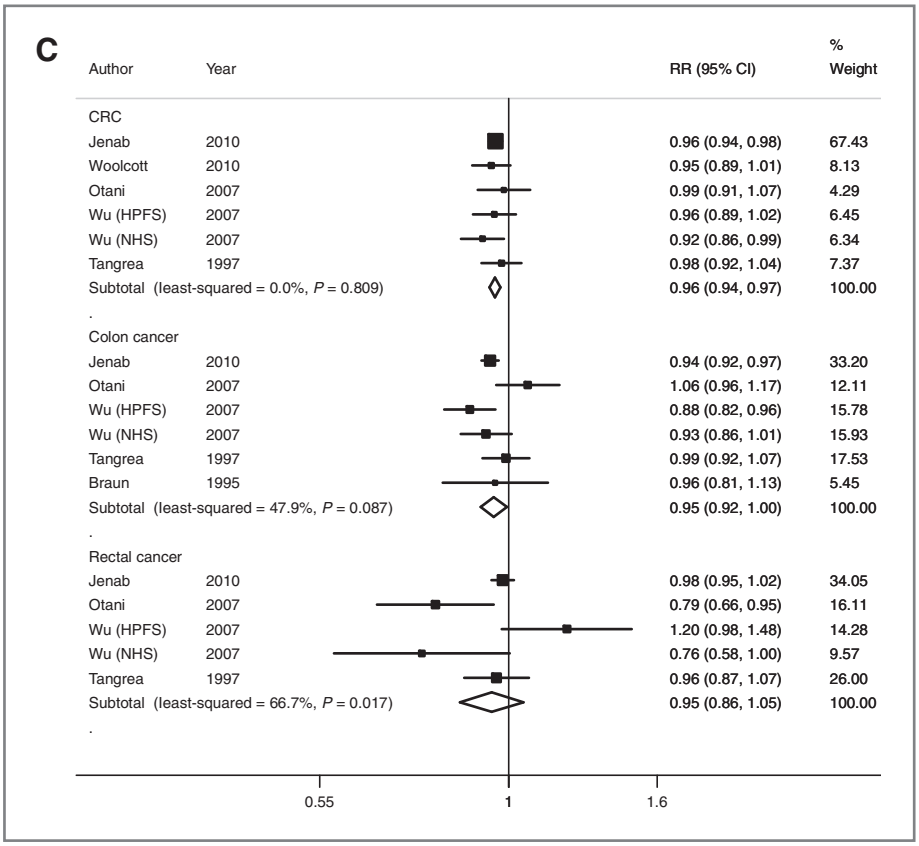

Figure 2. (*Continued*) C, circulating 25-hydroxyvitamin D (for an increase of 100 IU/L).

Fig. 2C; RR per 100 IU/L = 0.96, 0.94–0.97). Results were borderline significant for colon cancer (Table 1). We observed an inverse association between serum/plasma 25-hydroxyvitamin D and distal colon cancer (RR per 100 IU/L = 0.91 0.85–0.98, no heterogeneity: $I^2 = 0\%$, $P = 0.9$, 3 studies included; refs. 48, 49; data not tabulated). Results were not statistically significant for proximal colon (data not shown) and rectum cancers (Table 1). In the highest versus lowest meta-analyses, 25-hydroxyvitamin D level was also inversely associated with CRC risk 0.66 (0.52–0.84; Supplementary Appendix 2).

There was no strong evidence of nonlinearity of the association between 25-hydroxyvitamin D and CRC risk (for non-linearity, $P = 0.087$). The curve (Fig. 3) suggested that increasing 25-hydroxyvitamin D level was associated with a decreased risk of CRC in a linear dose-response manner, though a slight inflexion of the decrease in risk around the value of 1,000 IU/L (24 ng/mL) could be suspected. The range of intake used in this analysis was 200–1,800 IU/L (midpoints of the lowest and highest categories).

VDR polymorphisms

The most often reported polymorphisms were *BsmI* and *FokI*. The *BsmI* polymorphism was associated with a lower CRC risk (RR for BB versus bb = 0.57, 0.36–0.89, 8 studies), with high heterogeneity (Table 1, Fig. 4). The heterogeneity may be attributed to 1 study (50), for which deviation from Hardy–Weinberg equilibrium was observed. When we excluded it from the analysis, statistical heterogeneity was not detected ($I^2 = 0\%$, $P = 0.8$) and the inverse association persisted, although weakened (RR for BB versus bb = 0.89, 0.81–0.98). In the publication of Park and colleagues (51), no CRC case and only 1 control presented the BB genotype; thus, it was not possible to use those results in the meta-analysis. However, this study was included in the Bb versus bb analysis (summary RR = 0.81, 0.64–1.02, 9 studies). When this study (51) was excluded, the summary RR for Bb versus bb became statistically significant: 0.77 (0.61–0.98; data not tabulated).

We did not observe any statistically significant association for *FokI VDR* polymorphisms on 10 studies (Table 1). Study results were highly heterogeneous. Results by gender were not provided in the publications; thus, separate meta-analyses on men and women were not possible. However, for ff and CRC, the only study including a higher proportion of women than men (52) showed a statistically significant positive association (RR = 1.84, 1.15–2.94), whereas studies including a higher proportion of men than women (19, 50, 53) or an equal proportion of men/women (21, 51, 54–57) showed no association (RR = 0.95, 0.81–1.11, $I^2 = 33.1\%$, $P = 0.2$; and 1.00, 0.49–1.03, $I^2 = 86.2\%$, $P < 0.0001$, respectively; data not tabulated). For ff

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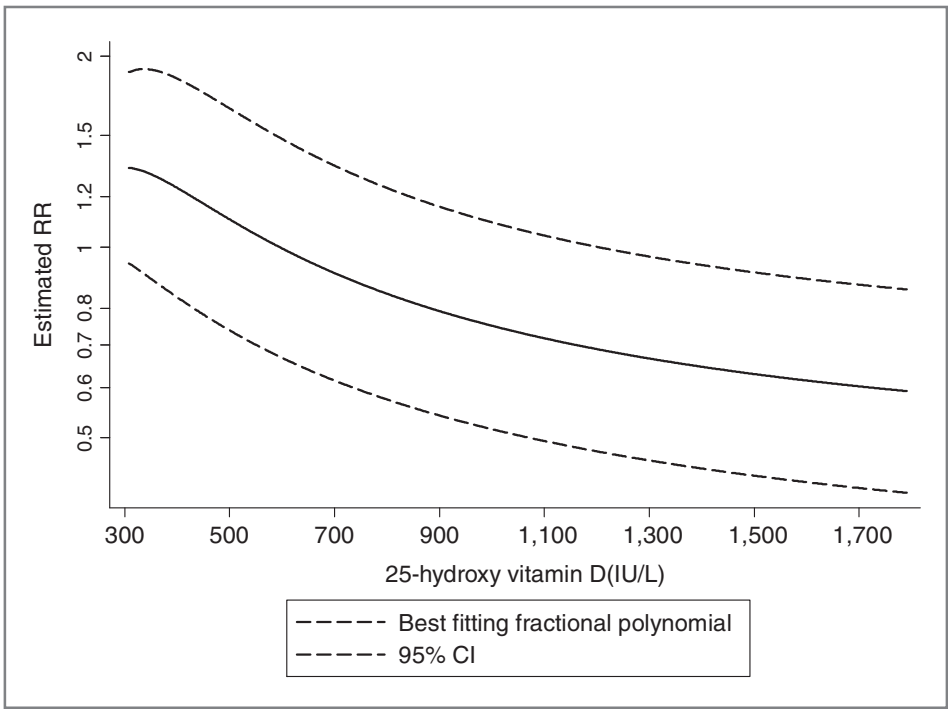

Figure 3. Nonlinear dose-response meta-analyses on circulating 25-hydroxyvitamin D and risk of CRC.

and colon cancer, the risk ratios also increased with the proportion of women in the study: more men than women (58): 0.71 (0.57–0.87), equal proportion of men/women (21): 1.13 (0.80–1.58), and more women than men (52, 59): 2.0 (1.32–3.03). However, for this analysis on ff and colon cancer, Egger's test ($P = 0.01$) and funnel plot suggested a publication bias (i.e., inverse relationship between RR and study size).

Five studies investigated *TaqI* (20, 51, 54, 57, 60) and *Apa I* (19, 20, 51, 54, 60) polymorphisms and CRC risk. No association was observed (Table I). From these, 4 studies also reported on *BsmI* (19, 20, 51, 54) and 4 on *Fok I* (19, 51, 54, 57). High heterogeneity in the analyses on *TaqI* (tt vs. TT) and CRC was due to 1 study (57) with very small number of cases ($n = 26$). No heterogeneity was detected when this study was excluded from the analysis (summary RR = 1.07, 0.82–1.39, $I^2 = 0\%$). High heterogeneity was also observed in the analysis of *ApaI* (AA vs. aa) and CRC. Although ethnicity was not statistically significant in metaregression ($P = 0.11$), probably, due to low statistical power, restriction to studies on Caucasian populations (19, 20, 54, 60) substantially decreased the heterogeneity (RR = 0.84, 0.68–1.02, $I^2 = 29.6\%$, $P = 0.2$). RR of the study on a non-Caucasian (Asian) population was 2.22 (1.12–4.40; ref. 51).

Four studies or less were identified on the *PolyA* and *Cdx2 VDR* polymorphisms. No association with CRC or colon cancer was observed, except a borderline significant positive association for Cc versus cc *Cdx2* polymorphism and CRC (Table 1).

Discussion

In dose-response meta-analyses, we observed inverse associations between dietary vitamin D and CRC risk and between supplemental and total vitamin D and colon cancer risk. The WCRF/AICR report in 2007 concluded a limited suggestive decreased risk of CRC for foods containing vitamin D (2). The present meta-analyses, including new results from 5 prospective cohort studies, add to the evidence for an inverse association between vitamin D intake and CRC risk. In a recent report (61), the American Institute of Medicine (IOM) has set at 600 IU/day the Recommended Dietary Allowance for vitamin D intake for most North Americans, except for people age 71 and older, who may require 800 IU/day. These recommendations were mostly based on the role of this nutrient in bone health. The order of magnitude of vitamin D intake studied in prospective observational studies on CRC and thus included in this dose-response meta-analysis (maximal dose around 730 IU/day for total vitamin D) is consistent with IOM recommendations.

Vitamin D status depends on intake from the diet and supplements but also on synthesis in the skin under the influence of sunlight. Thus, we also analyzed vitamin D status to obtain a better picture of the relationship between vitamin D and CRC risk. Consistent with the results on vitamin D intake, we observed inverse associations between circulating 25-hydroxyvitamin D and colorectal and colon cancer. These findings update those of previous meta-analysis on 25-hydroxyvitamin D and

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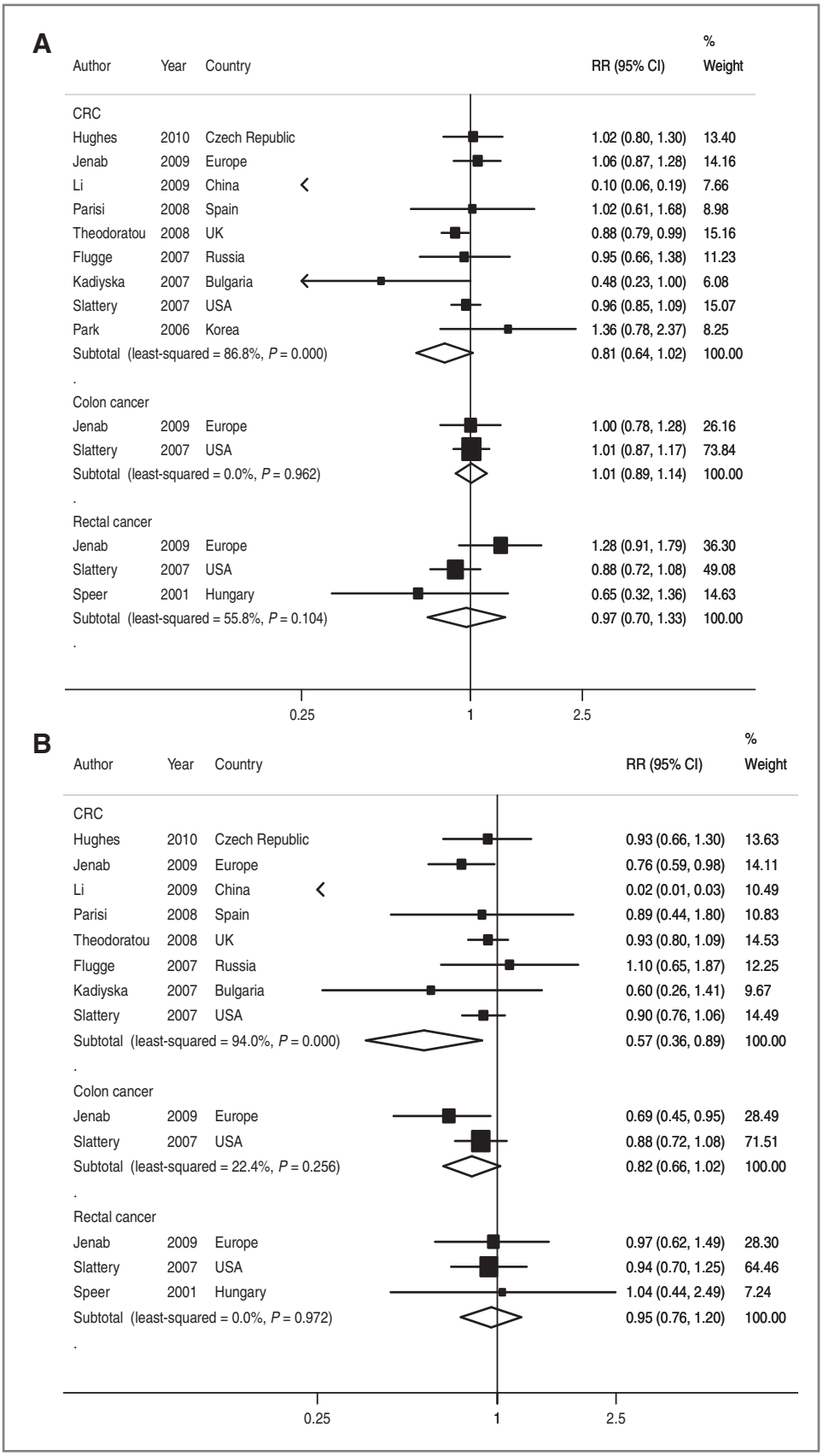

Figure 4. Meta-analyses on *BsmI VDR* polymorphism and risk of CRC. A, Bb (heterozygous type) vs. bb (wild type). B, BB (homozygous mutant type) vs. bb (wild type).

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CRC (9–11), suggesting the existence of an inverse association.

The associations between polymorphisms in the *VDR* gene and CRC risk have been investigated in several publications with inconsistent results, possibly because single studies may have lack of statistical power. Except for *BsmI* and *FokI*, published studies on CRC and other *VDR* polymorphisms are scarce. The available evidence suggests that the *BsmI* polymorphism (BB) may be associated with a lower CRC risk. There was no statistical evidence of publication bias. This association, which strengthens the evidence of the role of vitamin D in the etiology of CRC, requires confirmation in other studies. Beyond the potential effect of single-nucleotide *VDR* polymorphisms considered separately, their association in haplotypes (i.e., combinations of statistically associated single-nucleotide polymorphisms) could play an important role in the etiology of CRC (17). Interactions between the *VDR* gene and other genes have also been suggested. For instance, the androgen receptor gene could interact with the *Fok1 VDR* polymorphism and the sunlight exposure and vitamin D intake (62).

The question of the existence of an optimal vitamin D status is essential for medical practice and public health. In a meta-analysis performed in 2007 (10), Gorham and colleagues observed that a 50% lower risk of CRC was associated with a serum 25-hydroxyvitamin D level ≥1,400 IU/L (33 ng/mL) compared with <509 IU/L (12 ng/mL). Bischoff and colleagues (13) suggested that for several health outcomes (bone mineral density, CRC, among others), the most advantageous serum concentrations of 25-hydroxyvitamin D may be more than 1,272 IU/L (30 ng/mL) and probably in the range of 1,527 to 1,697 IU/L (36–40 ng/mL). The IOM committee recently stated that 20 ng/mL was the level needed for good bone health for practically all individuals (61). In an analysis including 30 studies reporting any adverse effect of high serum 25-hydroxyvitamin D in adults, no reproducible toxicity was detected below 100 ng/mL (63). However, an increased risk at high levels (≥40 ng/mL) has been suggested for pancreatic cancer (64), and the potential for a J- or U-shaped association between vitamin D status and prostate and esophagus cancers has been suggested (65, 66). Thus, the precise optimal level of 25-hydroxyvitamin D remains to establish. Our data suggest that CRC cancer risk decreases with increasing levels of circulating 25-hydroxyvitamin D in a linear dose-dependent manner (at least within the 200–1,800 IU/L range studied), although risk reduction could increase less rapidly above 1,000 IU/L (24 ng/mL). However, since the range of 25-hydroxyvitamin D levels is limited in observational studies, information on high 25-hydroxyvitamin D levels in association with CRC risk remains scarce and needs further research.

Several factors (hormonal, anthropometric, dietary, environmental, etc.) have been suggested to interact with vitamin D on the risk of CRC. First, in a reanalysis of the Women's Health Initiative dietary modification randomized control trial, a nonsignificant increased CRC risk was observed with the vitamin D/calcium supplementation among those who received estrogen therapy, whereas nonsignificant reduced risk was observed among the placebo group of the estrogen trial (67), suggesting that estrogen therapy could interact with vitamin D/calcium on CRC risk. Second, Lagunova and colleagues suggested that the direct relationship between obesity and CRC risk could be partly mediated by a decrease of 25-hydroxyvitamin D level with increasing body mass index (68). Next, it has been suggested that vitamin D and calcium may interact and both may be required to decrease the cancer risk (69). However, vitamin D remains associated with lower risk even after adjustment for calcium intake in several studies (49, 70), which is in favor of an independent effect of vitamin D. Nevertheless, the joint effect of both nutrients could be stronger than the sum of each independent effect (71). In the Health Professionals Follow-Up Study (HPFS; ref. 49), the inverse association between 25-hydroxyvitamin D and CRC risk was statistically significant only in men with calcium intake above 885 mg/day. However, the opposite was observed in the Nurses' Health Study (NHS; ref. 49). No interaction was detected between dietary calcium and circulating 25-hydroxyvitamin D level in the EPIC cohort (5). Several studies also investigated potential interactions between *VDR* polymorphisms and calcium and vitamin D intakes or status. An American study observed a significant 40% reduction in the risk of rectal cancer for the SS (*polyA*) or BB (*BsmI*) *VDR* genotypes when calcium intake was low (72). The positive association between the ff genotype and CRC risk could be stronger among individuals with lower calcium intake (52). However, the opposite was observed in a large Scottish case-control study (19). Finally, in the EPIC study, Jenab and colleagues observed that the inverse CRC risk association of higher 25-hydroxyvitamin D was stronger at lower intakes of retinol (5). This interaction was not observed in the HPFS and the NHS (49). No interaction between 25-hydroxyvitamin D and alcohol was detected in the EPIC study (5). To date, data are still insufficient to draw firm conclusions on gene–diet–vitamin D status interactions and CRC. Since we did not have original data, we were not able to systematically take into consideration or meta-analyze the potential interactions between vitamin D and dietary, lifestyle, environmental, and genetic effect modifiers.

Original aspects of our study included an updated meta-analysis of prospective studies on CRC risk and vitamin D intake and status with dose-response analyses, which strengthens the plausibility of a causal association. We also used nonlinear dose-response models for 25-hydroxyvitamin D data to investigate the potential for a threshold effect. Finally, we conducted meta-analyses of all single-nucleotide *VDR* polymorphisms for which sufficient data were available. These complementary investigations allowed us to draw an overview of the relationship between vitamin D and CRC risk.

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Limitations of our study should be considered. First, 3 publications were not included in the meta-analyses due to insufficient data. These publications suggested either no association of CRC risk with the main *VDR* polymorphisms studied (22) and dietary vitamin D intake (43) or an inverse association with dietary vitamin D intake (42).

Second, it is possible that the observed relationships could be partly due to unmeasured or residual confounding. For instance, CRC risk was statistically significant associated with dietary but not total vitamin D intake in dose-response analyses. This could be related to the fact that several medical conditions (among which some may be cancer precursors) may motivate the subjects (rightly or wrongly) to take supplements (73). In addition, there is a compelling evidence in the literature that soy intake can influence the metabolism of vitamin D (74) and therefore may be a potential confounder. To our knowledge, none of the included study adjusted their analyses on soy or isoflavone intake or phytoestrogen supplement use. Besides, most studies on vitamin D intake could not control for sun exposure. This lack of data on sun exposure was compensated by the consideration of studies on the basis of a biomarker of vitamin D status. However, the concentration of 25-hydroxyvitamin D in serum/plasma is considered as an accurate biomarker of vitamin D status (75), but a single cross-sectional measurement (as done in all studies reviewed) does not take into account the potential seasonal variations and could lead to nondifferential classification bias. Nevertheless, most of the studies included in this meta-analysis adjusted for known confounding factors such as age, body mass index, smoking, alcohol, physical activity, red/processed meat intake, energy intake, and season of blood draw (for studies on vitamin D status). Beyond a potential confounding effect, season of blood collection may also interact with vitamin D status on the risk of CRC. In the HPFS, the relationship between 25-hydroxyvitamin D and CRC risk was statistically significant for subjects whose blood collection occurred during the winter, but not during the summer (49). In the NHS, 25-hydroxyvitamin D was inversely associated with CRC risk only in areas with more than 335 langleys/day of UV light (38).

Next, the imperfections associated with published information may constitute limitations of the meta-analyses. Notably, some limitations are specific to studies that collected dietary data information. The associations estimated in our meta-analysis were weak. Measurement errors in the assessment of dietary/supplemental intake and uncertainty of information used from food composition tables are known to bias estimates. However, since we included only prospective studies, the measurement errors would most likely be nondifferential. Besides, the prospective design of the included studies also minimized the possibility of recall or selection bias. Dietary changes after baseline may, however, attenuate associations between dietary intake of vitamin D and cancer risk, as studies generally considered only baseline intake.

Finally, in some analyses, our statistical power was limited when investigating associations with specific outcome subtypes (i.e., proximal and distal colon cancer) and/or specific exposures (i.e., supplemental vitamin D intake). Similarly, other single-nucleotide *VDR* polymorphisms such as *tru91* or other variants (22, 54) have also been investigated in association with CRC risk, but to date, we were not able to do meta-analyses on these variants due to insufficient data.

Experimental studies support a protective effect of vitamin D on CRC. Some animal studies indicated that vitamin D status may influence the growth of intestinal tumors (76–79). Vitamin D status modulates various genes in the colorectal mucosa that may influence the cancer risk (71, 80). In humans, vitamin D may induce the differentiation and apoptosis (81, 82), both in colorectal adenoma or cancer cells (83) and in the normal colorectal epithelium (84–86).

In conclusion, the quantitative summary of the existing evidence from prospective cohort studies supports a modest although significant influence of vitamin D on colorectal carcinogenesis. The conclusions are supported by analysis on vitamin D intake but also on a biomarker of vitamin D status and a *VDR* polymorphism. Available studies in vitamin D supplementation did not provide an evidence of a benefit beyond that observed for dietary intake of vitamin D. Randomized controlled trials may more definitively establish a causal association, but the current data are sparse and inconclusive (87, 88) and long follow-up time will be needed before a substantial number of CRC cases could be identified in ongoing or future trials. So far, recommendations for CRC prevention should still mainly rely on the results of prospective observational studies.

Given the potential benefits from vitamin D against CRC, further research should be a priority. Beyond the protective effect on CRC risk suggested by this meta-analysis, vitamin D is implicated in fall and fracture prevention and dental health, and may also reduce the incident hypertension and cardiovascular mortality and convey immunomodulatory and anti-inflammatory benefits (89). This underlines the public health importance of reaching and maintaining an optimal vitamin D status at all life stages.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed. The views expressed in this review are the opinions of the authors. They may not represent the views of World Cancer Research Fund International/American Institute for Cancer Research and may differ from those in future updates of the evidence related to food, nutrition, physical activity, and cancer risk.

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