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REVIEW

The effect of vitamin D on the occurrence and development of colorectal cancer: a systematic review and meta-analysis

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Abstract

Purpose There has been a lot of controversies about the correlation between vitamin D and colorectal cancer (CRC). In this meta-analysis, we purposed to explore the relationship between vitamin D and the incidence of CRC/the prognosis of CRC.

Methods A systematic search for articles in databases (Pubmed, Web of Science, EBSCO and Cochrane Library) was terminated in April 2020. The primary outcomes were the incidence rate of CRC and the long-term survival of patients with CRC.

Results According to the estimated pooled OR from 21 eligible studies, covering 904,152 people, the use of vitamin D was inversely associated with the incidence of CRC [OR = 0.87, (0.82–0.92)]. Among the four studies included in this meta-analysis, covering 7486 patients, compared the overall survival (OS) of CRC between the vitamin D users and the non-users. Based on the estimated pooled HR, vitamin D potentially improved the long-term survival of CRC patients [HR = 0.91, (0.83–0.98)].

Conclusion This meta-analysis demonstrates that vitamin D not only has a positive impact on the incidence of CRC from either the dietary or supplemental sources but also benefits clinical outcomes and improves the long-term survival of CRC patients. However, further studies are recommended to clarify the above phenomena.

Keywords Vitamin D · Colorectal cancer · Meta-analysis · Incidence · Prognosis

Introduction

Colorectal cancer (CRC) is among the common malignancies, with over 1.8 million incident cases and 860,000 deaths annually [1]. Though the international incidence rates vary, migration studies have documented increasing rates among groups moving from low incidence to high incidence areas [2]. As a result, the role for an environmental factor (s) such as diet in CRC is depicted [3, 4].

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Vitamin D is the collective name for cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) [5]. There exists controversy on how vitamin D deficiency is associated with the aetiology of some common cancers. In a study, the receiver operating characteristic (ROC) curve for serum 25(OH)D level suggested that once the level fell below 30 ng/mL, the risk for advanced colorectal adenoma was not progressive but stepwise as levels fell below this serum level. It is worth evaluating a minimum period of vitamin D deficiency [6]. Observational evidence immensely supports that vitamin D is related to the incidence of CRC. Previous studies had revealed the intestine as an organ with the highest expression of vitamin D receptor (VDR) [7, 8]. Moreover, intestines harbors 1α, 25-dihydroxy vitamin D3 or calcitriol, the most active vitamin D metabolite, that mediates vital homeostatic functions [9]. Some vitro studies have demonstrated vitamin D-induced growth arrest and apoptosis of CRC cells, modulation of the Wnt signalling pathway, DNA repair, and immunomodulation [10, 11], thus supporting a causal relationship of vitamin D with CRC [12].

Moreover, various studies using animals, including some that analyze the effect of diets with vitamin D and carcinogen content, and others with xenotransplanted mice, indeed agreed with the beneficial effect of vitamin D, calcitriol, or its analogues on colorectal tumorigenesis [13]. Collectively, these findings demonstrate a protective function of vitamin D against CRC by reducing risk and attenuating the tumorigenic process. Several studies have also investigated the correlation between vitamin D and the incidence of CRC/the prognosis of CRC. However, individual studies have yield inconsistent results, potentially caused by limitations associated with an individual study. For instance, based on prospective studies, the use of vitamin D was inversely associated with the incidence of CRC in the Nurses' Health Study [14], but not in the Japan Public Health Centre [15]. Although several studies [16–19] have explored the correlation between vitamin D and the prognosis of CRC, a majority of them had small series with conflicting results. The association of vitamin D with the incidence of CRC and the prognosis of CRC remains elusive. To provide insight on these controversies, we conducted a comprehensive meta-analysis pooling the available data to examine the relationship between vitamin D and the incidence of CRC/the prognosis of CRC to guide its clinical application.

Methods

Search strategy

In this meta-analysis, we conducted a systematic search of databases (Pubmed, Web of Science, EBSCO and Cochrane Library) which was terminated in April 2020. The subject search was combined with free text terms and medical subject heading, including ('CRC' OR 'colorectal carcinomas' OR 'colorectal neoplasms' OR 'colon cancer' OR 'colon neoplasms' OR 'colonic neoplasms' OR 'rectum cancer' OR 'rectum neoplasms' OR 'rectal neoplasms' OR 'rectal cancer') AND ('vitamin D'). Moreover, the references in the literature were manually searched to avoid omitting relevant studies.

Selection criteria

Each study retrieved for inclusion was assessed by two authors independently. The inclusion criteria included the following: (1) Randomized controlled trials (RCTs) or observational studies including cohort and case-control studies. (2) Reports on the correlation between vitamin D and the incidence of CRC or the correlation between vitamin D and prognosis of CRC. (3) Result (including odds ratio (OR)) of the correlation between vitamin D and the incidence of CRC as well as the result (including hazard ratio (HR)) of the correlation between vitamin D and prognosis of CRC. Exclusion criteria included the following: (1) Articles that were not original. (2) Articles without relevant outcome or detailed data. (3) Duplicate reports. However, on an encounter with duplicate articles, the literature that had the newest or comprehensive data were included. (4) The disease was not CRC, like polyp, adenoma, and precancerous lesions.

Data extraction and study quality assessment

Data extraction and study quality assessment were independently conducted by two investigators. Uncertain inclusions of a study between the two investigators were resolved by consensus of two investigators and the third reviewer. The database was used to record the available information, including author, year of publication, country, cohort characteristics, sample size, time to recruit, follow-up time, vitamin D type, cancer type, total vitamin D dose, study design, and adjustment factors. This meta-analysis was conducted per the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [20]. The quality of RCTs and observational studies was determined by the Cochrane Collaboration's tool and the Newcastle-Ottawa Quality Assessment Scale (NOS) checklist, respectively, by two independent authors.

Statistical analysis

Statistical analyses were conducted using STATA 12.0 Software (Stata, College Station). OR, 95% confidence interval (CI) were utilized to analyze the correlation between vitamin D and the incidence of CRC. HR, 95% CI were utilized to analyze the correlation between vitamin D and prognosis of CRC. Cochran's Q statistic and I^2 statistics were applied to evaluate the heterogeneity in the studies. Considering the variability of vitamin D type and dose, a random-effects model was used for meta-analysis. The sources of heterogeneity were investigated through the subgroup analyses. Publication bias was assessed using Begg's and Egger's

regression asymmetry test. Furthermore, the sensitivity analysis was conducted to test the stability of the results by excluding each study successively.

Results

A total of 2245 studies were screened after the database search. Additionally, 4 studies were identified through other sources. Following the deletion of 1470 duplicates, 731 studies were excluded by screening their title and abstract. Additionally, 48 studies were evaluated via reading full-text articles. Finally, 25 eligible articles [14–19, 21–39] were included in quantitative synthesis (Fig. 1), 21 studies [14, 15, 21–39] for the correlation between vitamin D and the incidence of CRC and 4 studies [16–19] for the correlation between vitamin D and prognosis of CRC. The quality of 25 studies was assessed as shown in Supplementary Table 1.

The characteristics of 21 studies demonstrating the correlation between vitamin D and the incidence of CRC are shown

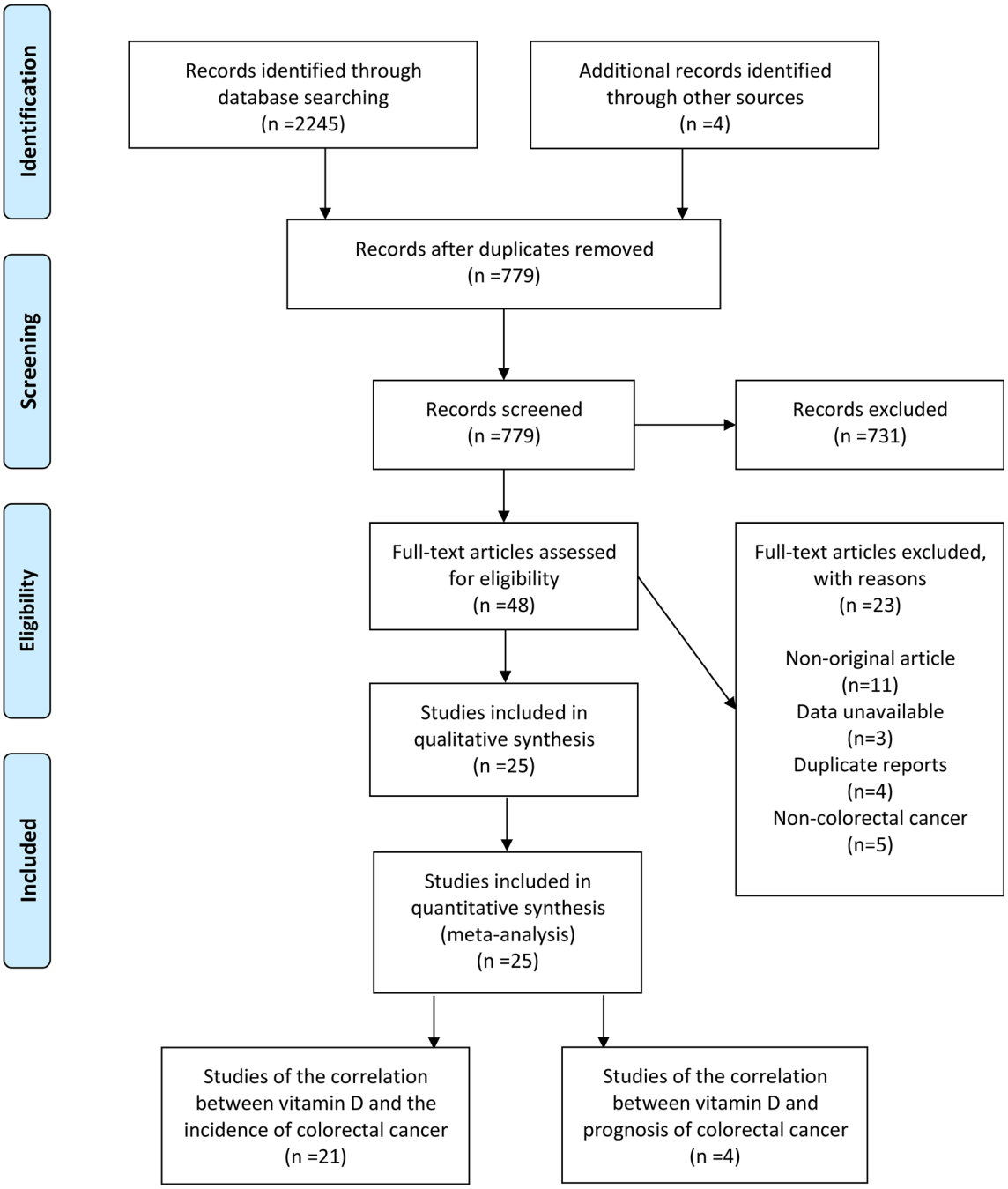

Fig. 1 Flow diagram describing inclusion and exclusion criteria

Table 1 Characteristics of all the studies included in the meta-analysis (the correlation between Vit D and the incidence of CRC)

Author	Year	Country	Cohort characteristics	Time to recruit	Median follow-up (year)	Age, year median (range)		Follow-up number	Cancer type	Vit D type	Total Vit D dose		Study	Adjustment
						Experiment	Control				Experiment	Control		
Lipworth	2019	US	NA	2011	5.3	67.1 ± 7.0	67.1 ± 7.1	25871	CRC	Total Vit D Supplementary Vit D	Vitamin D3 2000 IU/day	Placebo	RCT	Age, sex
McCullough	2003	US	Cancer Prevention Study II Nutrition Cohort	1992-1997	NA	50-74	50-74	121749 60866 (male) 66883 (female)	CRC	Total Vit D Dietary Vit D	> 110 IU	< 110 IU	POBS	Age, smoking, BMI, education, physical activity (exercise only), family history of CRC, energy, saturated fat, fruit, vegetables, multivitamin, HRT use (women only)
Terry	2002	Sweden	Swedish Mammography Screening Cohort Study in Women	1987-1990	11.3	40-74	40-74	61463	CRC	Total Vit D Dietary Vit D	> 2.6 ug/day	0.5- < 2.6 ug/day	POBS	Age, BMI, education, red meat, alcohol, energy, saturated fat, folic acid, vitamin C, calcium
Martínez	1996	US	The Nurses' Health Study	1980	> 12	30-55	30-55	89448	CRC	Total Vit D Dietary Vit D	High dose	Low dose	POBS	Age, BMI, physical activity, family history of CRC, aspirin, smoking, red-meat, alcohol
Lin	2005	US	The Women's Health Study	1993	10	> 45	> 45	36976	CRC	Total Vit D Dietary Vit D Supplementary Vit D	> 161 IU	< 161 IU	POBS	Age, randomized treatment assignment, BMI, family history of CRC, history of colon polyps, physical activity, smoking, red meat, alcohol, energy, saturated fat, multivitamin, menopausal status, baseline postmenopausal women HRT use
Wactawski-Wende	2006	US	Women's Health Initiative centers	1993-1998	7	50-79	50-79	36282	CRC	Total Vit D Supplementary Vit D	400 IU/day Supplement-ary Vit D	Placebo	RCT	NA
Park	2007	US	The Multiethnic Cohort Study	1993-1996	NA	45-75	45-75	85903 (male)	CRC	Total Vit D Dietary Vit D Supplementary Vit D	> 39 IU	< 39 IU	POBS	Age, smoking, family history of CRC, physical activity, history of intestinal polyps, nonsteroidal antiinflammatory drugs, BMI, dietary fiber, HRT use (for women only), multivitamins
						45-74	45-74	105108 (female)	CRC	Total Vit D Dietary Vit D Supplementary Vit D	> 39 IU	< 39 IU	POBS	Ethnicity, age, smoking, family history of CRC, physical activity, history of intestinal polyps, nonsteroidal antiinflammatory drugs, BMI, energy, dietary fiber intake, HRT use (for women only), multivitamins
Ishihara	2008	Japan	The Japan Public Health Center-based Prospective	1990-1994	7.8	30-75	30-75	35194 (male) 39445 (female)	CRC	Total Vit D Supplementary Vit D	> 5.6 ug (male) > 5.8ug (female)	< 5.6ug (male) < 5.8ug (female)	POBS	Alcohol, smoking, BMI, physical exercise, CRC screening, menopausal status (female only), red meat, vegetables, fruit, folate,

Table 1 (continued)

Author	Year	Country	Cohort characteristics	Time to recruit	Median follow-up (year)	Age, year median (range)		Follow-up number	Cancer type	Vit D type	Total Vit D dose		Study	Adjustment
						Experiment	Control				Experiment	Control		
			Study (JPHC Study)											vitamin B-6, vitamin B-12, energy, supplement use
Um	2019	US	The prospective Iowa Women's Health Study	1985	NA	65	65	17820	CRC	Total Vit D Supplementary Vit D	Users	Non-users	POBS	Age, family history of CRC, BMI, smoking, alcohol, physical activity, postmenopausal HRT use, energy, magnesium, fruit, vegetables, red and processed meat, dietary calcium, and dietary vitamin D
Boutron	1996	French	The C6te d'Or area	1985-1990	NA			480	CRC	Total Vit D Dietary Vit D	Quintiles 2-5	quintile1	ROBS	NA
Kampman	2000	US	The Kaiser Permanente Medical Care Program	1991	NA			4403	CC	Dietary Vit D Supplementary Vit D	Quintiles2-5	Quintiles1	ROBS	Age, BMI, family history, aspirin, NSAIDs, energy, activity, fiber, calcium
Slattery	2004	US	The Kaiser Permanente Medical Care Program	1997	NA	30-79	30-79	2157	RC	Total Vit D Dietary Vit D	Quartiles 2-4	Quartile 1	ROBS	Age, physical activity, energy intake, dietary fiber, BMI, NSAIDs
Marcus	1998	US	a case-control study of colorectal cancer in Wisconsin women	1990-1991	NA	< 75	< 75	1190	CC/RC	Total Vit D Dietary Vit D Supplementary Vit D	> 148 IU (CC)	< 148 IU (CC)	ROBS	energy
Lipworth	2009	Italy	NA	1992-1997	NA	6223-74	5820-74	6107	CC/RC	Total Vit D Dietary Vit D	High dose	Low dose	ROBS	Age, sex, study center, education, physical activity, family history, BMI, fruit, vegetables, energy
Sun	2011	Canada	Newfoundland Familial Colorectal Cancer Registries (NFCCR) and The Ontario Familial Colorectal Cancer Registries (OFCCR	2003-2006	NA	20-74	NA	4241	CRC	Total Vit D Dietary Vit D Supplementary Vit D	Quintiles2-5	Quintiles1	ROBS	Energy, age, sex, BMI, physical activity, first-degree relatives with CRC, polyps, diabetes, reported colon screening procedure, smoking, alcohol, education,household income, marital status, NSAID, multivitamin, reported HRT (females only), fruits, vegetables, red meat
Banque	2012	Spain	a tertiary general university hospital in the Barcelona metropolitan area	2007-2009	NA	68 ± 10.7	64 ± 10.3	735	CRC	Total Vit D Dietary Vit D	Tertiles2-3	Tertile1	ROBS	Age, sex, energy
Valles	2018	Spain	a population-based multicenter	2008-2014	NA	67.0 ± 10.8	63.3 ± 11.8	6090	CRC	Total Vit D Dietary Vit D	Users	Non-users	ROBS	NA

Table 1 (continued)

Author	Year	Country	Cohort characteristics	Time to recruit	Median follow-up (year)	Age, year median (range)		Follow-up number	Cancer type	Vit D type	Total Vit D dose		Study	Adjustment
						Experiment	Control				Experiment	Control		
			case-control study											
Hosseinzadeh	2019	Iranian	a case-control study of Iranian Population	2017-2018	NA	41–76	40–72	363	CRC	Total Vit D Dietary Vit D	Users	Non-users	ROBS	NA
Kearney	1996	US	The Health Professionals Follow-up Study	1986	6	40-75	40-75	47935	CC	Total Vit D Dietary Vit D Supplementary Vit D	> 161 IU	< 161 IU	POBS	Age, energy, family history for CC, previous polyp, screening, smoking, alcohol, aspirin, physical activity, BMI, red meat, saturated fat, dietary fiber
Kesse	2005	French	NA	1990	6.9	40-65	40-65	67484	CRC	Total Vit D Dietary Vit D	> 1.72 ug	< 1.72 ug	POBS	Education, smoking, family history of CC, BMI, physical activity, energy, alcohol
Järvinen	2005	Finland	NA	1966	24	> 15	> 15	9959	CRC	Total Vit D Dietary Vit D	Quartiles 2-4	Quartile 1	POBS	Age, sex, BMI, occupation, smoking, geographical area, energy

NA, not available; *RCT*, randomized controlled trial; *ROBS*, retrospective observational studies; *POBS*, prospective observational study; *Vit D*, vitamin D; *CC*, colon cancer; *CRC*, colorectal cancer; *RC*, rectal cancer; *BMI*, body mass index; *HRT* use, hormone replacement therapy

Table 2 Characteristics of all the studies included in the meta-analysis (the correlation between vitamin D and prognosis of CRC)

Author	Year	Country	Cohort characteristics	Age, yearmedian (range)		Time to recruit patients	Total number of follow-up	Vit D type	Patients of number		Vit D dose		Length of follow-up	Study	Adjustment
				Experiment	Control				Experiment	Control	Experiment	Control			
Jeffreys	2015	UK	UK Clinical Practice Research Datalink (CPRD)	≥ 55	≥ 55	2002 - 2009	4122	Total VitD Supplementary Vit D	556	3566	Users	Non-users	30.4 mo	ROBS	Age, smoking, alcohol, BMI, area-level deprivation
							556	Total VitD Supplementary Vit D	426	130	High dose*	Low dose*			
Lewis	2016	US	the North Carolina Central Cancer Registry (NCCCR)	65.9±9.4	62.6±10.5	2009	453	Total VitD Supplementary Vit D	95	358	Users	Non-users	2 yr	POBS	Age, sex, race, marriage, education, income, smoking, alcohol
Antunac	2018	Croatia	NA	64 56–71	62 56–65	1992-1993	71	Total VitD Supplementary Vit D	37	34	Users	Non-users	46 mo	POBS	NA
Yang	2014	US	The Cancer Prevention Study-II Nutrition Cohort	64	64	1992-1993	2284	Total VitD Dietary Vit D	NA	NA	Quartile 1	Quartile2-4	7.5 ± 4.6 yr	POBS	Age, sex, tumor stage, energy, folate

NA, not available; *POBS*, prospective observational studies; *ROBS*, retrospective observational studies; *Vit D*, vitamin D; *Yr*, year; *Mo*, month; *BMI*, body mass index

*High intake: the patients took vitamin D intake 3+ prescriptions; Low intake: the patients took vitamin D intake 1–2 prescriptions

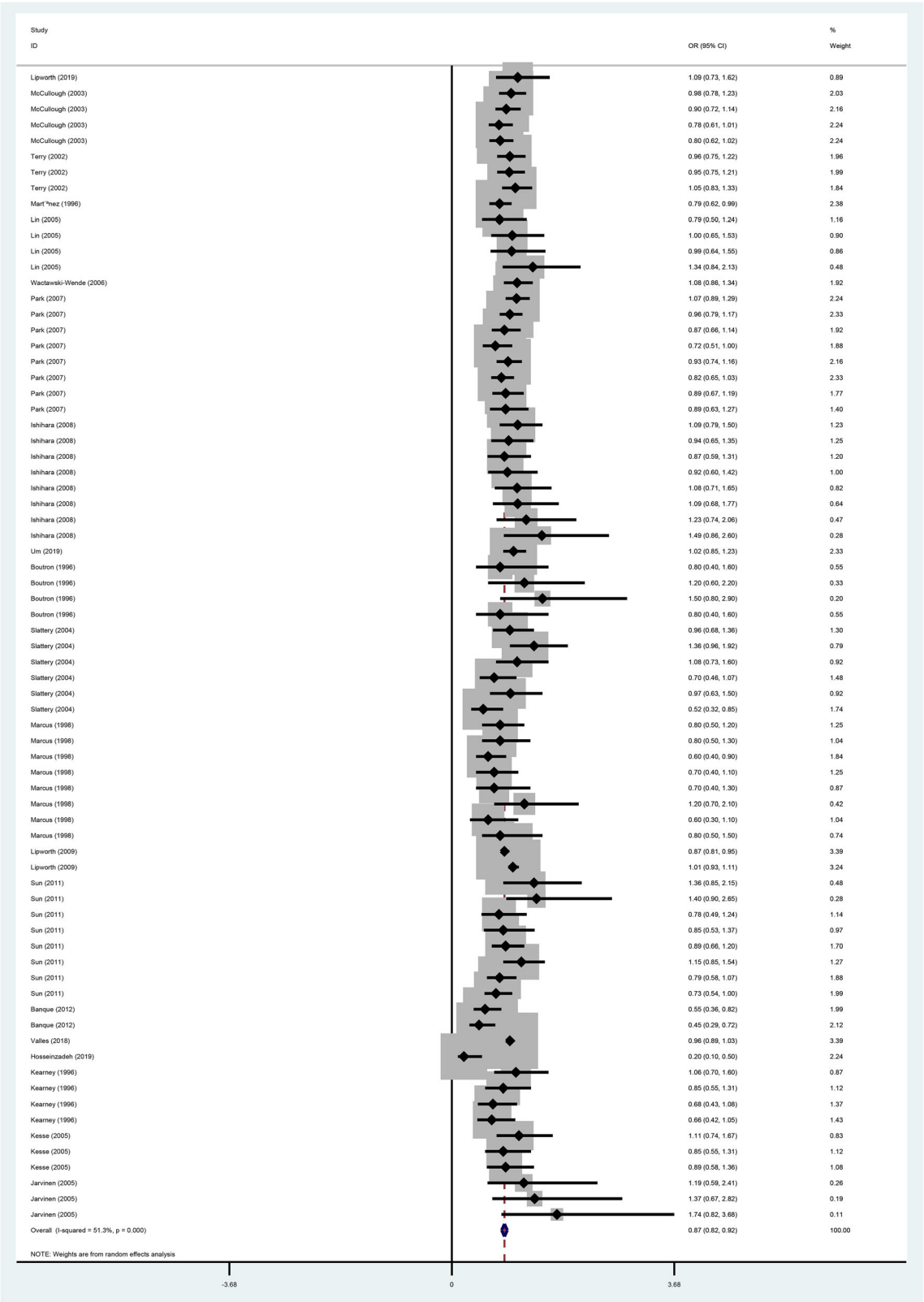

Fig. 2 Forest plots of the correlation of total vitamin D and colorectal cancer incidence

in Table 1. Geographic locations were categorized as Asia, Europe, and North America. Total vitamin D intake was from dietary and vitamin D supplement. Cancer types were CRC classified as colon cancer and rectal cancer. Adjustment

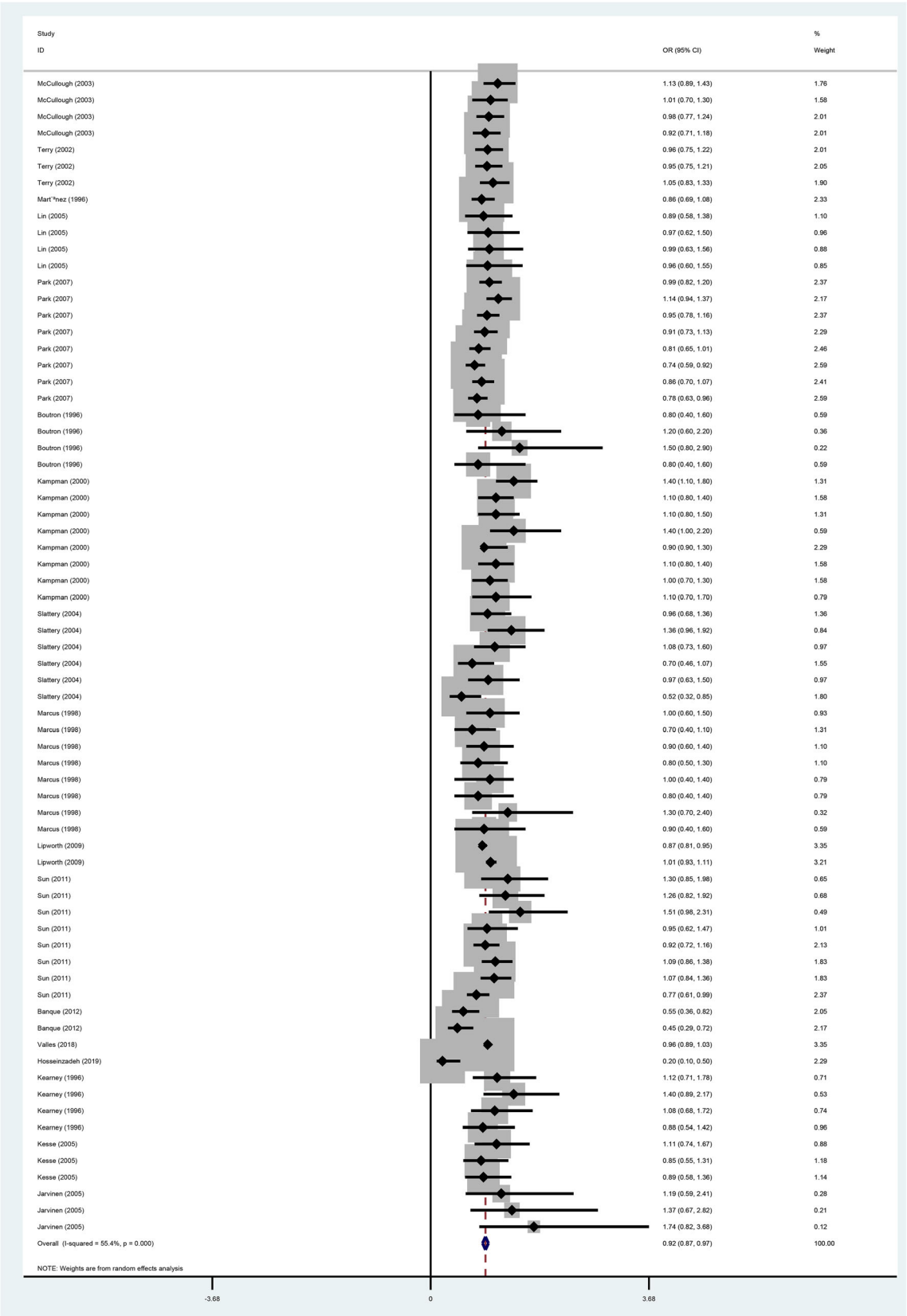

Fig. 3 Forest plot of the correlation of dietary vitamin D and colorectal cancer incidence

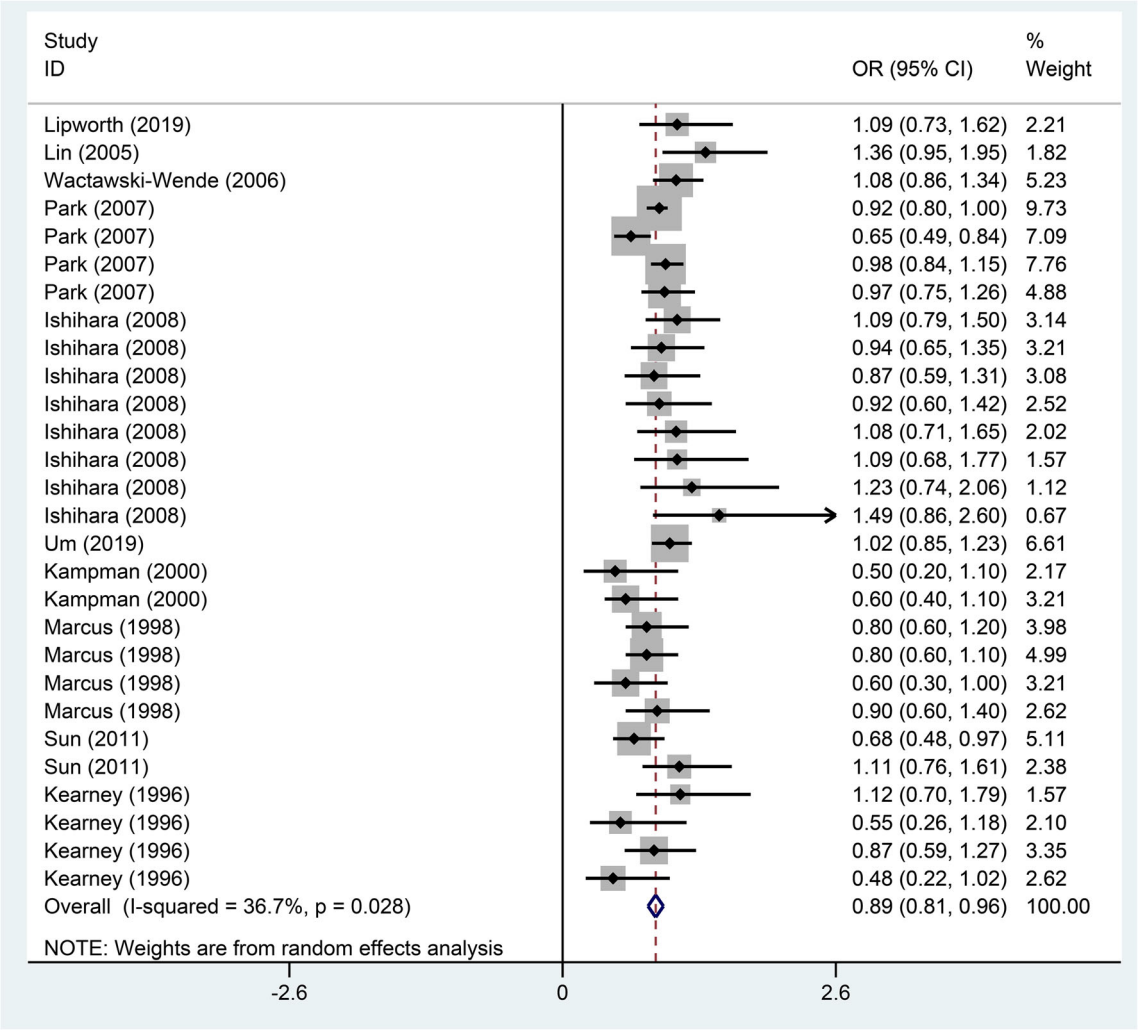

Fig. 4 Forest plot of the correlation of supplementary vitamin D and colorectal cancer incidence

factors were mainly sex, age, education, energy, body mass index, and smoking. The characteristics of 4 studies of the correlation between vitamin D and the prognosis of CRC are shown in Table 2. Geographic location was categorized as Europe and North America. Total vitamin D intake was from dietary and vitamin D supplement. Adjustment factors were mainly sex, age, alcohol, energy, and smoking.

Vitamin D and risk of CRC incidence

A total of 21 studies reported OR in CRC among vitamin D (total intake) higher intake compared with the low intake. The directions of the estimated OR and 95% CI were not consistent among the studies. According to the estimated pooled OR, the use of vitamin D was inversely associated with the incidence of CRC [OR = 0.87, (0.82–0.92)]. Heterogeneity was prominent (I^2 = 51.3%) (Fig. 2). Having found an inverse association between total vitamin D and incidence of CRC, we further probed whether dietary vitamin D and supplementary vitamin D could reduce the risk of CRC. The results of the meta-analysis of 17 studies are shown in Fig. 3. Our assessments revealed that dietary vitamin D was associated with a decrease in the incidence of CRC [OR = 0.92, (0.87–0.97)]. The results of the meta-analysis of 9 studies are displayed in Fig. 4. Similarly, supplementary vitamin D was related to a decline in the incidence of CRC [OR = 0.89, (0.81–0.96)].

Subgroup analysis

The relationship between total vitamin D usage and the incidence of CRC among male and female were examined in 5 and 11 studies, respectively. The pooled ORs for male and female were 0.90 (95%CI, 0.84–0.97) and 0.87 (95%CI, 0.81–0.92), respectively. To compare OR in colon cancer and rectal cancer, 7 and 8 studies were used, respectively. The pooled ORs for colon cancer and rectal cancer were 0.82 (95%CI, 0.73–0.90) and 0.88 (95%CI, 0.78–0.97), respectively. Concerning the subsites of colon cancer, the pooled ORs for proximal colon cancer and distal colon cancer were 0.83 (95%CI, 0.74–0.91) and 0.83 (95%CI, 0.76–0.91),

Table 3 Subgroup analysis of the correlation between Vit D and the incidence of CRC

		No. of studies	OR	95%CI	*p*	Heterogeneity (I^2) (%)
Total Vit D	Male	5	0.90	0.84-0.97	$p < 0.05$	13.1
	Female	11	0.87	0.81-0.92	$p < 0.05$	10.0
	Colon cancer	7	0.82	0.73-0.90	$p < 0.05$	34.8
	Rectal cancer	8	0.88	0.78-0.97	$p < 0.05$	23.6
	Proximal colon cancer	6	0.83	0.74-0.91	$p < 0.05$	0
	Distal colon cancer	6	0.83	0.76-0.91	$p < 0.05$	0
	North America	12	0.87	0.82-0.91	$p < 0.05$	14.9
	European	8	0.84	0.72-0.96	$p < 0.05$	79.7
Dietary Vit D	North America	9	0.94	0.90-0.99	$p < 0.05$	21.5
	European	8	0.84	0.72-0.96	$p < 0.05$	79.7
Supplementary Vit D	North America	9	0.86	0.77-0.94	$p < 0.05$	48.7

Vit D, vitamin D; *CRC*, colorectal cancer; *OR*, odds ratio; *CI*, confidence interval

respectively. Accordingly, the pooled ORs in Europe and North America were 0.84 (95%CI, 0.72–0.96) and 0.87 (95%CI, 0.82–0.91). From the subgroup analysis of the above aspects, the potential effect of vitamin D to reduce the incidence of cancer was consistent.

The relationship between dietary vitamin D usage and the incidence of CRC in Europe and North America was retrieved in 9 studies and 8 studies, respectively. With the estimated pooled OR, vitamin D was inversely associated with the incidence of CRC in North America [OR = 0.94, (0.90, 0.99)] and in Europe [OR = 0.84, (0.72, 0.96)]. However, the estimated pooled OR showed a supplementary vitamin D examined in 9 studies was inversely associated with the incidence of CRC in North America [OR = 0.86, (0.77–0.94)] (Table 3).

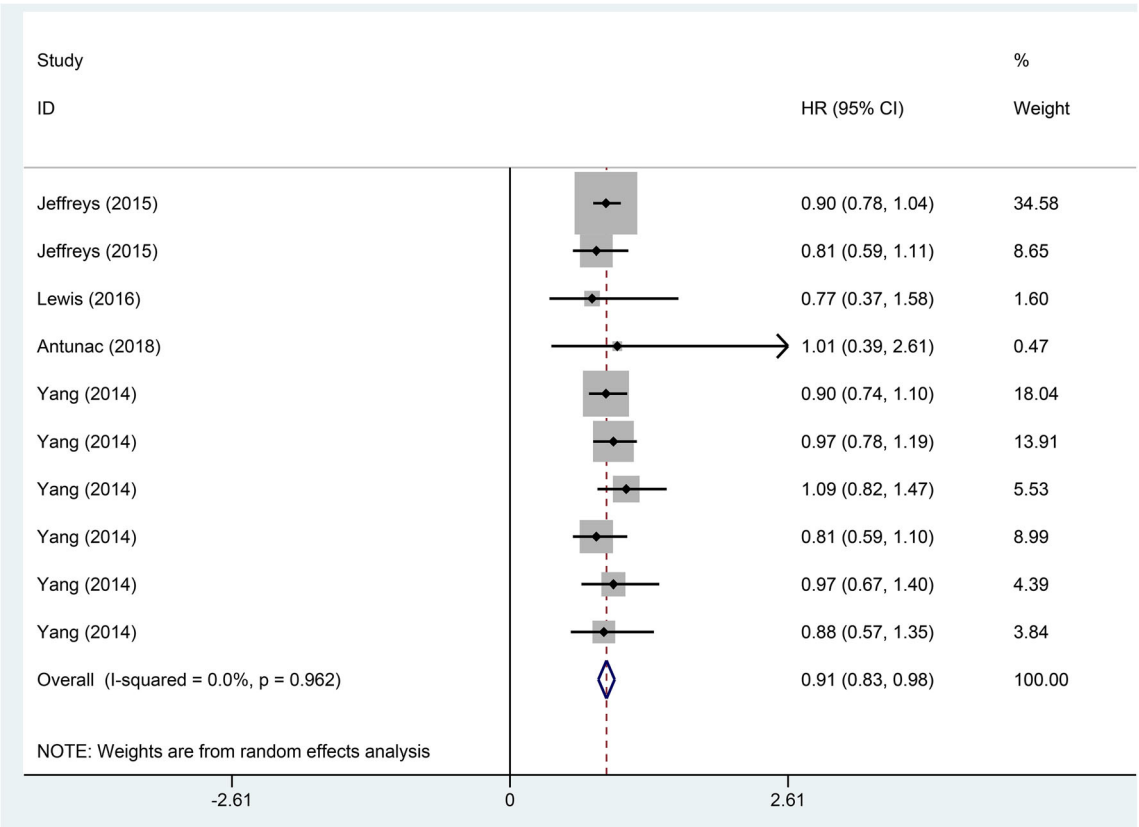

Fig. 5 Forest plot of the influence of total vitamin D on the overall survival of colorectal cancer

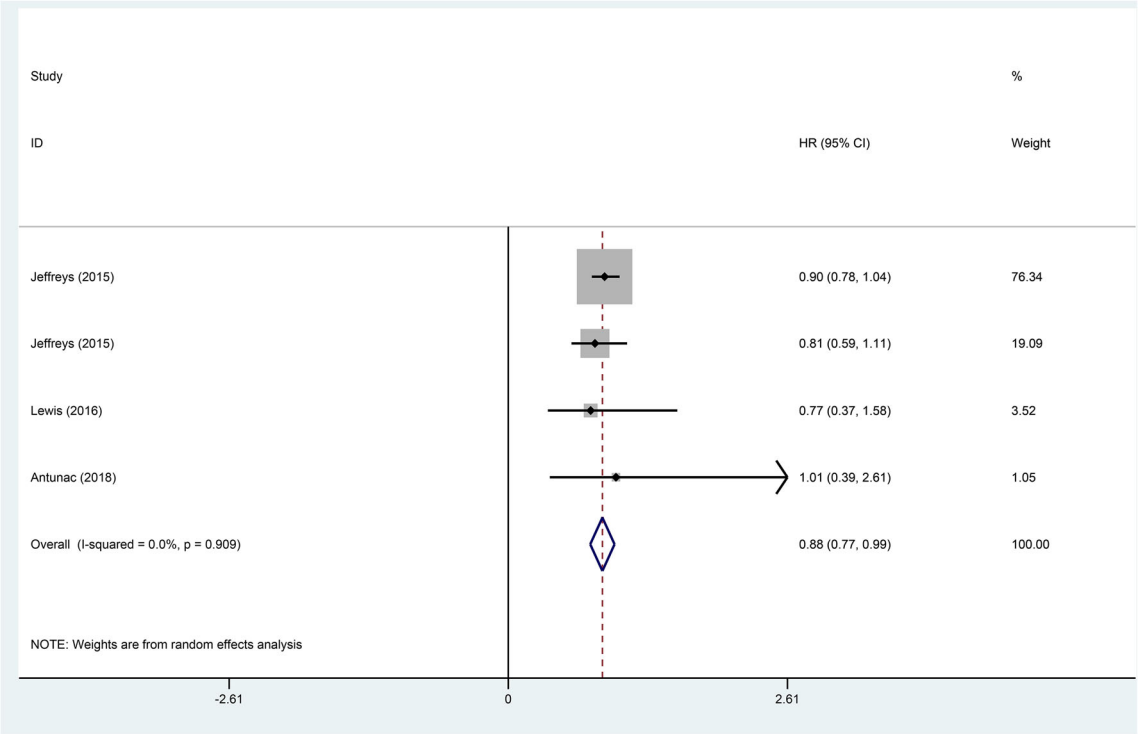

Fig. 6 Forest plot of the influence of supplementary vitamin D on the overall survival of colorectal cancer

Vitamin D and prognosis of CRC

We included four studies in the analysis to compare the OS of CRC between vitamin D users and non-users. The estimated pooled HR revealed that the use of vitamin D was associated with longer OS [HR = 0.91, (0.83–0.98)] (Fig. 5). Only 3 studies were used to compare the OS of CRC between the supplementary vitamin D users and non-users. According to the estimated pooled HR, the use of supplementary vitamin D improved OS of CRC [HR = 0.88, (0.77–0.99)] (Fig. 6).

Publication bias and sensitivity analysis

No significant publication bias was observed on the influence of total vitamin D and CRC incidence using Egger's plot (p = 0.278) or Begg's test (p = 0.697) (Supplementary Fig. 1). Sensitivity analysis was performed to test the stability of the results by excluding each study successively. The detailed sensitivity analysis results are illustrated in Supplementary Fig. 2. Similarly, there was no significant publication bias on the influence of dietary vitamin D and CRC incidence (Supplementary Fig. 3). The detailed sensitivity analysis results are indicated in Supplementary Fig. 4. Moreover, there was no significant publication bias on the influence of supplemental vitamin D and CRC incidence (Supplementary Fig. 5). The detailed sensitivity analysis performed to test the stability of their results is shown in Supplementary Fig. 6.

Discussion

In the present study, we conducted a meta-analysis on 21 articles to evaluate the correlation between vitamin D and the incidence of CRC whereas the 4 articles were evaluated on the correlation between vitamin D and prognosis of CRC. Notably, vitamin D intake was shown to be related to a decline in the incidence of CRC as well as improving the long-term survival of CRC patients. The effect was consistently observed in subgroup analyses of gender, CRC sites, colonic cancer subsites, and geographical differences. However, this estimate was robust across the sensitivity analysis. Hence, our findings provide an insight into the protective action of vitamin D against CRC by reducing CRC risk and improving the prognosis of patients with CRC.

Previous studies demonstrated that vitamin D potentially reduces the risk of colorectal adenomas [40], a finding that was inconsistent with reports from other studies [41, 42]. Elsewhere, a meta-analysis [43] reported that neither dietary intake of vitamin D nor supplemental intake of vitamin D was significantly associated with the incidence of colorectal adenoma. Thus, this discrepancy might be attributed from multiple factors, such as the limited number of articles on either dietary or supplemental vitamin D intake, differences in the dose of supplemental vitamin D, the absorption rate of dietary intake of vitamin D, and metabolism of vitamin D, and other confounding factors, such as age, physical activity, and sun exposure. On the contrary, another meta-analysis [44]

indicated that vitamin D intake was inversely associated with colorectal adenomas incidence and recurrent adenomas. The result further supported the role of vitamin D in preventing colorectal adenoma incidence and their recurrence. More importantly, vitamin D may display an additional protective effect other than their preventive effects against colorectal adenomas [44]. It is deductive to speculate the intake of vitamin D inhibits the progression of adenoma or precancerous polyps to CRC, thereby reducing the risk of CRC.

Some studies have found that vitamin D has slight neoplasm inhibitory impacts, for example, promoting bile acid catabolism and modulating > 200 genes involved in cell cycle regulation, DNA repair, immunomodulation, and protection against oxidative stress and inflammation [45–48]. Similarly, vitamin D may control the development of colorectal cells via the attachment of vitamin D identifying receptors [46]. In $Smad3^{-/-}$ mice with inactivated TGF-β signalling pathways increased dietary vitamin D intake significantly suppressed p-P38 MAPK activity and lowered the accumulation of colonic inflammatory cells by increased 25(OH) D circulation, which ultimately reduced the incidence of colon carcinomas [49]. Besides, vitamin D facilitates the differentiation of colon carcinoma cells via the promotion of the expression of adhesion proteins, such as E-cadherin, and the inhibition of the Wnt/β-catenin signalling pathway [50].

Although controversies exist on the correlation between vitamin D and the incidence of CRC several studies [15, 22, 24] had revealed that there was no protective effect on CRC risk. The non-significant results may be attributed to inadequate measures of vitamin D intake; natural dietary sources of vitamin D are limited. Conversely, an American cohort study [21] reported a significant protective effect of vitamin D on CRC hazard. An inverse association between the use of vitamin D, the prognosis of CRC by Jeffreys et al. [17] concurs with our finding, though not consistent with a report by Antunac et al. [16]. Also, a recent meta-analysis [51] demonstrated a clinically beneficial effect from vitamin D supplementation on survival outcomes in CRC patients.

Interestingly, both dietary and supplemental sources of vitamin D showed significant effects. However, there are food products that are rich in vitamin D3 [52] such as fish oils, fish, and fortified-products (dairy products). For instance, fish consumption was revealed to have an inverse correlation with CRC risk in humans according to a previous meta-analysis [53]. Therefore, we advise that individuals vulnerable to vitamin D deficiency should have a well-mixed diet with modest fish. Considering that dietary sources of vitamin D were limited, supplemental vitamin D was also necessary. Following numerous reports from previous studies [16, 33], vitamin D supplementation potentially prevents or slows the progression of CRC probably due to inadequate duration of the trial since the development of CRC is associated with long latency. Therefore, in our work, vitamin D supplementary used may be insufficient to demonstrate a protective effect. Additionally, published meta-analyses of the overall risk of colon cancer also correlate to serum level of 25(OH)D at or around 30 ng/mL [6]. Of interest, the Endocrine Society recommends children under one year of age require 400–1000 IU daily, children one year and older 600–1000 IU daily, and all adults 1500–2000 IU daily to sustain a circulating serum level of 25(OH)D > 30 ng/mL [54], which may have a protective effect on the incidence of CRC. The subgroup analysis of gender indicated the total vitamin D intake was significantly associated with a lower risk of CRC both in male and female. Several cohort studies [26, 27] in male have shown no association or only weak inverse association of total vitamin D intake with CRC risk probably due to higher misclassification of vitamin D intake in male than in the female. On the other hand, a cohort study [27] in female found no association between total vitamin D intake and CRC risk. Different physiological mechanisms may be operational; these mechanisms may involve gender-specific gut motility or other hormonal influences [55]. Sex hormone metabolism potentially modifies or mask the associations between vitamin D status and CRC risk [26], since the vitamin D receptor has been linked with the estrogen receptor system [56, 57]. The intriguing finding in our study was that vitamin D was inversely associated with the incidence of CRC in both male and female. This may be due to the large sample size of our study, though further studies are recommended to ascertain this.

From the studies that provided the colon subsite-specific data [15, 23, 26, 28, 31, 33], total vitamin D was inversely associated with distal and proximal colon cancers. The two sides of the colorectum differ in respect to the embryological origin and bile acid metabolism, and in some cases, tumors in these sites may develop along different carcinogenic pathways [58]. Though there were differences across colonic subsites in molecular characteristics and associations with genetic and environmental factors[58], our study indicated that there were no differences via the subgroup analysis of colonic subsites (distal and proximal colon cancers). For instance, our study showed that total vitamin D has a slightly stronger association with colon cancer than rectal cancer, [OR = 0.82, (0.73–0.90)] versus [OR = 0.88, (0.78–0.97)], despite the limited evidence from epidemiologic studies and clinical trials. In the previous studies, there was no inconsistency on whether the use of vitamin D could affect the incidence of CRC by colorectal sites. Some cohort studies found total vitamin D intake has an inverse association with colon cancer risk only [26, 31]. In another cohort study, total vitamin D intake was observed to have a negative relationship with rectal cancer risk merely [28]. Furthermore, other studies have indicated that vitamin D is not associated with the incidence of colon cancer or rectal cancer [24, 33]. Thus, further investigation of

vitamin D with risk of colorectal sites neoplasms is of paramount importance.

Herein, we reported an inverse relationship between total vitamin D usage and the incidence of CRC both in Europe and in North America. Nonetheless, pooling data from European studies resulted in a stronger association than that of North America between dietary vitamin D intake and the incidence of CRC. This provides support for the importance of differences in dietary habits, race, the relative composition of foods that make up dairy products, and other demographic differences across populations that could contribute to the variability. Notably, the sample size in Asian use lacked reliable data to evaluate the association between vitamin D and the incidence of CRC.

Previous study has indicated that a 50% lower risk of CRC was associated with a serum 25(OH)D level > 33 ng/mL, compared to < 12 ng/mL[59]. Additionally, Sy and Bautista [60] also noted the overall risk of colon polyps would be related to serum 25(OH)D level at or around 30 ng/mL. More importantly, the study found that vitamin D insufficiency is highly prevalent among patients with a family history of colon cancer [6]. Above all, we suggest that people with a positive family history could control regularly their vitamin D level to prevent the incidence of CRC. In a study [61] by Sellers et. al., total and supplemental vitamin D intakes were associated inversely with risk among family history positive women. The cellular effect of vitamin D metabolites is influenced by the biology of the vitamin D receptor complex [6]. Interestingly, Peters et al. [62] did not find attributable patterns of vitamin D receptor variants in families with an increased occurrence of colon cancer. So, it still requires to be further explored whether people with a positive family history need to take regularly vitamin D. Our result demonstrated that vitamin D intake can improve the prognosis of CRC patients. Previous study has shown that vitamin D insufficiency is highly common among patients with CRC [63–65]. Therefore, CRC patients of vitamin D deficiency should be advised to take the vitamin D to a normal level. Additionally, we also advise CRC patients with a normal level to take vitamin D supplementation because vitamin D toxicity is extremely uncommon. Studies have shown in adults that 10000 IUs daily for at least 5 months did not cause any toxicity [66]. More importantly, it still needs more research to further guide clinical application.

The use of vitamin D contributed to a significant reduction in CRC incidence, which is inconsistent with a previous meta-analysis [67]. However, there were several strengths to our study. To our knowledge, this is the first comprehensive meta-analysis that assessed the relationship between vitamin D and the incidence of CRC as well as between vitamin D and the prognosis of CRC. In our study, relatively larger sample size was used, thereby updating and extending earlier results. Moreover, based on our study, the pooled estimates were stable following the exclusion of any trial at a time with sensitivity analysis. On the contrary, there were some associated limitations to our meta-analysis. For instance, we found that heterogeneity existed in our meta-analysis as indicated by the I^2. It is predictable because of the presence of inter-studies differences in study design (prospective observational studies, retrospective observational studies and RCTs), enrolled populations, duration of follow-up, and the cohort characteristics. The studies included did not evaluate the serum 25(OH)D baseline status of CRC patients, which is hard to assess whether the CRC patients had a prior deficiency. Less consistency also existed on the dose-response relation; therefore, the optimal dose of vitamin D still needs to be further evaluated via large-scale prospective studies to lower the risk of CRC and improve the long-term survival of CRC patients.

Conclusion

This meta-analysis demonstrates a meaningful beneficial effect between the incidence of CRC and vitamin D from either dietary or supplement sources. The effect was concordantly observed via subgroup analyses of gender, CRC sites, colonic cancer subsites, and geographical differences. Although vitamin D could benefit clinical outcomes and improve the long-term survival of CRC patients, their certainty requires further studies. Therefore, there is a need to fully evaluate the optimal dosing of vitamin D using adequately powered RCTs and to augment the duration of follow-up.

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Author contribution XY designed the research process. YBX searched the database for corresponding articles. MXQ and JZH extracted useful information from the articles above. DMG and TY used statistical software for analysis. LHX and YBX drafted the meta-analysis. XY polished this article. All authors had read and approved the manuscript and ensured that this was the case.

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Data availability The datasets supporting the conclusions of this article are included within the article.

Declarations

Ethics approval and consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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