Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Additively protective effects of vitamin D and calcium against colorectal adenoma incidence, malignant transformation and progression: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 10 June 2019
Accepted 7 November 2019

Keywords:
Vitamin D
Calcium
Colorectal adenoma
Colorectal cancer
Risk
Mortality

SUMMARY

Background: Colorectal cancer (CRC) exhibits a linear progression from normal colonic epithelium, adenoma initiation, carcinoma transformation and even to metastasis. Diet changes might influence carcinogenesis and prognosis. We aimed to determine the effects of vitamin D and calcium on colorectal adenoma incidence, malignancy development and prognosis.

Methods: Systematic literature searches (PubMed, Embase, and Cochrane Library databases) and hand searches were performed by September 30, 2019. A random-effects model was adopted to pool relative ratios (RRs) for colorectal tumour incidence or hazard ratios (HRs) for CRC mortality. Stratified analyses were performed by gender, tumour location, calcium intake level and ethnic group.

Results: Total 854,195 cases from 166 studies were included. The colorectal adenoma incidence was inversely correlated with the circulating 25-hydroxyvitamin D [25(OH)D] level (RR: 0.80, 95% CI: 0.71–0.89), vitamin D intake (RR: 0.87, 95% CI: 0.82–0.92) and calcium intake (RR: 0.86, 95% CI: 0.81–0.91). The CRC incidence was decreased by circulating 25(OH)D (RR: 0.67, 95% CI: 0.59–0.77), vitamin D intake (RR: 0.85, 95% CI: 0.78–0.93) and calcium intake (RR: 0.75, 95% CI: 0.70–0.79). High-level circulating 25(OH)D triggered better overall survival (HR: 0.67, 95% CI: 0.57–0.79) and CRC-specific survival (HR: 0.63, 95% CI: 0.53–0.74). Stratified analyses showed that vitamin D and calcium significantly suppressed colorectal tumour incidence among women. Left-sided CRC risk was reversely related to circulating 25(OH)D (RR: 0.60, 95% CI: 0.41–0.88) and vitamin D intake (RR: 0.73, 95% CI: 0.57–0.93). Circulating 25(OH)D decreased colorectal adenoma (RR: 0.63, 95% CI: 0.48–0.82) and CRC (RR: 0.69, 95% CI: 0.56–0.86) risk in populations with higher calcium intake. European and American populations benefited more from vitamin D intake against colorectal tumour. A significant dose–response relationship was observed between intake of vitamin D or calcium and colorectal tumour incidence.

Conclusions: Vitamin D and calcium play additively chemopreventive roles in colorectal adenoma incidence, malignant transformation and progression, especially for women and left-sided CRC patients.

1. Introduction

Colorectal cancer (CRC) incidence ranked the third among all types of malignancies worldwide in 2018, with an estimated 1.8 million new CRC cases. However, the mortality has ranked the second with 881,000 deaths [1]. As we know, CRC exhibits a linear progression from normal colonic epithelium to adenoma initiation and malignant transformation to carcinoma and even to metastasis [2]. Although early stages of CRC and some pre-cancerous lesions, including hyperplastic polyps (HPs), sessile serrated polyps (SSPs) and conventional adenomas (Ads), can be detected early and removed through CRC screening, aggressive CRCs continue to have relatively high recurrence and mortality rates. Thus, preventing

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https://doi.org/10.1016/j.clnu.2019.11.012

CRC in all stages, including initiation and progression, is of social and clinical significance.

Recently, the 2018 WCRF/AICR Continuous Update Project Report argued that diet and lifestyle alteration might interact with genetic, epigenetic and modifiable hormonal factors. Additionally, such molecular and metabolic alterations could enhance life quality of cancer patients during and after treatment, reduce the risk of recurrence and metastasis, and decrease overall and cancer-specific mortality [3]. Therefore, screening for and validating nutrient elements that prevent colon adenoma and CRC are considered as an important adjuvant strategy to decrease CRC incidence and mortality rates.

As important nutrients for the human body, vitamin D and calcium have been considered candidate chemopreventive factors for cancer and attracted considerable attention from oncologists. Vitamin D is mainly produced in the skin with exposure to ultraviolet B (UV−B) radiation from the sun; it can also be acquired from dietary sources and supplements. Combined with vitamin D−binding protein (VDBP) in blood vessels, pro-vitamin cholecalciferol (vitamin D_3) moves from the skin to the liver, where it is metabolized to 25-hydroxyvitam'2in D [25(OH)D], the major form used in the clinical assessment of vitamin D status [4]. Interestingly, many studies have tried to clarify the relationship between vitamin D status and incidence of or mortality from colorectal adenoma or CRC, but varying findings have led to uncertainty regarding the effect of vitamin D on colorectal adenoma and CRC risk. For example, McCullough et al. reported that higher circulating 25(OH)D was significantly associated with lower CRC incidence in women [5]. However, Manson et al. found that vitamin D supplementation did not significantly lower the risk of invasive cancer compared with placebo [6].

In addition to maintaining healthy bones, calcium is thought to play a major role in the regulation of cell proliferation, differentiation and carcinogenesis by combining with secondary bile acids and ionized fatty acids [7]. However, there is still some controversy about the associations between calcium intake and colorectal tumour initiation and development. Zhang et al. reported that calcium intake could decrease the risk of colorectal cancer in 2016 [8]. However, Jenab et al. demonstrated that the role of calcium in the prevention of CRC was extremely dependent on the individual's level of vitamin D [9]. Surprisingly, Crockett et al. observed that calcium and combined supplementation with calcium and vitamin D might be related to an increased risk of SSP [10].

Thus far, the roles of vitamin D and calcium in CRC initiation and progression remain largely unclear. Besides these paradoxical results, the roles of vitamin D and calcium in the overall progression of CRC have still not been assessed because of the limitations of the available data and the restrictions of single research projects. In this study, we performed a systematic review and dose−response meta-analysis to clarify the effects of vitamin D and calcium on the tumour development process from colorectal adenoma initiation to cancer and progression.

2. Methods

2.1. Literature search and eligibility criteria

Systematic literature searches in PubMed, Embase, Cochrane Library database and hand searches were performed by September 30, 2019. The keywords were below: ('colon cancer' or 'colon carcinoma' or 'colon tumour' or 'colon neoplasm' or 'rectal cancer' or 'rectal carcinoma' or 'rectal tumour' or 'rectal neoplasm' or 'colorectal cancer' or 'colorectal carcinoma' or 'colorectal tumour' or 'colorectal neoplasm' or 'CRC' or 'colon adenoma' or 'rectal adenoma' or 'colorectal adenoma'), ('vitamin D' or '25(OH)D' or '25-hydroxyvitamin D' or 'calcifediol' or 'calcium' or 'Ca^{2+}') and ('risk' or 'incidence' or 'recurrence' or 'prognosis' or 'motality' or 'survival'). Manual review and validation were conducted subsequently in the titles, abstracts, full texts and references for additional available studies after eliminating potential duplicates.

Besides, the eligibility criteria for included studies were as followed: (1) the study of interest was vitamin D or calcium intake (dietary, supplemental, and total) or the serum or plasma 25(OH)D; (2) the outcome of interest was incidence, recurrence or morality of colorectal adenoma or CRC; (3) RR or HR estimates with 95% CIs for the highest versus lowest categories of vitamin D or calcium intake or circulating 25(OH)D levels were available or calculable; (4) studies based on observational design (cohort or nested case−control studies) or randomized controlled trial (RCT) were all included; (5) for overlapping data, only studies most relevant to our issue were included (6) for subgroup analysis, data with vague definitions were excluded.

2.2. Data extraction

The data were collected independently by two reviewers following a standardized data extraction procedure, and any discrepancies were settled by consensus or by a third reviewer. The following information about each study was extracted: first or corresponding author; publication; year of publication; title; study design; country in which the study was conducted; and population characteristics, such as sample size and sex. Additionally, we extracted data on circulating 25(OH)D concentration, total/dietary/supplemental vitamin D or calcium intake, and the corresponding ORs for colorectal tumour incidence risk or HRs for CRC mortality with 95% CIs. In addition, some information that was unavailable online was obtained from the corresponding authors of relevant studies. The methodological and reporting quality of observational studies were validated by the Newcastle−Ottawa Scale and ranked in order (scores of 8−9 points indicate high quality; 5 to 7 points indicate medium quality; fewer than 5 points indicate low quality) [11]. Besides, risk of bias assessment for RCTs was assessed by the Cochrane Collaboration's tool through following evaluation issues consisting of random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessments, incomplete outcome data, selective reporting and other bias. A low risk of bias was judged if all issues were at low risk, while a high risk of bias was validated if one or more evaluation issues tended to be at high risk [12].

2.3. Statistical analysis

All analyses were conducted using STATA software (version 15.0; Stata Corporation, College Station, Texas, USA). Pooled RRs or HRs and their corresponding 95% CIs were calculated by means of a random-effects model by comparing the highest and the lowest categories of circulating 25(OH)D concentration and total/dietary/supplemental vitamin D or calcium intake, which were displayed in forest plots. The statistical heterogeneity among these studies was assessed by the I^2 index, with significant heterogeneity defined as $I^2 > 50\%$ [13]. Then, the analysis was stratified by gender, anatomic location, level of calcium intake and ethnic group to explore potential sources of heterogeneity. Publication bias was assessed statistically by Begg's tests and graphically by funnel plots, with the existence of publication bias assumed for a p-value < 0.05. Additionally, potential dose−response relationships between total vitamin D intake or total calcium intake and the risk of colorectal adenoma or CRC were evaluated by generalized least squares (GLST) for the trend estimation of the summarized data [14]. In addition, restricted cubic splines with four knots at fixed

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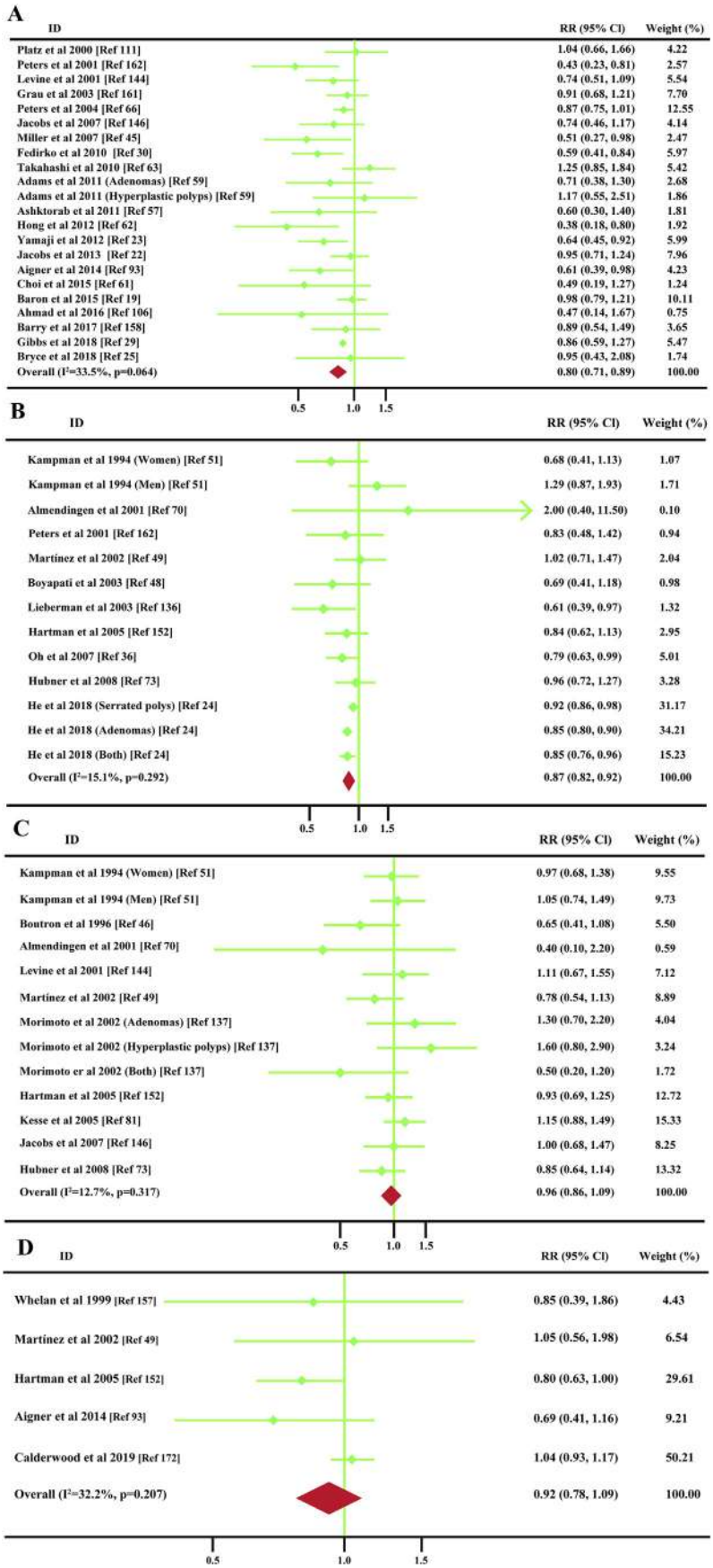

Fig. 1. Forest plots of association between (A) circulating 25(OH)D, (B) total vitamin D intake, (C) dietary vitamin D intake and (D) supplemental vitamin D intake and colorectal adenoma risk.

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percentiles (5, 35, 65 and 95%) of the distribution were utilized to construct the non-linear dose–response curve. For closed intervals of categories, the midpoint dose was used to compute the arithmetic mean of the upper and lower bounds of the quantiles. For open-ended categories, the lowest limits were defined as zero, and the top quantiles were estimated as 1.5 times the lower limit of the respective interval [15].

3. Results

3.1. Study characteristics

As shown in Supplementary Figure S1, a total of 166 studies were available and included in the current analysis after removing repeated and irrelevant articles as determined by reviewing the title, abstract and full text of each article [6–9,16–30,31–60,61–90,91–120,121–150,151–177]. Among these studies, there were 70 studies for circulating 25(OH)D, 68 for vitamin D intake, and 93 for calcium intake. Additionally, 58 studies investigated the risk of colorectal adenoma, whereas 86 and 27 studies investigated the incidence and prognosis of CRC, respectively. Otherwise there were 148 observational studies and 18 RCTs (Supplementary Table S1). The quality of the observational studies was generally moderate to good (see Supplementary Figure S2) and all RCTs were deemed as at low risk of bias.

3.2. Association between vitamin D or calcium and the risk of colorectal adenoma incidence

As we know, 25(OH)D is the primary circulating form of vitamin D, and its blood concentration reflects dietary sources and vitamin D supplementation; this measure is felt to be the best indicator of vitamin D status. Therefore, we performed a meta-analysis to investigate the relationship between circulating 25(OH)D and colorectal adenoma. The results revealed that a high level of circulating 25(OH)D had a significantly protective effect on the risk of colorectal adenoma incidence (RR: 0.80, 95% CI: 0.71–0.89; Fig. 1A). Furthermore, as shown in Table 1, the analysis was stratified by gender, level of calcium intake and ethnic group due to the relatively high heterogeneity ($I^2 = 33.5\%$, $p = 0.064$). Interestingly, we found that there was a significant negative association between circulating 25(OH)D and colorectal adenoma risk among women (RR: 0.63, 95% CI: 0.45–0.89) but not among men (RR: 0.89, 95% CI: 0.68–1.16). However, the protective effect of circulating 25(OH)D against colorectal adenoma was more dramatically observed in the group with high calcium intake (RR: 0.63, 95% CI: 0.48–0.82) compared to the group with low calcium intake (RR: 0.73, 95% CI: 0.54–0.99). In addition, colorectal adenoma incidence was inversely associated with 25(OH)D level in European and American populations (RR: 0.82, 95% CI: 0.75–0.91) but not in Asian populations (RR: 0.67, 95% CI: 0.40–1.14). These results indicate that high circulating 25(OH)D could decrease colorectal adenoma incidence, especially in European and American women with high calcium intakes.

Although a protective role of circulating 25(OH)D against colorectal adenoma is observed, it must still be verified whether vitamin D intake functions similarly. Surprisingly, significant associations were observed between colorectal adenoma incidence and total intake of vitamin D (RR: 0.87, 95% CI: 0.83–0.92, Fig. 1B) but not dietary intake of vitamin D (RR: 0.96, 95% CI: 0.86–1.09, Fig. 1C) or supplemental intake of vitamin D (RR: 0.92, 95% CI: 0.78–1.09, Fig. 1D). Unfortunately, the number of the studies on vitamin D intake was insufficient for stratification into subgroups based on population characteristics.

The results above demonstrate that high levels of calcium intake help circulating 25(OH)D reduce the risk of colorectal adenoma. Therefore, we analyzed the relationship between colorectal adenoma incidence and calcium intake. Intriguingly, total calcium intake (RR: 0.88, 95% CI: 0.83–0.93, Fig. 2A), dietary calcium intake (RR: 0.78, 95% CI: 0.71–0.85, Fig. 2B), and supplemental calcium intake (RR: 0.85, 95% CI: 0.80–0.90, Fig. 2C) were all negatively correlated with the risk of colorectal adenoma incidence. Moreover, stratification by ethnic group showed that higher total calcium intake was significantly associated with lower colorectal adenoma risk in Asian populations (RR: 0.54, 95% CI: 0.31–0.92) and European and American populations (RR: 0.88, 95% CI: 0.84–0.94). Similar results were found in the subgroup analysis of dietary intake of calcium (Asian population RR: 0.65, 95% CI: 0.48–0.90; European and American populations RR: 0.78, 95% CI: 0.71–0.86) (Supplementary Table S2).

3.3. Association between vitamin D or calcium and the risk of CRC

Colorectal adenoma is considered a precancerous lesion of CRC (2) whose incidence is inhibited by circulating 25(OH)D. We want to know whether circulating 25(OH)D could also play a protective role in CRC incidence. As expected, there was a strong negative association between circulating 25(OH)D and CRC risk (RR: 0.68, 95% CI: 0.60–0.78, Fig. 3A). As shown in Table 2, a stratified analysis showed that high levels of circulating 25(OH)D tend o decrease CRC risk (RR: 0.57, 95% CI: 0.43–0.75) in women, but this effect was not found in men (RR: 0.91, 95% CI: 0.75–1.11). Moreover, the protective effect of circulating 25(OH)D for CRC was found for left-sided colorectal cancer (distal colon and rectum) (RR: 0.60, 95% CI: 0.41–0.88) but not for right-sided colon cancer (proximal colon) (RR: 0.69, 95% CI: 0.45–1.05). Interestingly, high-circulating 25(OH)D displayed a protective effect against CRC only with high levels of calcium intake (RR: 0.69, 95% CI: 0.56–0.86). Additionally, higher-circulating 25(OH)D was significantly related to a lower incidence of CRC only in European and American populations (RR: 0.67, 95% CI: 0.58–0.76).

There were significant negative relationships between CRC incidence risk and total intake of vitamin D (RR: 0.81, 95% CI: 0.74–0.89, Fig. 3B), dietary intake of vitamin D (RR: 0.88, 95% CI: 0.81–0.95, Fig. 3C) and supplemental intake of vitamin D (RR: 0.87, 95% CI: 0.77–0.99, Fig. 3D). Interestingly, stratification analysis by gender and tumour location showed that total intake of vitamin D had a significant protective effect against colorectal cancer among

Table 1
Subgroup analysis for the association between circulating 25(OH)D and colorectal adenoma incidence.

Subgroups	No. of studies	RR	95% CI	I^2	P value
Women	8	0.63	0.45 to 0.89	51.1%	0.046
Men	7	0.89	0.68 to 1.16	43.7%	0.099
Calcium intake (low)	6	0.73	0.54 to 0.99	61.6%	0.023
Calcium intake (high)	6	0.63	0.48 to 0.82	53.1%	0.059
Asian populations	4	0.67	0.40 to 1.14	73.7%	0.010
European and American populations	17	0.82	0.75 to 0.91	14.1%	0.285

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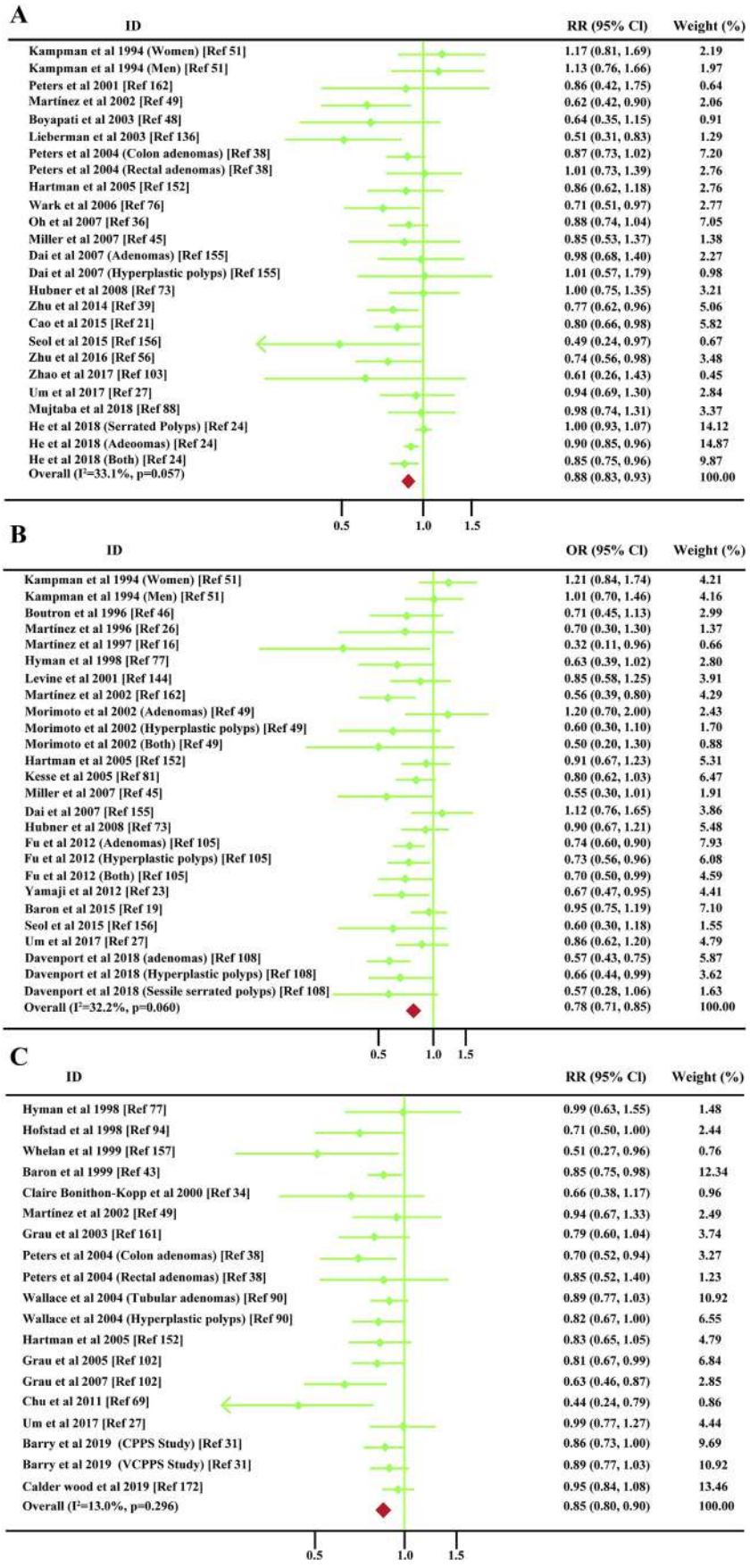

Fig. 2. Forest plots of association between (A) total calcium intake (B) dietary calcium intake and (C) supplemental calcium intake and colorectal adenoma risk.

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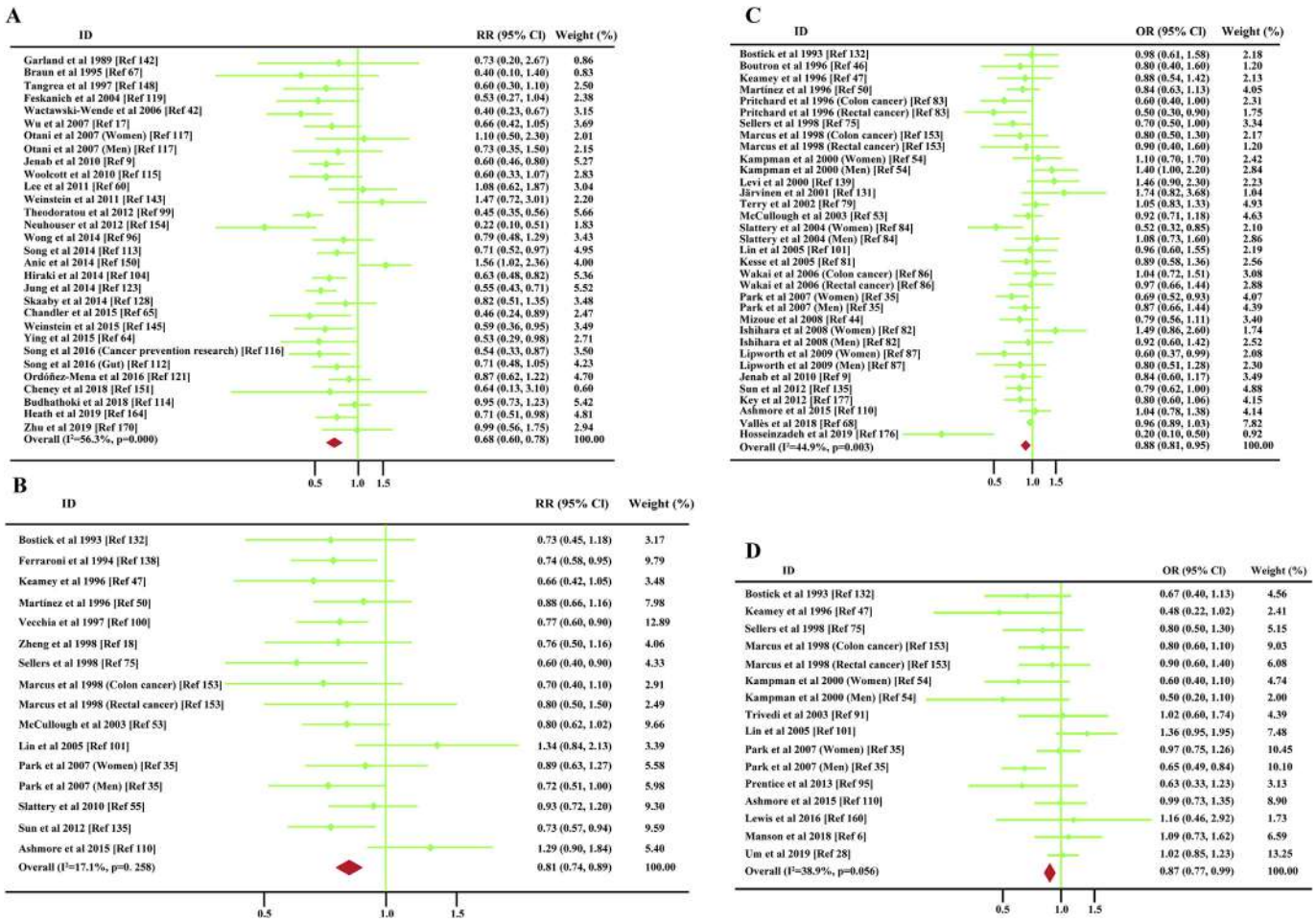

Fig. 3. Forest plots of association between (A) circulating 25(OH)D, (B) total vitamin D intake, (C) dietary vitamin D intake and (D) supplemental vitamin D intake and CRC risk.

Table 2
Subgroup analysis for the association between circulating 25(OH)D and CRC incidence.

Subgroups	No. of studies	RR	95% CI	I^2	P value
Women	11	0.57	0.43 to 0.75	70.6%	0.000
Men	10	0.91	0.75 to 1.11	28.8%	0.179
Right-sided CRC (proximal colon)	4	0.69	0.45 to 1.05	18.3%	0.299
Left-sided CRC (distal colon and rectum)	4	0.60	0.41 to 0.88	0.0%	0.781
Calcium intake (low)	2	0.79	0.59 to 1.05	27.1%	0.241
Calcium intake (high)	2	0.69	0.56 to 0.86	0.0%	0.387
Asian populations	3	0.84	0.58 to 1.22	39.8%	0.190
European and American populations	26	0.67	0.58 to 0.76	55.7%	0.000

women (RR: 0.81, 95% CI: 0.72–0.92) and for left-sided colorectal cancer (RR: 0.62, 95% CI: 0.40–0.96; Table 3). Similarly, higher dietary intakes of vitamin D were also significantly associated with lower CRC risk among women (RR: 0.85, 95% CI: 0.74–0.98; Table 3).

To investigate whether calcium intake can prevent CRC as well as colorectal adenoma, we systemically analysed the association between CRC risk and calcium intake. The results revealed a significant protective effect against CRC for total calcium intake (RR: 0.75, 95% CI: 0.71–0.79, Fig. 4A), dietary calcium intake (RR: 0.78, 95% CI: 0.73–0.84, Fig. 4B), and supplemental calcium intake (RR: 0.82, 95% CI: 0.78–0.86, Fig. 4C). Furthermore, we validated the association between each calcium intake mode and CRC incidence risk by gender, tumour location and ethnic group, which showed that all three types of calcium intake modes could decrease CRC risk except total calcium intake for right-sided CRC (Supplementary Table S3). Taken together, the results suggest that vitamin D and calcium could significantly repress malignant transformation of CRC, even though the protective effect of vitamin D was more frequently observed for women with left-sided CRC and high calcium intakes.

3.4. Association between vitamin D or calcium and mortality

The results above have demonstrated that vitamin D and calcium play protective roles against both colorectal adenoma and CRC. However, their roles in CRC prognosis remain unclear. Compared with lower-circulating 25(OH)D, patients with higher circulating 25(OH)D exhibited more favourable clinical outcomes with higher overall survival (HR: 0.69, 95% CI: 0.61–0.78, Fig. 5A)

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Table 3
Subgroup analysis for the association between vitamin D intake and CRC incidence.

Type of vitamin D intake	Subgroups	No. of studies	RR	95% CL	I^2	P value
Total vitamin D intake	Women	9	0.81	0.72 to 0.92	9.6%	0.354
	Men	4	0.80	0.63 to 1.02	66.6%	0.029
	Right-sided CRC (proximal colon)	2	0.71	0.47 to 1.08	0.0%	0.948
	Left-sided CRC (distal colon and rectum)	2	0.62	0.40 to 0.96	0.0%	0.472
Dietary vitamin D intake	Women	15	0.85	0.74 to 0.98	41.6%	0.034
	Men	9	0.94	0.82 to 1.06	0.0%	0.815
	Right-sided CRC (proximal colon)	4	0.71	0.49 to 1.04	36.8%	0.191
	Left-sided CRC (distal colon and rectum)	4	0.95	0.77 to 1.16	7.1%	0.374

and CRC-specific survival (HR: 0.64, 95% CI: 0.56–0.73, Fig. 5B). However, no significant association was found between calcium intake and overall survival (Fig. 5C) or CRC-specific survival (Fig. 5D).

3.5. Dose–response analysis between vitamin D or calcium intake and colorectal adenoma or CRC risk

Two studies were available for a dose–response analysis of the association between total vitamin D intake and the incidence of colorectal adenoma, and 8 studies were available for CRC risk. Additionally, 4 studies were included to calculate the dose–response relationship between total calcium intake and the risk of colorectal adenoma, and 15 studies were included for CRC incidence. As shown in Fig. 5 (E–H), the best–fit curves showed that each 200-IU/d increase in total vitamin D intake was associated with a 10% (RR: 0.90; 95% CI, 0.85–0.95) decrease in the risk of colorectal adenoma and a 5% (RR: 0.95; 95% CI, 0.92–0.98) decrease in the risk of CRC. Each 400-mg/d increase in total calcium intake was associated with a 2% (RR: 0.98; 95% CI, 0.96–0.99) decrease in the risk of colorectal adenoma and a 5% (RR: 0.95; 95% CI, 0.94–0.96) decrease in the risk of CRC.

3.6. Publication bias

No publication bias was observed for the included studies based on the analysis of funnel plots and Begg's test (Figure S4).

4. Discussion

Although an increased number of studies have tried to elucidate the roles of vitamin D and calcium in CRC, discrepancies about their effect on CRC tumourigenesis and prognosis remain. In the present study, we clarified the roles of vitamin D and calcium in the whole CRC development process, including colorectal adenoma, CRC and prognosis through a comprehensive and systematic analysis. As shown in Fig. 6, high levels of circulating 25(OH)D, vitamin D intake and calcium intake could decrease colorectal adenoma incidence risk, and CRC risk was suppressed by high levels of circulating 25(OH)D, vitamin D intake and calcium intake; however, only high circulating 25(OH)D benefitted both overall and CRC-specific survival.

Considering the whole sequence of CRC development, including the initiation of adenoma, malignant transformation and prognosis in the late stage, allowed for a more intuitive and systematic understanding of the effects of vitamin D and calcium on overall CRC progression. In our study, circulating 25(OH)D and total vitamin D intake have a significantly protective effect on the risk of colorectal adenoma. Nevertheless, neither dietary intake of vitamin D nor supplemental intake of vitamin D was significantly associated with the incidence of colorectal adenoma. This discrepancy might result from multiple factors, for example, the limited number of articles on dietary or supplemental vitamin D intake; differences in the dose of supplemental vitamin D, 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. In our opinion, supplementation with vitamin D, including through dietary intake, should be based on circulating 25(OH)D in order to prevent colorectal adenoma. More importantly, calcium and vitamin D displayed an additively protective effect in addition to their preventive effects against colorectal adenoma itself.

In addition to many epidemiological studies, previous biological experiments both *in vitro* and *in vivo* have demonstrated potential preventive effects and explored the molecular mechanisms of the anticancer effects of vitamin D and calcium, which are consistent with our current results. In $Smad3^{-/-}$ mice with inactivated TGF-β signalling pathways, increased dietary vitamin D intake significantly suppressed p-P38 MAPK activity and decreased the accumulation of colonic inflammatory cells by increasing circulating 25(OH)D, which ultimately reduced the incidence of colon carcinoma [178]. Additionally, vitamin D facilitated 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 [179]. Similarly, extracellular Ca^{2+} interacting with calcium sensing receptors (CaSR) could also regulate cells differentiation and malignant progression by induction of E-cadherin and suppression of β-catenin [180]. Additionally, calcium may reduce plasma inflammatory factors, such as IL-6 and IL-1β, and prevent oxidative DNA damage in patients with colorectal adenoma [181]. In the current study, we found that both vitamin D and calcium decrease CRC incidence risk. More interestingly, the protective effects of vitamin D were only found for left-sided cancers among European and American women, which reminded us of the interaction between oestrogen and vitamin D in protecting against colorectal adenoma and CRC. Coincidentally, Harmon et al. reported that increased concentrations of plasma 25-hydroxyvitamin D were related to treatment with oestrogen-containing drugs, another report showed that postmenopausal hormone replacement therapy triggered upregulation of the vitamin D receptor (VDR) pathway and downregulation of immune and inflammatory pathways, reducing the incidence of colon cancer [182]. Additionally, Boyapati et al. reported that vitamin D homeostasis may be modulated by VDR polymorphisms, which plays a significant role in colorectal adenoma risk. For example, participants with at least one b allele (BsmI genotype) were at much lower risk of colorectal adenoma [48]. Furthermore, Beckett et al. demonstrated that in women, the presence of ancestral alleles for BsmI ("b") significantly reduced the risk of AP [183].

However, our stratification analysis indicated that calcium was negatively correlated with CRC incidence in all subgroups, which demonstrated a strong protective effect of calcium against CRC. As with colorectal adenoma, there was an additively protective effect of calcium and vitamin D against CRC. Interactions between vitamin D and calcium in modulating cell growth and differentiation have been identified. It has been reported that $1,25(OH)_2D_3$ could upregulate the expression of CaSR and facilitate CaSR-mediated anti-proliferative effects [184]. Additionally, intracellular calcium

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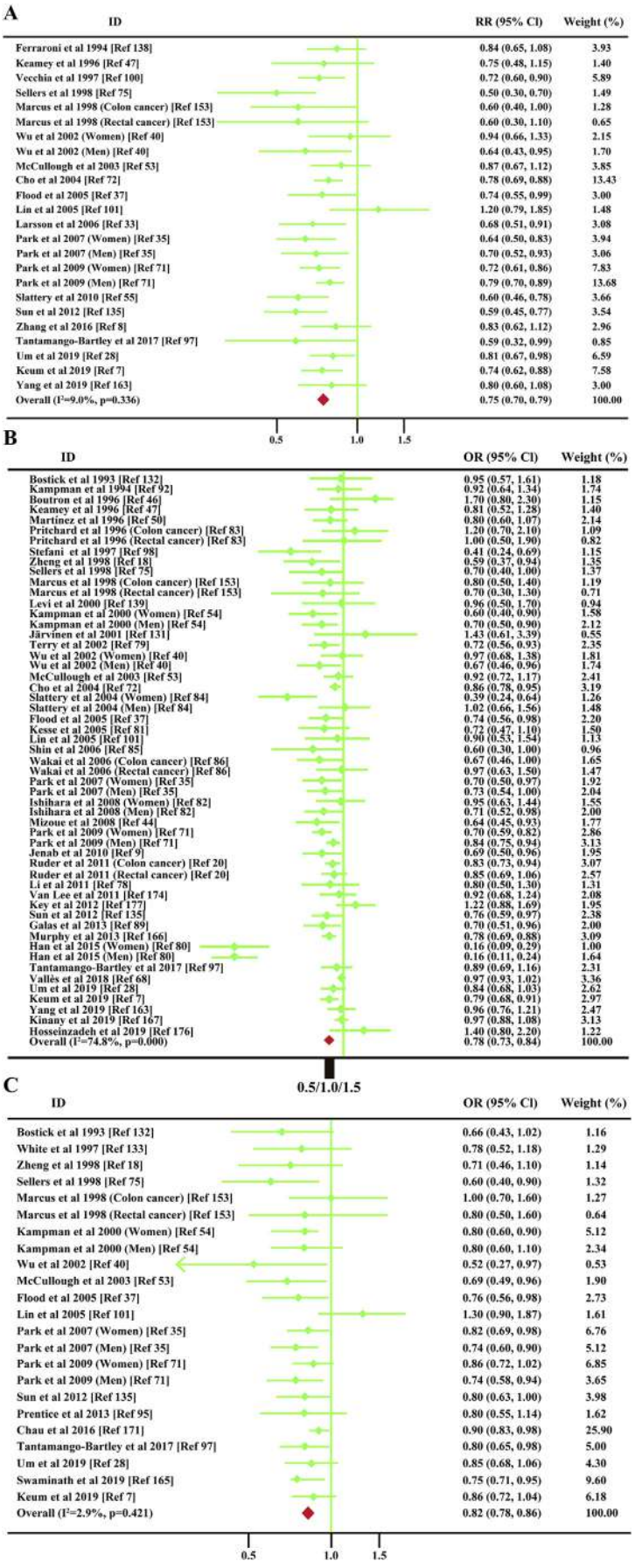

Fig. 4. Forest plots of association between (A) total calcium intake (B) dietary calcium intake and (C) supplemental calcium intake and CRC risk.

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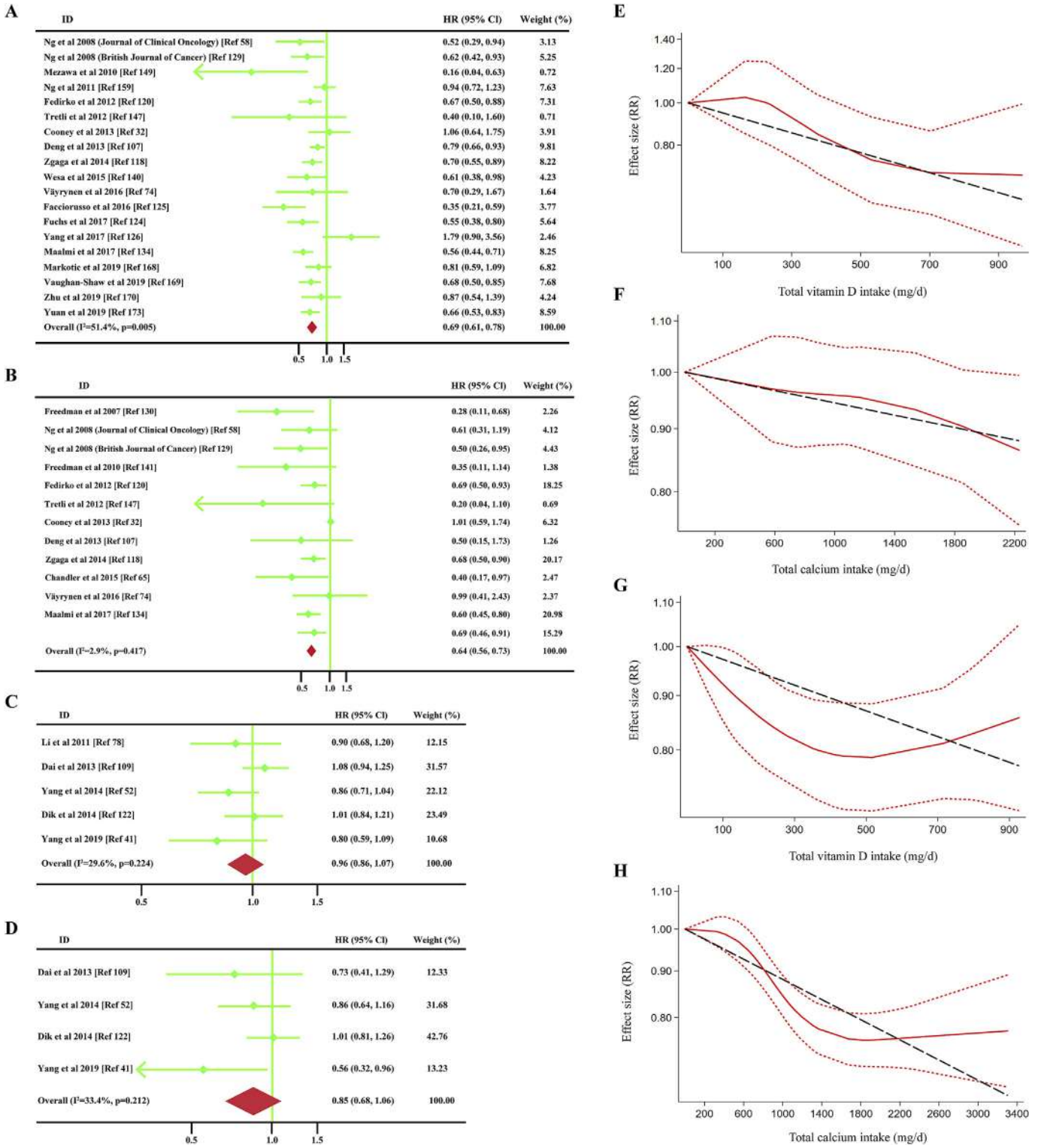

Fig. 5. Forest plots of association between circulating 25(OH)D and overall mortality (A) or CRC-specific mortality (B). Forest plots of association between total calcium intake and overall mortality (C) or CRC-specific mortality (D). Dose–response relationships between total vitamin D intake (E) or total calcium intake (F) and colorectal adenoma risk for cohort studies. Dose–response relationships between total vitamin D intake (G) or total calcium intake (H) and CRC risk for cohort studies.

suppresses the vitamin D catabolizing enzyme CYP24, which triggers a steady-state of concentration of circulating vitamin D [185]. Although vitamin D could benefit clinical outcomes and prolong the lives of CRC patients, no relationship between calcium intake and CRC survival was observed in our study, which may result from the limited number of relevant studies.

In conclusion, we incorporated data from previous RCT studies into our analysis and clarified a potentially beneficial role of vitamin D and calcium in the entire CRC progression process, including colorectal adenoma incidence, malignant transformation and prognosis, especially an additively protective effect in women and left-sided CRC patients. Some unpublished pooling projects,

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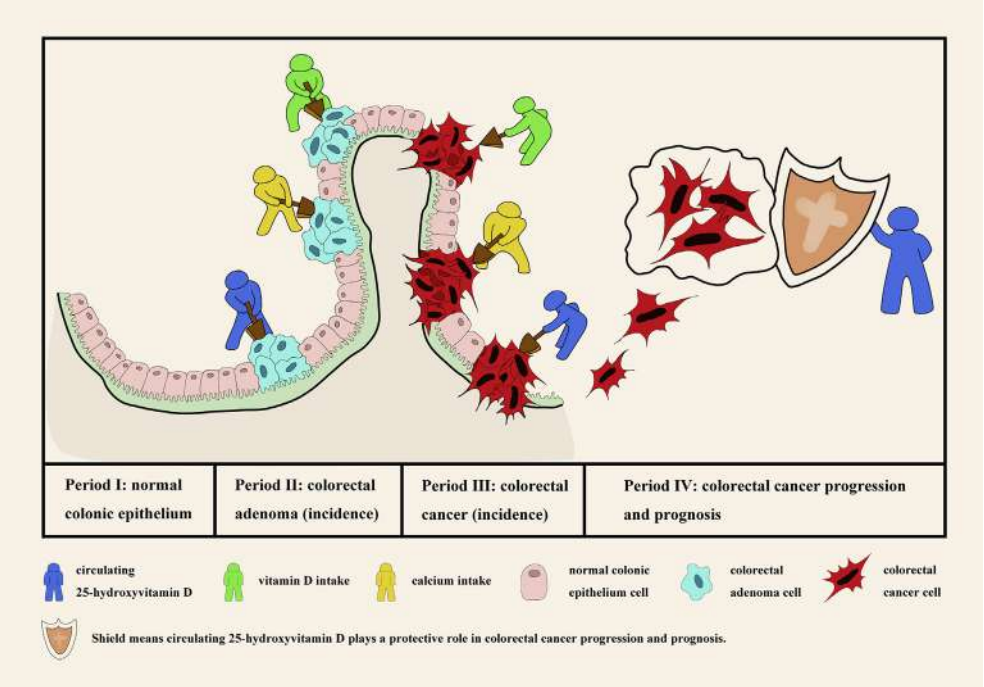

Fig. 6. Summary of our study for the roles of vitamin D and calcium in the whole CRC development process including colorectal adenoma, CRC and prognosis. The high level of circulating 25(OH)D, vitamin D intake and calcium intake could decrease colorectal adenoma incidence risk, and CRC risk was suppressed by the high level circulating 25(OH)D, vitamin D intake and calcium intake, however, only the high level circulating 25(OH)D could benefit both overall survival and CRC-specific survival.

such as the JANUS Serum Bank and the New York University Women's Health Study, were missed in the present study because their data sets are unavailable. Additional randomized controlled trials with larger populations and longer follow-up periods are required due to the variance in the assessments of previous studies.

Author contributions

H.Z. and Y.W. contributed to conception and design of the study. D.H., S.L., Y.Z. and J.X. contributed to conception, design of the study and editing of the manuscript. D.H., S.L., Y.Z., M.W., and D.X. contributed to statistical analysis. E.X. and M.L. contributed to the analysis and interpretation of data. All of the authors commented on drafts of the paper and approved the final draft of the manuscript.

Conflicts of interest

The authors declare no potential conflicts of interest.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81871937, 81672730 and 81572716), the Fundamental Research Funds for the Central Universities and the 111 Project (B13026), the Fundamental Research Funds for the Central Universities (2019QNA7005).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.11.012.

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Please cite this article as: Huang D et al., Additively protective effects of vitamin D and calcium against colorectal adenoma incidence, malignant transformation and progression: A systematic review and meta-analysis, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2019.11.012

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