Review article

Impact of Vitamin D Supplementation on Levels of Serum Cholecalciferol and Cytokines in Individuals with Colorectal Cancer: A Systematic Review and Meta-Analysis of Relevant Clinical Trials

Abstract

Background: This study assesses the impact of vitamin D supplementation on serum cholecalciferol levels and some cytokines in colorectal cancer (CRC) patients. **Methods:** We conducted a thorough search for relevant RCTs in PubMed, Scopus, and Google Scholar using appropriate keywords until December 2024. We calculated weighted mean differences (WMDs) and 95% confidence intervals (CIs) through random-effects analysis. **Results:** Five studies were included. Combining data from four studies showed a significant increase in serum 25 (OH) cholecalciferol levels after supplementation (WMD: 23.72; 95% CI: 12.92, 34.52). However, results from two studies indicated no significant changes in serum CRP (WMD: -2.48; 95% CI: -7.42, 2.46) and IL-6 (WMD: -2.49; 95% CI: -6.89, 1.92) levels. Conversely, TNF-α significantly decreased after administration (WMD: -0.81; 95% CI: -1.18, -0.45). There were no significant changes in anti-inflammatory cytokine IL-10 levels (WMD: 0.29; 95% CI: -0.43, 1.01). **Conclusions:** This study demonstrates a significant rise in serum 25 (OH) cholecalciferol and a significant decrease in TNF-α, with no notable changes in serum CRP, IL-6, and IL-10 levels in CRC patients after vitamin D treatment.

Keywords: *Cholecalciferol, colorectal cancer, inflammation, meta-analysis, vitamin D*

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Introduction

Colorectal cancer (CRC) is a significant cause of cancer-related deaths worldwide, ranking as the second leading cause of cancer mortality globally, with approximately 935,000 annual deaths.[1] It accounts for about 10% of all cancer cases.[2] In Germany, over 60,000 new cases and 24,000 deaths are reported each year.[3] The growing incidence of CRC results in substantial financial burdens on healthcare systems.[4]

Earlier studies have found that vitamin D deficiency is common among CRC patients.[5,6] Vitamin D deficiency has been linked to the risk of severe CRC,[7] which might be partially explained by increment in the body inflammation.[8-10] Specific cytokines and inflammatory markers might play crucial roles in tumor development and progression. Tumor necrosis factor-alpha (TNF-α) is known to promote cancer cell proliferation by inducing the expression of other proinflammatory cytokines. Interleukin-6 (IL-6) is another key player; it facilitates tumor growth by promoting angiogenesis and enhancing the survival of cancer cells, creating a microenvironment conducive to tumor expansion. Similarly, C-reactive protein (CRP), an acute-phase reactant, is indicative of systemic inflammation and has been associated with poorer outcomes in CRC patients.[11] Due to the association between vitamin D deficiency and increased risk of inflammation, one might suggest that vitamin D supplementation can reduce inflammation and improve clinical symptoms in CRC patients. However, earlier studies reported conflicting results. Some clinical trials reported significant influence of vitamin D supplementation on inflammation,[12,13] while others found no significant changes in inflammatory biomarkers.[14]

To the best of our knowledge, no previous studies have summarized the effects of vitamin D on inflammation biomarkers, such as cytokines and serum 25 (OH) cholecalciferol concentrations in CRC patients. Some studies have examined

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vitamin D in combination with other substances and highlight the necessity to a comprehensive meta-analysis focusing on RCTs about vitamin D alone. This systematic review and meta-analysis aimed to explore the impact of vitamin D on the levels of cytokines and serum 25-hydroxycholecalciferol in patients with CRC.

Methods

Search strategy

We searched PubMed, SCOPUS, and EMBASE for relevant studies published until December 2024 using the following MESH and non-MESH keywords:

PubMed: ((“Cholecalciferol”[Mesh] OR “Calcitriol”[Mesh] OR “Vitamin D”[Mesh] OR “Ergocalciferols”[Mesh] OR “vitamin D3”[tiab] OR “Vitamin D2”[tiab] OR “25-hydroxyvitamin D”[tiab] OR “25 (OH) D”[tiab] OR “Cholecalciferol”[tiab] OR “Calcitriol”[tiab] OR “Vitamin D”[tiab] OR “Ergocalciferols”[tiab]) AND (“colorectal cancer”[tiab] OR “colorectal neoplasm”[tiab] OR “colorectal”[tiab]) AND (trial[tiab] OR supplement[tiab] OR supplementation[tiab])).

Embase: ((“Cholecalciferol”:ab, ti OR “Calcitriol”:ab, ti OR “Vitamin D”:ab, ti OR “Ergocalciferols”:ab, ti OR “25-hydroxyvitamin D”:ab, ti OR “25 (OH) D”:ab, ti) AND (“colorectal cancer”:ab, ti OR “colorectal neoplasm”:ab, ti OR “colorectal”:ab, ti) AND (trial: ab, ti OR supplement: ab, ti OR supplementation: ab, ti)).

Scopus: (TITLE-ABS (Cholecalciferol* OR Calcitriol* OR Vitamin D* OR Ergocalciferols* OR 25-hydroxyvitamin D* OR 25 (OH) D*) AND (colorectal cancer* OR colorectal neoplasm* OR colorectal*)

We eliminated duplicates and did not impose restrictions on publication time or language. We also examined reference lists of included RCTs to avoid overlooking relevant publications, excluding unpublished information, gray literature, dissertations, or congress articles. Furthermore, the first 20 pages of Goggle Scholar and Cochrane Central Register of Controlled Trials (CENTRAL) for RCTs were also checked to avoid missing any study.

Inclusion and exclusion criteria

We first screened studies based on their title/abstract. At the second stage of screening, we evaluated full text of those studies. The relevant studies were as follows: All randomized clinical trials examining the impact of vitamin D supplementation on serum levels of cholecaciferol or any serum cytokine in CRC patients were included. Studies were excluded if they: 1) were animal studies, focused on pregnant or lactating women, or involved children; 2) lacked random allocation; 3) were observational; 4) examined the impact of additional supplements combined with vitamin D; 5) measured outcomes immediately after supplementation as this may not show the long-term effects of vitamin D on inflammatory biomarkers; 6) lacked a control group; or 7) measured inflammatory cytokines in cell lines or examined gene expression of those cytokines. Specifically, we excluded studies that combined vitamin D supplementation with other substances, such as calcium or omega-3 fatty acids, due to the potential confounding or synergetic effects these substances.

In total, 323 records were found in PubMed, 389 in Scopus, and 302 in Embase. After removing duplicates, 408 records were entered to the screening process. In total, 18 articles passed the initial screening stage by the title/abstract, from which five articles were selected for the final analysis after full-text screening.

Data extraction

Two independent reviewers collected the following information from included studies: first author, publication year, sample size, participants’ gender, number of participants in each group, age, vitamin D dosage, study duration, outcomes, and mean ± SD outcomes at baseline and after intervention. Other statistics like standard errors (SEs) or 95% CI were converted to SD before analysis. Measurements in various units were standardized to the most widely used unit.

Statistical analysis

We used random-effects analysis to calculate pooled weighted mean differences (WMDs) and 95% CIs between intervention and control groups.[15] The Cochran’s Q test and I^2 statistic assessed study heterogeneity. We conducted subgroup analysis based on the intervention dosage (<2000 IU/day vs >200 0IU/day). Stata version 11.2 (Stata Corp, College Station, TX) was used for analyses, with a significance level of $P < 0.05$. Due to the limited number of available studies, we were unable to do other subgroup analyses. Publication bias was assessed by the visual inspection of funnel plot as well as using Egger regression test. Sensitivity analysis was performed to explore possible effect of any individual study on overall results. Methodological quality of included studies was evaluated using the Cochrane Risk of Bias Tool for RCTs.

Results

Five studies were included in this systematic review and meta-analysis.[3,14,16-18] The PRISMA flowchart of study

selection is presented in Figure 1. In addition, the PRISMA checklist was completed for the study [Supplementary Table 1]. General characteristics of those studies are summarized in Table 1. Those studies were published between 2010 and 2023, involving 235 CRC patients, 122 patients in the intervention and 113 controls. Studies were done on both genders (79 females and 156 males). Participants' age varied from 18 to 75 years. Quality assessment of those studies showed that all of them had at least four domains with low risk of bias [Supplementary Table 2].

Vitamin D consumed in doses ranged from 800 IU/day to 50,000 IU/week, and the intervention duration varied from 8 weeks to 6 months. The measured outcomes included serum levels of 25 (OH) cholecalciferol,[3,16-18] C-reactive protein (CRP),[14,17] tumor necrosis factor-alpha (TNF-α),[14,17] interleukin (IL)-6,[14,17] and IL-10.[14,18] Other inflammatory biomarkers were not included in the meta-analysis because they were reported in only one study.

Our meta-analysis indicated a significant increase in serum 25 (OH) cholecalciferol levels following vitamin D supplementation (WMD: 23.72; 95% CI: 12.92, 34.52) [Figure 2], such that vitamin D supplementation led to an average increase of 23.72 ng/mL in serum 25 (OH) cholecalciferol levels in CRC patients. Subgroup analysis by the intervention dose revealed that supplementation with higher doses resulted in a more pronounced increase in serum levels of 25 (OH) cholecalciferol [Figure 3], emphasizing the existence of a dose–response relationship. Reanalysis after excluding one study with the shortest duration revealed a mean increase of 20.69 ng/mL in 25 (OH) cholecalciferol after vitamin D supplementation (WMD: 20.69; 95% CI: 11.73, 29.64) (data did not show).

Assessment of funnel plot [Supplementary Figure 1] and Egger regression test (P = 0.12) reveled no evidence for the existence of publication bias. In addition, sensitivity assessment showed that there were no individual studies with great impact on the overall results [Supplementary Figure 2].

Regarding proinflammatory biomarkers, pooling data from two studies showed no significant changes in serum CRP (WMD: -2.48; 95% CI: -7.42, 2.46) and IL-6 (WMD: -2.49; 95% CI: -6.89, 1.92) [Figure 4a and b]. However, TNF-α significantly decreased (WMD: -0.81; 95% CI: -1.18, -0.45) by vitamin D administration [Figure 5-a]. No significant change was seen in serum concentrations of anti-inflammatory cytokine

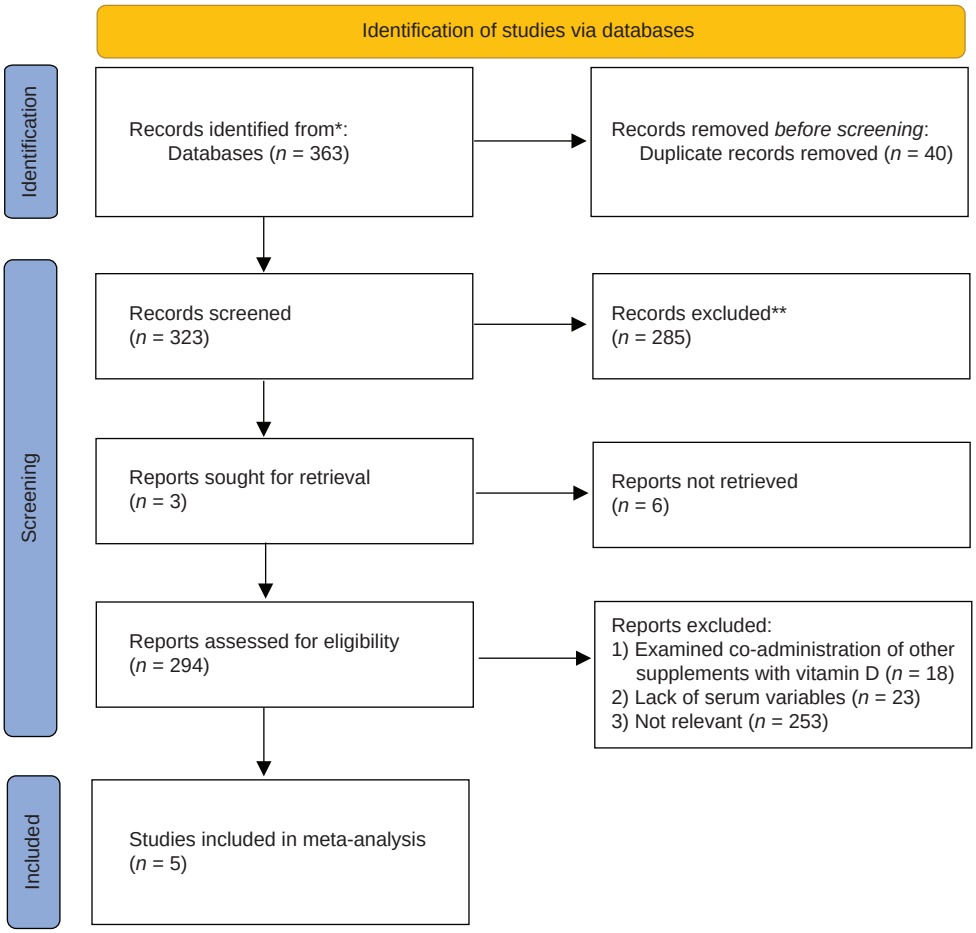

Figure 1: PRISMA flowchart of study selection

IL-10 (WMD: 0.29; 95% CI: -0.43, 1.01) after vitamin D supplementation [Figure 5-b].

Discussion

This systematic review and meta-analysis found a significant increase in serum 25-hydroxycholecalciferol and a significant decrease in serum TNF-α levels in CRC patients after receiving vitamin D supplements, with no significant changes in serum CRP, IL-6, and IL-10 levels.

Despite the clear findings from observational studies, few RCTs have examined vitamin D supplementation in CRC patients. A recent meta-analysis of observational studies indicated a lower risk of CRC occurrence among individuals with higher vitamin D intake.[19] The primary limitation of that meta-analysis was the observational design of the study, which makes it impossible to confer a causal relationship. Moreover, observational studies can be confounded by numerous factors; therefore, further RCTs are required to establish a causal association. Two prospective cohort studies found a strong correlation between serum 25-hydroxycholecalciferol levels and inflammation in CRC patients.[20] Our analysis demonstrated a significant rise in serum 25 (OH) cholecalciferol levels following vitamin D supplementation in CRC patients, which is consistent with some earlier trials.[3,13,18] A combined analysis of these RCTs revealed that vitamin D supplementation led to an average increase of 23.72 ng/mL in serum 25 (OH) cholecalciferol levels. The clinical significance of this increase becomes

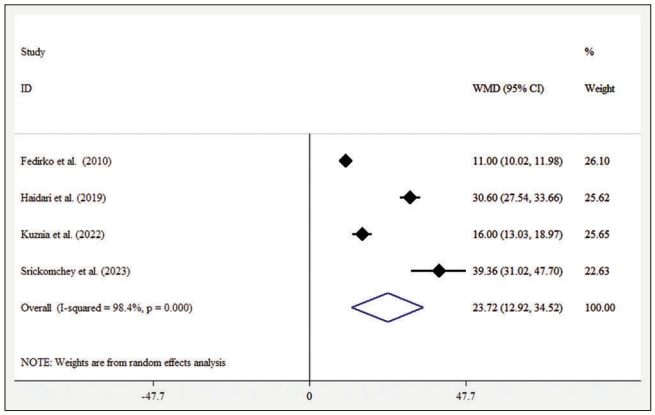

Figure 2: Forest plot for the effects of vitamin D supplementation on serum 25 (OH) cholecalciferol concentrations in patients with colorectal cancer. Diamonds show pooled estimates from random-effects analysis. Horizontal lines show 95% CIs

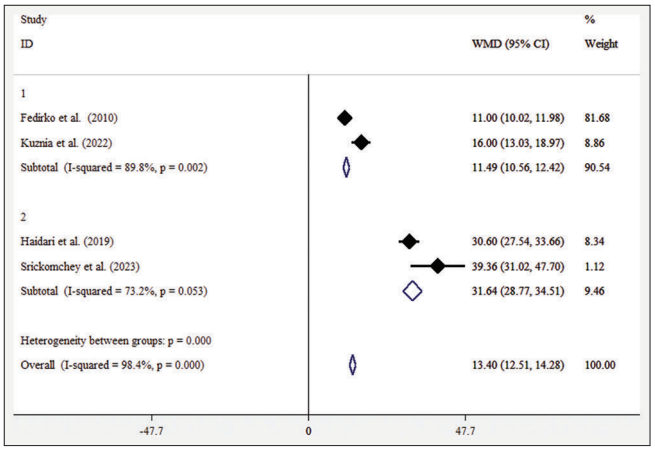

Figure 3: Forest plot for the effects of vitamin D supplementation on serum 25 (OH) cholecalciferol concentrations stratified by the intervention dose (<2000IU/day vs. >2000IU/day) in patients with colorectal cancer. Diamonds show pooled estimates from random-effects analysis. Horizontal lines show 95% CIs

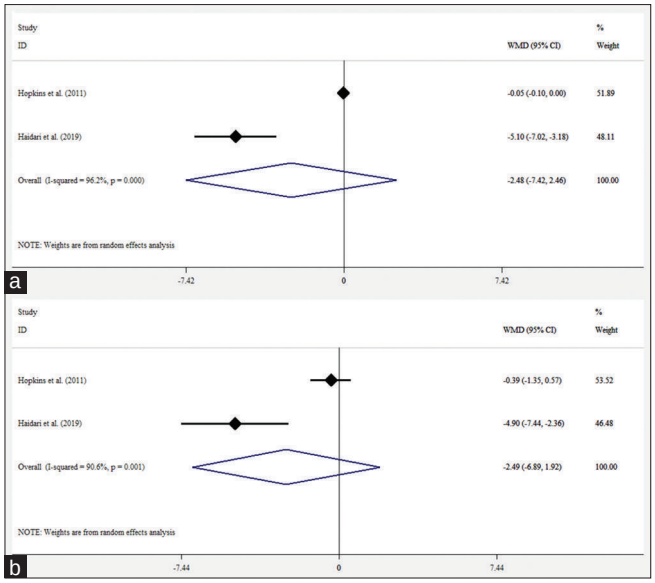

Figure 4: Forest plot for the effects of vitamin D supplementation on serum CRP (a) and IL-6 (b) concentrations in colorectal cancer patients. Diamonds show pooled estimates from random-effects analysis. Horizontal lines show 95% CIs

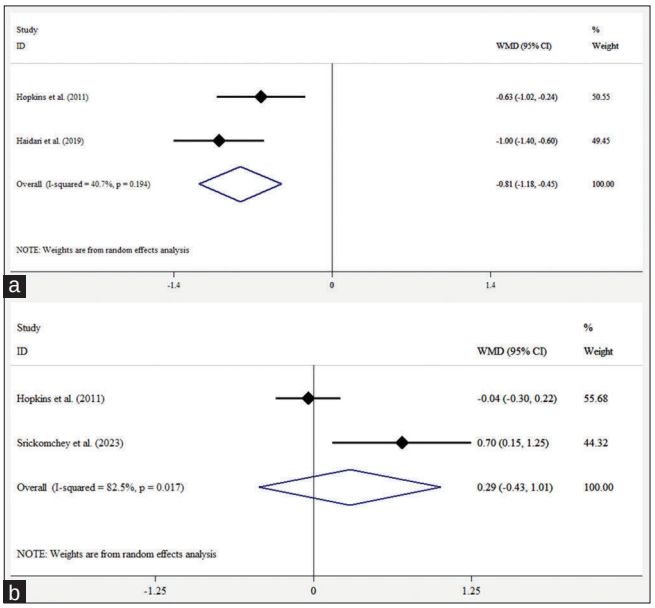

Figure 5: Forest plot for the effects of vitamin D supplementation on serum TNF-α (a) and IL-10 (b) concentrations in colorectal cancer patients. Diamonds show pooled estimates from random-effects analysis. Horizontal lines show 95% CIs

Table 1: General characteristics of included studies

Code/ Author (year)	Subjects and gender	Age range (y1) and mean	Supplement dosage (mg[2]/ d[3])	Duration (wk[4]/d)	Outcomes	Outcome	
						Intervention mean±SD[5] and number	Control mean±SD and number
Fedirko *et al*., 2010	46 Int: 23 Cnt: 23 F: 14 M: 32	30-75	800 IU/day	6 months	Serum 25 (OH) vitamin D	25 (OH) vitamin D (ng/mL) Before (mean±SE): 21.0±1.7 After: 29.5±1.7	Before: 20.7±1.7 After: 18.2±1.8
Hopkins *et al*., 2011	46 Int: 23 Cnt: 23 F: 14 M: 32	30-75	800 IU/day	6 months	CRP, TNF-α, IL-6, IL-10	CRP (µg/mL) Before (mean±SD): 1.39±2.79 After: 0.99±1.97 TNF-α (pg/mL) Before: 2.92±1.78 After: 2.73±2.52 IL-6 (pg/mL) Before: 0.78±4.68 After: 0.67±3.76 IL-10 (pg/mL) Before: 0.48±1.53 After: 0.43±1.38	CRP: Before: 1.77±3.80 After: 1.88±4.16 TNF-α Before: 4.13±1.92 After: 4.57±2.05 IL-6 Before: 1.13±4.54 After: 1.41±2.67 IL-10 Before: 0.54±1.57 After: 0.53±1.96
Kuznia *et al*., 2022	74 Int: 38 Cnt: 36 F: 24 M: 50	≥18 Mean: 61.8	2000 IU/day	12 weeks	Serum 25 (OH) vitamin D	25 (OH) vitamin D (nmol/L) Change (mean, 95%CI): 45 (36, 54)	Change: 5 (-1, 14)
Haidari *et al*., 2019	41 Int: 21 Cnt: 20 F: 17 M: 24	26-73	50,000/week	8 weeks	Serum 25 (OH) vitamin D, CRP, TNF-α, IL-6	25 (OH) vitamin D (ng/mL) Change (mean±SD): 25.7±6.0 CRP (mg/dL) Change: -4.2±3.7 TNF-α (pg/mL) Change: -1.0±0.7 IL-6 (pg/mL) Change: -5.2±5.3	25 (OH) vitamin D Change: -4.9±3.8 CRP Change: 0.9±2.5 TNF-α Change: 0.0±0.6 IL-6 Change: -0.3±2.6
Srickomchey *et al*., 2023	28 Int: 17 Cnt: 11 F: 10 M: 18	30-75	8000 IU/day	3 months	Serum 25 (OH) vitamin D, IL-10	25 (OH) vitamin D (ng/mL) Before (mean±SD): 29.2±10.1 After: 72.05±25.41 IL-10 (pg/mL) Before: 1.18±0.5 After: 1.52±1.17	25 (OH) vitamin D Before: 32.4±10.7 After: 35.89±16.51 IL-10 Before: 1.19±1.2 After: 0.83±0.47

clearer when considering that a serum vitamin D level of ≥20 ng/mL is considered adequate.[21,22] This increment might also be associated to the reduced inflammatory environment in the body which is associated to the cancer progression, treatment response, and overall survival.[20,23] A cross-sectional study in CRC patients found significant association between serum vitamin D levels and gene expression of some cytokines.[24] Although our analysis about the impact of vitamin D on inflammatory biomarkers is limited by the number of studies, we found a significant decrease in TNF-α, while CRP and IL-6 levels remained unchanged. This highlights the need for more RCTs to validate these results. The lack of significant alterations in CRP and IL-6 levels among CRC patients receiving vitamin D supplementation might be explained by some reasons. CRC is associated with a complex inflammatory

environment, and the tumor microenvironment may modulate cytokine responses.[25] Tumors can secrete factors that either stimulate or inhibit cytokine production, potentially overshadowing any anti-inflammatory effects of vitamin D. Indeed, future studies should focus on secretary behavior of CRC tumors in different stages of disease. It seems that each tumor stimulates or inhibits secretion of a specific group of proinflammatory cytokines. TNF-α is a proinflammatory cytokine that plays a role in tumor progression, and high levels of it have been reported among patients with CRC.[24] Reduction in this proinflammatory cytokine is an important finding for the CRC patients, but this finding should be interpret by the tumor secretary behavior. In addition, the dosage and duration of vitamin D supplementation may influence its effectiveness in altering inflammatory markers. Unfortunately, the limited numbers of relevant studies made it impossible to do subgroup analyses to have more discussion in this area. Factors such as genetic polymorphisms, baseline vitamin D levels, and the presence of comorbidities can also affect inflammatory responses to vitamin D supplementation.

The specific way in which vitamin D supplementation may impact inflammation in CRC patients is not fully understood. Vitamin D changes gut microbiota, through which it can reduce serum inflammation.[12] Vitamin D can promote the growth of beneficial bacteria, such as those in the *Lactobacillus* and *Bifidobacterium* families. These bacteria are known to produce SCFAs, particularly butyrate. Butyrate is a primary energy source for colon cells and has potent anti-inflammatory effects. By encouraging the growth of these SCFA-producing bacteria, vitamin D indirectly reduces inflammation.[12]

In addition, vitamin D might change gene expression of inflammatory cytokines.[24] For instance, vitamin D supplementation reduced Poly ADP ribose Polymerase (PARP) in inflammatory cascades in an RCT on a cancer line.[26] Moreover, vitamin D reduces inflammation by inhibiting p38MAPK activation in lamina propria cells.[27] Furthermore, activation of Vitamin D Receptor (VDR) can lead to apoptosis and inhabitation of cancer cells' proliferation, angiogenesis, and metastatic potential.[28] In immune cells like macrophages and T cells, the activated VDR complex can directly suppress the genes that code for key proinflammatory cytokines, such as TNF-α.[26] The VDR also interacts with a key inflammatory pathway involving a protein complex called NF-κB.[28] NF-κB is a master regulator of inflammation; when activated, it triggers the expression of numerous proinflammatory genes.[25] Vitamin D can inhibit NF-κB activation, effectively "turning off" a significant portion of the inflammatory response before it can even begin.[28]

To the best of our understanding, our meta-analysis is the first systematic review and meta-analysis focused on the effects of vitamin D supplementation (alone) on serum cholecalciferol and inflammation among patients with CRC. Nonetheless, it is imperative to know certain limitations of our study. The limited number of included studies is the first concern. Earlier RCTs have focused on medical and herbal treatments for CRC, and less attention has been done for the dietary supplements. This highlights the importance of nutritional assessments and even dietary supplementations in cases of insufficiency. Moreover, dietary supplements might have additional benefits for the patients, even among those with sufficient intakes. Additionally, discrepancies in disease stage among participants across these studies may also be considered as a potential source of bias. A tumor might have different behaviors in different stages of a disease, in particular for secretion of cytokines, so it might show different responses to vitamin D supplementation. Furthermore, differences in the supplement dosage or duration of study can also affect the results. Our study was done exclusively on English-language studies, which may result in missing some relevant researches from non-English sources. Finally, it is crucial to acknowledge the impact of unmeasured confounding factors, such as participants' initial vitamin D levels, which may also influence inflammatory outcomes. Considering this factor and other important confounding factors such as patients' weight and physical activity as well as their medical treatments increases the validity of findings. Future RCTs should investigate vitamin D's effects on various inflammatory markers in CRC patients.

Conclusions

Our study showed a significant increase in serum 25-hydroxycholecalciferol and a significant decrease in serum TNF-α levels, with no significant changes in serum CRP, IL-6, and IL-10 levels in CRC patients after vitamin D supplementation. The considerable increment in serum vitamin D levels (>23 ng/ml) and the decrement in TNF-α (>0.8 pg/ml) show clinically important impact of vitamin D supplementation among CRC patients, which is worthy of attention particularly among those with vitamin D insufficiency. Future studies using different vitamin D doses and durations on patients with different stages of the disease and measuring a various list of pro- and anti-inflammatory cytokines are needed to confirm our results. Stratification of participants based on CRC stages or baseline vitamin D status will result in better understanding of how these factors may influence the final outcomes.

Author's contributions

M.J.S. and O.Q.B.A.; Conceptualization and Writing- Original draft preparation. U.K.R., A.H.A., R.S.Z., N.A., M.A., and R.A-S; Investigation, Data curation, Methodology, Software, and Formal analysis. B.F.; Conceptualization, Validation, Writing- Reviewing and Editing and Supervision. All authors read and approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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25. West NR, McCuaig S, Franchini F, Powrie F. Emerging cytokine networks in colorectal cancer. Nat Rev Immunol 2015;15:615-29.
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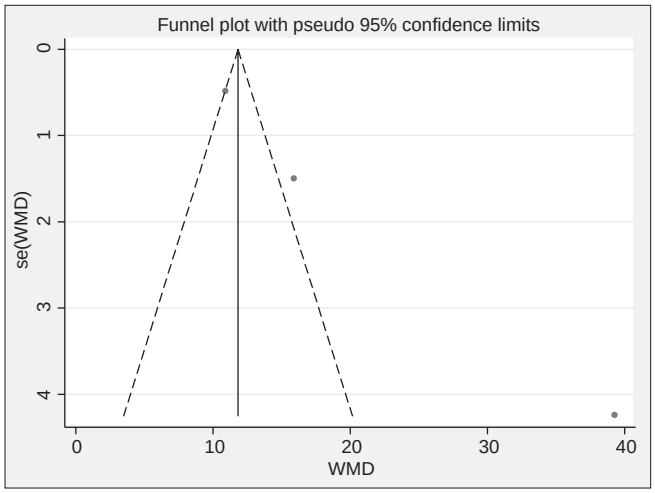
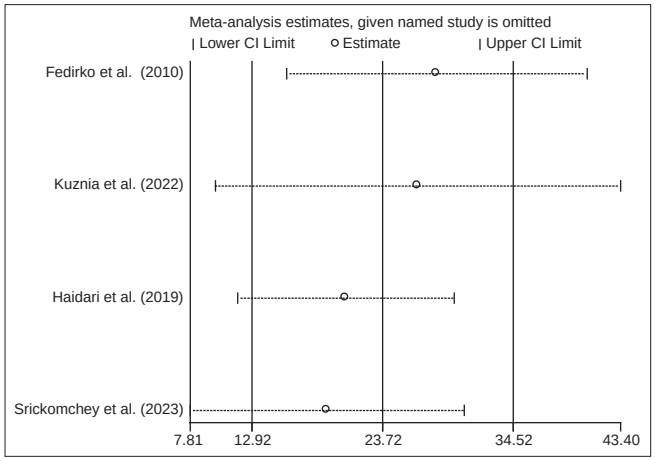
27. Meeker S, Seamons A, Paik J, Treuting PM, Brabb T, Grady WM, *et al*. Increased dietary vitamin D suppresses MAPK signaling, colitis, and colon cancer. Cancer Res 2014;74:4398-408.
28. Fuchs M, Yuan C, Sato K, Niedzwiecki D, Ye X, Saltz L, *et al*. Predicted vitamin D status and colon cancer recurrence and mortality in CALGB 89803 (Alliance). Ann Oncol 2017;28:1359-67.

Supplementary Figure



Supplementary Figure 1: Funnel Plot



Supplementary Figure 2: Sensitivity Analysis

Supplementary Table 1: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Line 2
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 32-45
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 56-69
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	Line 70-75
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 97-108
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 77-78
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 79-96
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 109-112
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 113-114
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 114-116
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 116-117
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 123-124
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 115
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 99-100
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 116-117
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 118-119
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	Line 118-123
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 122-123
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 124-125
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 123-124
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Line 125-126

Contd...

Supplementary Table 1: Contd...

Section and Topic	Item #	Checklist item	Location where item is reported
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 128-129
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Line 128-129
Study characteristics	17	Cite each included study and present its characteristics.	Line 129-130
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Line 123-126
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Line 138-152
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Line 133-134
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Line 138-152
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 138-152
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Line 150-151
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Line 149-150
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Line 149-151
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 158-182
	23b	Discuss any limitations of the evidence included in the review.	Line 194-200
	23c	Discuss any limitations of the review processes used.	Line 197-198
	23d	Discuss implications of the results for practice, policy, and future research.	Line 200-201
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Line 216
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Line 217
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Line 216-217
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 214
Competing interests	26	Declare any competing interests of review authors.	Line 215
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Line 218

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2: Quality assessment of the included studies, based on Cochrane assessment method

First author, year	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants & personnel)	Blinding (outcome assessment)	Incomplete outcome data	Other sources of bias
Fedriko *et al*. 2010	L	U	L	L	U	L	H
Haidari *et al*., 2019	L	L	H	L	H	L	U
Kuznia *et al*., 2022	L	L	H	L	U	L	H
Srickomchey *et al*., 2023	L	L	L	L	U	H	H

L: Low risk; H: High risk; U: Unclear