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Effects of vitamin D supplementation on inflammatory response in patients with cancer and precancerous lesions: systematic review and meta-analysis of randomized trials.

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Systematic Review

Keywords: Cancer, precancer, Vitamin D3 supplement, inflammation, biomarker

Posted Date: March 24th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2722981/v1

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Abstract

Purpose

Inflammation plays a key role in tumor development and progression. Vitamin D has potential tumor suppressing effects through modulation of inflammatory processes. The aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to summarize and evaluate the effects of vitamin D_3 supplementation (VID3S) on serum inflammatory biomarkers among patients with cancer or pre-cancerous lesions (PROSPERO Reg #: CRD42022295694).

Methods

We searched PubMed, Web of Science and Cochrane databases until November 2022. The effects of VID3S were estimated from pooled standardized mean differences (SMDs) with their 95% confidence intervals (CIs) for inflammatory biomarker follow-up levels between intervention and control groups. The study was conducted according to the PRISMA guidelines and quality assessment of included studies was conducted using the Cochrane Risk of Bias tool.

Results

Eight RCTs with a total of 592 patients who had cancer or pre-cancerous conditions were included in the meta-analyses. VID3S significantly lowered serum levels of tumor necrosis factor (TNF)-α [SMD (95%CI): -1.65 (-3.07; -0.24)]. VID3S also reduced serum levels of interleukin (IL)-6 and C-reactive protein (CRP) but the effects did not reach statistical significance [SMD (95%CI): -0.83 (-1.78; 0.13) and – 0.09 (-0.35; 0.16), respectively]. VID3S did not have any effect on IL-10 serum levels [SMD (95%CI): 0.00 (-0.50; 0.49)].

Conclusions

Our study shows evidence of a significant reduction of TNF-α levels by VID3S for patients with cancer or precancerous lesions. Patients with cancer or precancerous lesions may benefit from personalized VID3S in suppressing tumour-promoting inflammatory response.

Introduction

Low levels of serum 25-hydroxyvitamin D [25(OH)D], the most commonly used marker of vitamin D status, have been found to be associated with poor survival outcomes in patients with various forms of cancers including colorectal cancer (CRC) [1], breast [2], prostate [3], lung [4], pancreatic [5] and liver cancer [6]. As a result, it has been suggested that vitamin D_3 supplementation (VID3S) of cancer patients may be helpful to improve their prognosis even though evidence from randomized controlled trial (RCTs) remains sparse [7, 8]. However, several meta-analyses of (RCTs) have consistently reported a significant 13% reduction of cancer mortality by VID3S in older adults [9–11]. Moreover, a recent meta-analysis of RCTs reported a significant 35% reduction of CRC mortality by VID3S among patients with prior CRC diagnosis [12]. VID3S has also shown benefits on recurrence and metabolic profiles in patients with adenomas [13].

While the exact mechanism by which vitamin D may influence cancer outcomes is still elusive, recent evidence suggests various pathways including modulation of inflammatory processes [14, 15]. Inflammatory markers are associated with neoplastic growth, higher tumor grade, and increased mortality in cancer patients [16, 17]. Consequently, it seems plausible that VID3S could be a potential supportive therapy to improve cancer outcomes via modulation of inflammatory processes.

The aim of this study is to summarize and evaluate the effects of VID3S on serum inflammatory biomarkers among patients with cancer or pre-cancerous lesions through a systematic review and meta-analysis of published RCTs.

Materials And Methods

The protocol of this systematic review was registered in the international prospective register of systematic reviews before data extraction (PROSPERO, registration no. CRD42022295694). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [18] were followed for systematic review and meta-analysis.

Search Strategy and Data Extraction

The target of this review were original RCTs including patients with cancer or precancerous lesions where the intervention was VID3S, with or without co-interventions. Observational studies, unpublished studies, abstracts, reviews, dissertations, theses, editorials, study protocols, clinical guidelines, commentaries, and letters were excluded. Studies were included in meta-analyses if they had reported follow-up mean values and their respective standard deviations of inflammatory serum biomarkers for both the intervention and control groups.

Systematic searches were conducted using Medline (PubMed interface), the Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Web of Science databases from inception until November 2022. One researcher (T.G) with the help of a librarian conducted the searches and screened studies for review inclusion. The PRISMA flow diagram of the study identification and selection is provided in Fig. 1 and the search strings are given in **Supplementary Table 1**. For database searches, we used medical subject headings (MeSH), free-text words, synonyms, and related terms for the concepts: “vitamin D

supplementation", "cancer", "adenoma", "inflammatory biomarker", and "randomized controlled trial". No time restrictions for the searches were applied but non-English publications were excluded.

The EndNote software version 9 was used for reference management. For included studies, two researchers (T.G, A.Z) independently extracted the following data using a standardized data extraction form: first author, publication year, country, number of participants, cancer site and stage, sex, VID3S dosage, mean baseline serum concentration of 25(OH)D, compliance rate, outcome biomarker under investigation, mean/standard deviation of serum biomarker levels at follow-up for intervention and control groups, and maximum follow-up time. Initial discrepancies in extracted data were resolved by further review and discussion. For studies that did not report any of the predefined data domains, contacts were made to the authors requesting for the details.

Assessment of study quality

The Cochrane risk-of-bias (CRoB 2) tool [19] for randomized trials was used in the quality assessment of included studies for various domains including completeness of outcome data, blinding, sequence generation, allocation concealment, and selective outcome reporting. Risk of bias judgement was independently performed by two researchers (T.G, A.Z) and summarized as low, high, or uncertain based on the extracted data items. In cases of critical point disagreements between the two researchers, consensus was reached by further discussion among all authors.

Statistical Analyses

Serum inflammatory biomarker levels were assessed in various units of measurement in different RCTs. Therefore, standardized mean differences (SMDs) between intervention and control groups of biomarker levels at follow-up were used in the meta-analyses. Effect sizes were considered large, moderate, or small if SMD was > 0.7, 0.4–0.7 or < 0.4, respectively [20]. SMDs were summarized together with their respective 95% CIs and presented in forest plots. Meta-analyses were not conducted if there were insufficient numbers of studies (< 2) for a given outcome biomarker. To investigate the sources of heterogeneity and variation of intervention effects, subgroup analyses were conducted for subgroups defined by intervention duration, baseline 25(OH)D status, VID3S dosage regimen, cancer/precancerous condition, and study country of origin. Visualisation of heterogeneity was done using forest plots while statistical assessment was done by Cochran's Q test and I^2 index (< 25% low, 25% – 50% moderate, > 50% high heterogeneity). Where possible, sensitivity analyses were conducted to address high heterogeneity. Analyses for publication bias were not conducted for meta-analyses with fewer than 10 studies. All statistical analyses were conducted using random effects models with open access Review Manager (RevMan) computer program, version 5.4. The level of significance was set at $p = 0.05$ in two-sided testing for all statistical tests.

Results

Search strategy and study selection

The process of the study selection is depicted in Fig. 1. Out of 4,788 individual studies, 26 were considered in the full-text screening. One [21] more study was included via cross-referencing. Nine studies [13, 21–28] were finally included in this systematic review and eight studies were included in the meta-analyses with a total of 592 patients. Other studies were excluded based on predefined criteria as depicted in **Supplementary Table 2**.

Description of studies included in the meta-analyses

General information about the included studies can be found in Table 1. The eight studies included in the meta-analyses had sample sizes ranging from 30 to 100. Six of the eight studies were conducted in Iran. Four studies [24, 25, 27, 28] investigated the effects of VID3S on inflammatory markers among breast cancer patients, while two studies [13, 23] focused on patients with cervical intraepithelial neoplasia (CIN). The other two studies investigated the effects of VID3S on inflammatory biomarkers among patients with CRC [26] and colorectal cancer adenoma [22]. Five trials provided VID3S as weekly [24–26] or bi-weekly [13, 23] oral bolus doses of 50 000 international units (IU), and the remaining three trials [22, 27, 28] gave daily doses ranging from 20 IU to 4000 IU. Intervention follow-up times ranged from 8 to 24 weeks, and intervention compliance rates were reported to be over 80% for five studies [13, 22–24, 26] while the other three studies [25, 27, 28] did not report on compliance rates. Baseline mean 25(OH)D serum levels were reported in seven studies. Four studies [22, 24, 27, 28] had patients in the intervention arm with mean 25(OH)D levels in the sufficient range [i.e. 25(OH)D > 20 ng/mL] while three studies [13, 23, 26] had mean 25(OH)D levels in the deficient range [i.e. 25(OH)D < 12 ng/mL]. Five studies [13, 22, 23, 25, 26] reported on the effects of VID3S on serum C-reactive protein (CRP) concentrations while serum concentrations of tumor necrosis factor-alpha (TNF-α) [22, 24, 26, 28] and interleukin (IL)-6 [22, 26–28] were each reported on in four studies. Two studies [22, 28] reported on serum levels of IL-10. Four biomarkers could not be included in the meta-analyses because of insufficient studies (see **Supplementary Table 3**). In addition, two studies [22, 26] reported on the effects of VID3S with calcium/omega-3 fatty acid co-supplements (see study details in **Supplementary Table 4** and meta-analyses results in **Supplementary Fig. 1**). Serum inflammatory biomarkers were assayed using enzyme linked immunosorbent assay (ELISA) technique in all studies except in one [21] that did not report on the details of biomarker assay technique used.

Table 1
General information of studies included in the meta-analyses.

First author, year, reference	Country	Mean Age (SD)	Cancer site&stage	F (%)	Baseline mean 25(OH)D ng/mL (intervention/placebo)	Intervention (Vitamin D3 Dosage)	Number of participants (intervention/placebo)	Biomarker investigated	Biomarker Se at Follow-Up: (SD)
									Intervention
Hopkins et al, 2011 [22]	USA	60.2 (8.1)	Colorectal Adenoma	30	21.0 /20.4	400 IU twice daily	22/21	CRP (μg/ml)	0.99 (1.97)
						400 IU twice daily	22/21	TNF-α (pg/ml)	2.73 (2.52)
						400 IU twice daily	22/21	IL-6 (pg/ml)	0.67 (3.76)
						400 IU twice daily	22/21	IL-10 (pg/ml)	0.43 (1.38)
Vahedpoor, et al 2017 [23]	Iran	36.9 (7.4)	CIN, I	100	10.8/11.2	50 000 IU every 2 weeks	29/29	CRP (μg/ml)	1.96 (3.72)
Vahedpoor et al, 2018 [13]	Iran	41.9 (7.2)	CIN, II-III	100	11.5/12.4	50 000 IU every 2 weeks	29/29	CRP (μg/ml)	3.80 (1.57)
Shahvegharasl et al, 2019 [25]	Iran	41.1 (5.6)	BC, I-III	100	NR	50 000 IU every week	22/22	CRP (μg/ml)	4.19 (3.89)
Mohseni et al, 2019 [24]	Iran	47.7 (8.0)	BC	100	28.0/15.3	50 000 IU every week	26/26	TNF-α (pg/ml)	14.5 (1.60)
Haidari et al, 2020 [26]	Iran	57.1 (11.4)	CRC, II/III	23.8	11.6/11.2	50 000 IU every week	21/20	CRP (μg/ml)	1.44 (0.8)
				23.8	11.6/11.2	50 000 IU every week	21/20	TNF-α (pg/ml)	4.93 (2.34)
				23.8	11.6/11.2	50 000 IU every week	21/20	IL-6 (pg/ml)	33.54 (28.8)
El-Bassiouny et al, 2022 [27]	Egypt	49.6 (5.8)	BC, II	100	21.4/20.7	20 IU daily	50/50	IL-6 (pg/ml)	39.68 (10.47)
[1]Naderi et al, 2022 [28]	Iran	48.0 (8.0)	BC, 0-II	100	41.2/43.4	4000 IU daily	10/10	TNF-α (pg/ml)	17.96 (4.37)
								IL-6 (pg/ml)	0.3 (0.19)
								IL-10 (pg/ml)	83.04 (67.31)

Notes:

F female; USA United States of America; BC Breast Cancer; CIN Cervical Intraepithelial Neoplasia; NR Not Reported; IU International Units; i.v intravenous; SD S CRP C-reactive protein; TNF-α tumor necrosis factor alpha; IL interleukin; μg microgram; ng nanogram; pg picogram; ml millilitre.

[1]Study compared vitamin D supplementation group and those on yoga intervention.

Only two studies reported mean time of blood sample collection after surgery: Li et al (day 1–6 after surgery for the follow-up) and Naderi et al (> 3 years pos baseline and follow-up)

Risk of bias assessment

The results of the risk of bias assessment are shown in **Supplementary Table 5**. Five studies [13, 21–23, 25] had a good overall quality, two [24, 26] had fair quality and the remaining two [27, 28] had poor quality. Three studies [26–28] had a high attrition rate (> 15%). In terms of randomization, one study employed triple blinding, six employed double blinding and one employed single blinding (results not shown).

Effect of VID3S on CRP

The meta-analysis on CRP serum levels was conducted with five studies [13, 22, 23, 25, 26] comprising a total of 244 patients who had cancer or precancerous lesions. VID3S did not show a significant effect on CRP serum levels after 8–24 weeks of supplementation (SMD, 95%CI: -0.09, -0.35; 0.16) (Fig. 2, **panel A**).

The quality of four [13, 22, 23, 25] of the included studies was good while one study [26] had a fair quality. Furthermore, a sensitivity analysis of three studies [13, 23, 26] with 157 patients with a mean 25(OH)D at baseline in the deficiency range suggested a possible modest effect of VID3S in reducing serum CRP levels, but the effect did not reach statistical significance (SMD, 95%CI: -0.14, -0.46; 0.17) (Fig. 2, **panel B**). In both meta-analyses, no heterogeneity was observed.

Effect of VID3S on TNF-α

The pooled result of four studies [22, 24, 26, 28] with 156 patients who had cancer or precancerous lesions showed that 8–24 weeks of VID3S had a large effect in reducing TNF-α serum levels (SMD, 95%CI: -1.65, -3.07; -0.24) (Fig. 3, **panel A**). For this meta-analysis, the quality of included studies was fair for two studies [24, 26] while one [22] had good quality and one [28] had poor quality. Because considerable heterogeneity was observed for this analysis (I^2 = 93%, p < 0.01), a sensitivity analysis was conducted including only studies with daily dosage regimens of VID3S (total participants = 63). The results indicated a large effect in reducing serum TNF-α without heterogeneity in the meta-analysis (SMD, 95%CI: -0.85, -1.37; -0.33) (Fig. 3, **panel B**).

Effect of VID3S on IL-6

The meta-analysis of four studies [22, 26–28] investigating the effect of VID3S on IL-6 serum levels for a total of 204 patients with cancer or precancerous lesions suggested a large decrease in IL-6 levels, which though did not reach statistical significance (SMD, 95%CI: -0.83, -1.78; 0.13) (Fig. 4, **panel A**). VID3S duration was between 8 and 24 weeks. Two studies [27, 28] included in the meta-analysis were of poor quality, and considerable heterogeneity was observed (I^2 = 89%, p < 0.01), with apparently much lower effects in the better quality studies. A follow-up sensitivity analysis of two studies [22, 26] with good and fair quality (total participants = 84) showed a small (though statistically non-significant) effect in reducing IL-6 levels (SMD, 95%CI: -0.21, -0.64; 0.22) with no heterogeneity (I^2 = 0%, p = 0.95) (Fig. 4, **panel B**). It is important to note that baseline mean 25(OH)D serum levels were in the normal range in each of these two studies.

Effect of VID3S on IL-10

The pooled result of two studies [22, 28] for 63 patients who had cancer/precancerous lesions and mean 25(OH)D levels in the normal range at baseline did not show any effect of daily dosage regimens of VID3S for 12–24 weeks on serum IL-10 levels (SMD, 95%CI: 0.00, -0.50; 0.49) (Fig. 5). In this meta-analysis, one study [22] had good quality while one study [28] had poor quality and no heterogeneity was observed (I^2 = 0%, p = 0.74).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analyses with the objective of evaluating potential anti-inflammatory effects of VID3S in adults with cancer or precancerous lesions based on RCT evidence. Our study showed evidence of significant reduction of serum TNF-alpha levels. In addition, meta-analyses suggested a potentially large effect on IL-6 levels and a potentially small effect on CRP levels by VID3S, but the effect estimates were not statistically significant. No differences in IL-10 follow-up serum levels were observed after VID3S.

The role of vitamin D in modulation of inflammatory processes is mediated via the regulation of vitamin D responsive gene expression in several human cells [29]. Mechanistic studies suggest that vitamin D may downregulate the expression of nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB) and also inhibit immune-cell-mediated inflammatory responses via vitamin D receptors (VDRs) that are expressed in human cells [30]. Thus, it is plausible that VID3S may be of clinical value in reducing tumor-promoting inflammatory cytokines such as CRP, TNF-α and IL-6 in colorectal, prostate, breast, pancreatic and liver cancers, in which these markers are highly expressed [29].

In our meta-analysis, a small non-significant effect of VID3S was observed in reducing CRP serum levels in patients who had mean 25(OH)D levels in the vitamin D deficiency range. Similarly small but significant CRP changes after VID3S have previously been reported for patients with rheumatoid arthritis and vitamin D deficiency [31]. Higher but still safe doses of VID3S and long-term treatment might be needed to achieve larger effects [32]. On the other hand, a recent meta-analysis of RCTs showed a significant effect of daily VID3S in reducing serum levels of high-sensitivity CRP (but no effect on TNF-α and IL-6) among patients with type 2 diabetes mellitus [33].

There was a large and significant effect of VID3S in reducing serum TNF-α levels for patients with cancer/precancerous lesions. A sensitivity analysis for studies that had a daily oral dosage regimen of VID3S showed a more precise effect estimation of reduction in TNF-α serum levels. Daily dosage regimens may offer a number of benefits over bolus doses [34]. In agreement with our findings, treatment of prostate cancer (PCa) cell lines with calcitriol has demonstrated downstream inhibition of TNF-α production [35]. However, large and sustained effects in the suppression of TNF-α may require higher vitamin D doses as reported in a study showing a dose-dependent suppression of TNF-α by vitamin D in *Mycobacterium tuberculosis* infected mononuclear cells [36].

Our meta-analysis has shown a large but statistically non-significant effect by VID3S in reducing IL-6 serum levels for patients with cancer/precancerous lesions. Calcitriol downregulates IL-6 expression in both normal colon and colorectal cancer cells [29, 37]. In addition, an in vitro study by Nonn and colleagues showed that normal and PCa cells treated with vitamin D exhibited inhibition of TNF-α-stimulated IL-6 production [35]. However, VID3S had no effect on serum IL-6 in a meta-analysis of RCT studies with healthy, obese and overweight adults [38], suggesting that healthy individuals may not benefit from the anti-inflammatory effects of VID3S.

Our results showed no effect of VID3S on serum IL-10, an anti-inflammatory cytokine. Similar to our findings, treatment of human colon cancer cell lines with vitamin D has previously shown strong effects on TNF-α and IL-6 levels, but only a weak effect in increasing IL-10 levels [39]. In an RCT by Naderi and colleagues, IL-10 gene expression was increased much more by high dose (4,000 IU/day) VID3S and yoga co-intervention than by low-dose (2,000 IU/day) VIDS3 and yoga among breast cancer patients [28]. These findings support the hypothesis that high VID3S may have clinically significant IL-10 mediated anti-inflammatory effects in cancer patients. However, more evidence is required to establish VID3S dosages necessary to attain IL-10 level changes.

Potential sources of heterogeneity

Variations in intervention such as dosage, duration and compliance rates are possible sources of heterogeneity. Our study included individual trials that had patients with different mean vitamin D status at baseline. Some studies have shown benefits in attaining sufficient serum 25(OH)D states among deficient populations with large single bolus doses, while others have shown benefits with daily low doses of VID3S [24, 26, 40, 41]. However, higher doses are more prone to high calcaemic toxicity [42]. Recommendations by the European expert panel have suggested large loading doses of 6000 IU/day for 4–12 weeks for patients at high risk of 25(OH)D deficiency, followed by 800–2000 IU/day as maintenance doses with the aim of reaching serum therapeutic levels of 12–20 ng/mL [43]. Heterogeneity may also arise from variations in geography, study design or quality, sample sizes, age, sex, race or ethnicity, VDR gene polymorphisms, obesity states, site and stage of cancer [22, 24, 44–48].

Limitations

Most of the trials included in our study recruited patients with a sufficient mean baseline vitamin D status and who may not benefit much from VID3S. In addition, considerable heterogeneity observed in most of our meta-analyses makes it difficult to infer the findings to a specific patient group. Unfortunately, our study could not investigate all the potential sources of heterogeneity because of the limited number of included studies. Likewise, publication bias could not be systematically examined given the low numbers of RCTs. Overall, both the limited number of studies and the limited number of participants within studies limited the possibility to draw strong conclusions on the effects of VID3S on inflammatory response among our target population.

Conclusions

Although evidence is still very limited, with a low number of mostly small and partly poor-quality studies, we found evidence of a significant reduction of serum TNF-α levels by VID3S for patients with cancer and precancerous lesions. This main result supports hypotheses that patients with carcinomas or precancerous lesions may benefit from anti-inflammatory effects of personalized VID3S. However, existing evidence is still sparse. Further high-quality RCTs are needed, which ideally should include much larger numbers of patients and treat them for at least 12 weeks with sufficiently high daily vitamin D_3 doses. Future studies should also pay particular attention to the role of the baseline vitamin D status and potential interactions of VID3S with genetic and clinical factors, such as specific types of cancer therapy or treatment with various types of anti-inflammatory drugs.

Declarations

Acknowledgements: TG and HB designed research and BS contributed to the design of the study; TG and AZ collected the data; TG analyzed data; TG and HB wrote the paper. PS-K and MH contributed in providing critical feedback on the manuscript. All authors read and approved the final manuscript.

Funding information: There was no extramural funding for this systematic review and meta-analysis.

Data availability: Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Disclosure statement: The authors have nothing to disclose.

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Abbreviations

Abbreviation	Full name
CIN	Cervical Intraepithelial Neoplasia
CRC	Colorectal cancer
CRP	C-reactive protein
IL	Interleukin
NF-kB	Nuclear factor-kappa light chain B
PCa	Prostate cancer
RCT	Randomised Controlled Trial
SMD	Standardised Mean Difference
TNF-α	Tumor necrosis factor-alpha
VDR	Vitamin D receptor
VID3S	Vitamin D3 supplementation
25(OH)D	25-hydroxyvitamin D
95% CI	95% confidence interval

Figures

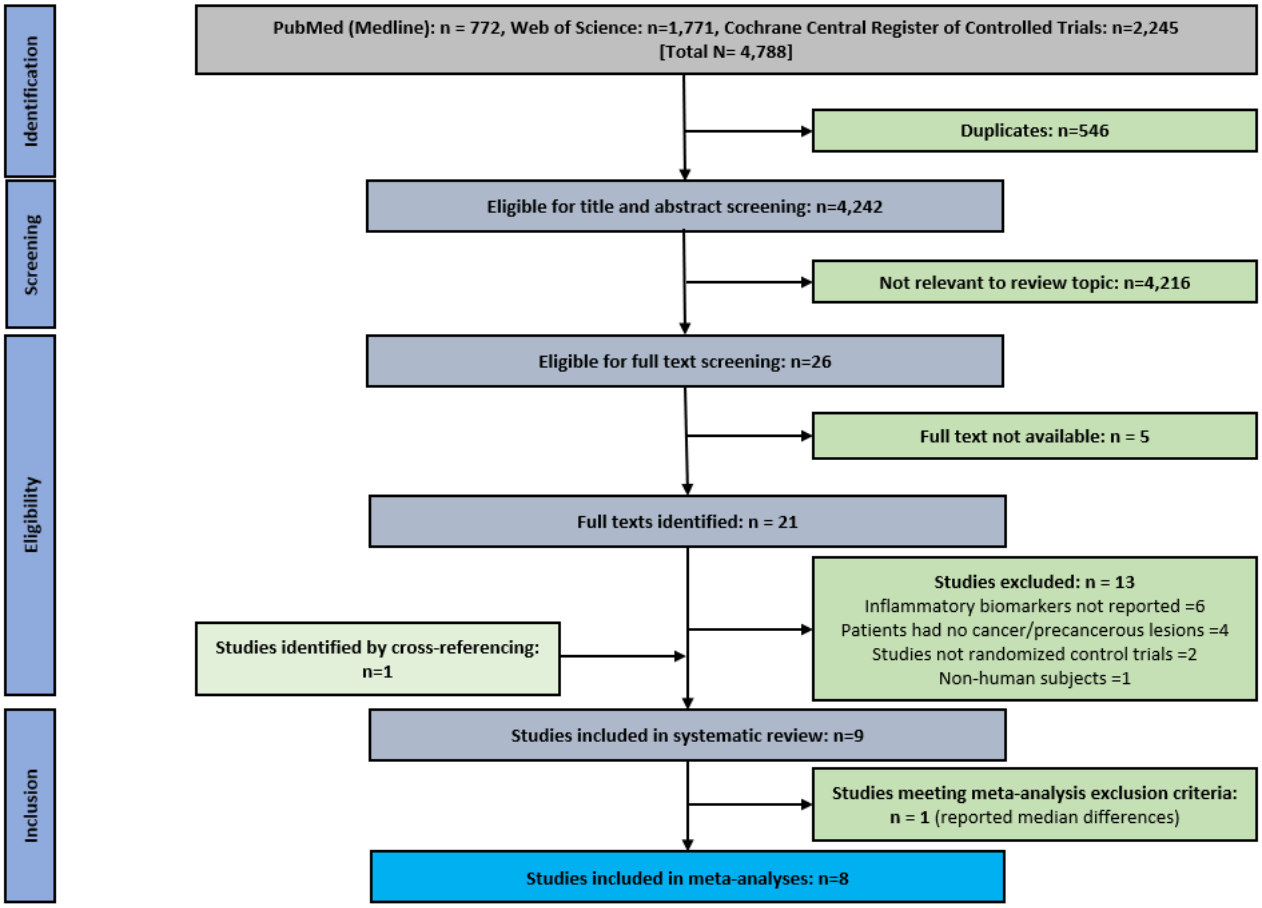
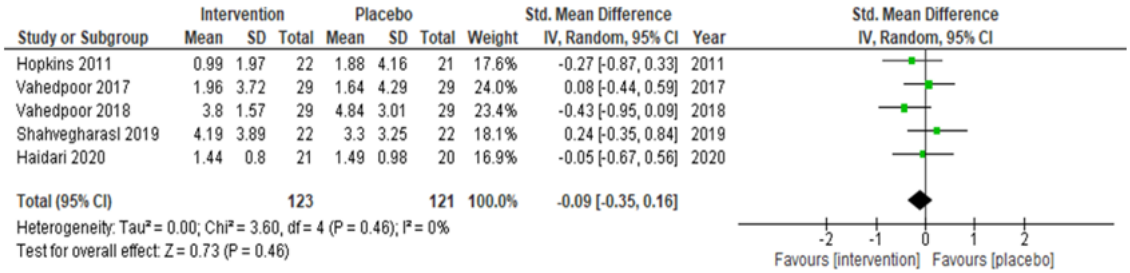


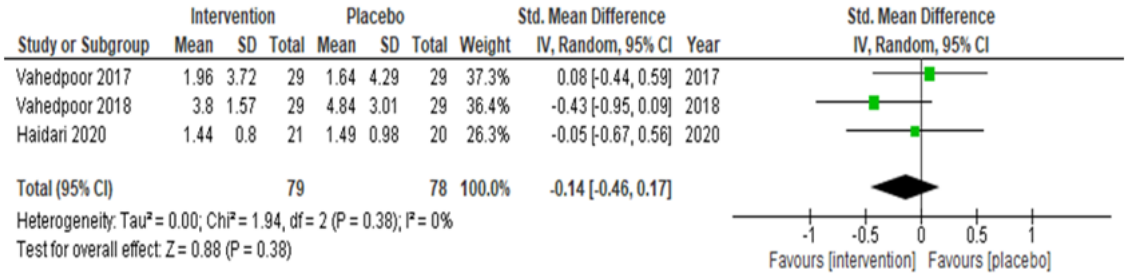
Figure 1

PRISMA study selection flow diagram.

Panel A: All five identified studies (n = 244).



Panel B: Studies with mean baseline 25(OH)D levels of patients < 12 ng/mL (n = 157).

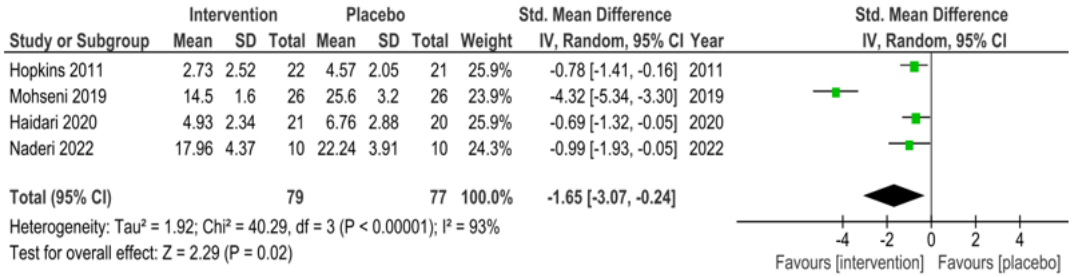


n-number of study participants

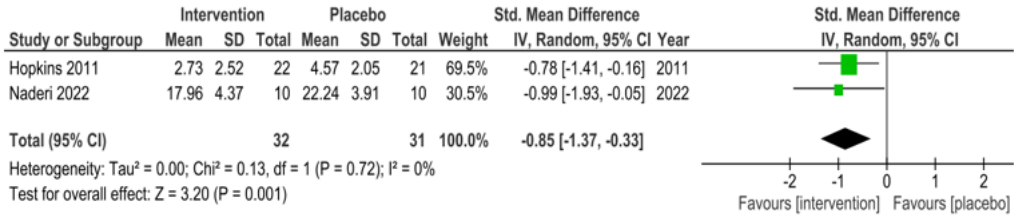
Figure 2

Effect of vitamin D3 supplementation on C-reactive protein serum levels for patients with cancer/precancer conditions after 8 - 24 weeks intervention.

Panel A: Studies with any type of VD3S (n = 156).



Panel B: Studies with daily VD3S schemes (n = 63).

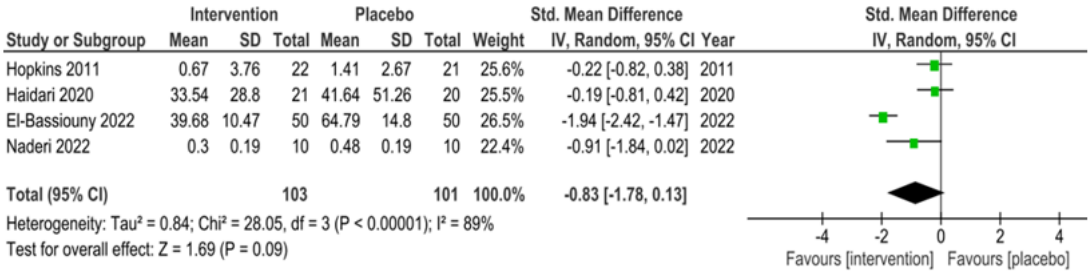


n-number of study participants

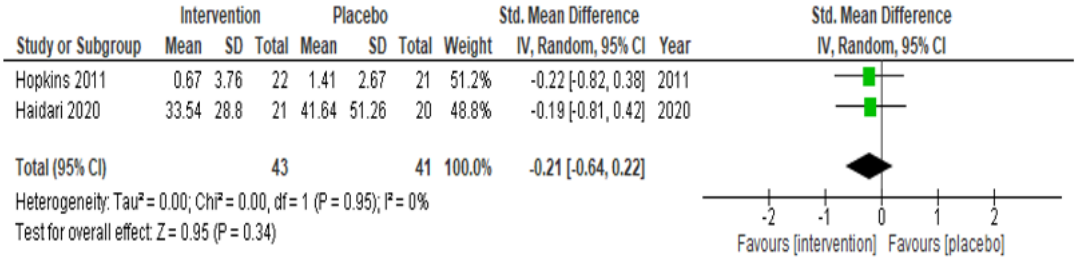
Figure 3

Effect of vitamin D3 supplementation on tumor necrosis factor-α serum levels for patients with cancer/precancer conditions after 8 - 24 weeks intervention.

Panel A: All four identified studies (n = 204).



Panel B: Sensitivity analysis of studies with good and fair quality (n = 84).



n-number of study participants

Figure 4

Meta-analyses of studies on the effect of vitamin D3 supplementation over 8 - 24 weeks on interleukin-6 serum levels in studies among patients with cancer/precancerous conditions.

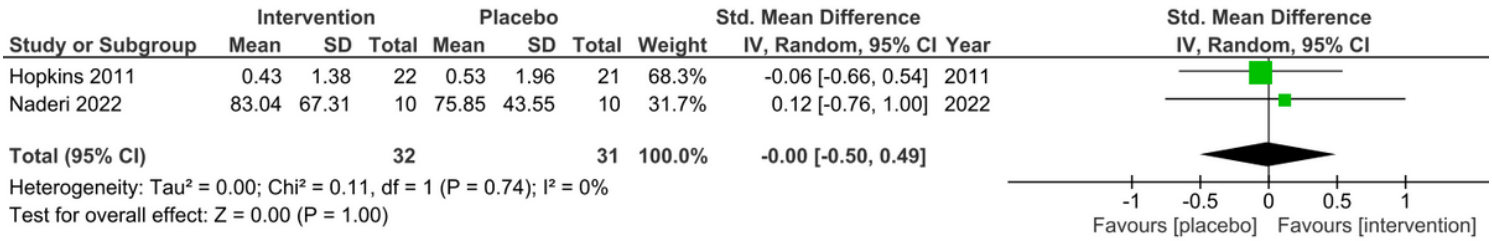


Figure 5

Effect of vitamin D3 supplementation on interleukin-10 serum levels for patients with cancer/precancer conditions after 12 - 24 weeks intervention (n = 63).

Supplementary Files

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