UNIVERSITY OF NICOSIA

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Efficacy of vitamin D supplementation on colorectal cancer survivorship: systematic review and meta-analysis of randomized studies

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Research Project

Title

Efficacy of vitamin D supplementation on colorectal cancer survivorship: systematic review and meta-analysis of randomized studies

Abstract

Background: Nutrient status is associated with survival outcomes in colorectal cancer (CRC), a global health issue. This systematic review and meta-analysis examines whether vitamin D supplementation improves CRC patient survival and may be a beneficial addition to CRC management.
Methods: We reviewed and meta-analyzed randomized controlled trials on vitamin D supplementation and CRC survival. PubMed and Web of Science searches found relevant studies through January 2024. Trials that reported vitamin D dosage, patient survival, and hazard ratios with 95% confidence intervals were included. PFS and OS were the main objectives. A random-effects meta-analysis methodology was used to aggregate data and evaluate the overall benefit of vitamin D supplementation, including research heterogeneity and publication bias.
Results: The meta-analysis of five trials found that vitamin D supplementation increased CRC survival, with a pooled hazard ratio near statistical significance (n = 815, logHR = -0.29; 95% confidence interval (CI): -0.59–0.02, *P*=0.07). Low variability among research suggests the vitamin D impact is consistent across study designs and demographics.
Conclusions: The findings imply vitamin D supplementation may improve CRC survival. The findings are intriguing, but more large-scale, well-designed trials are needed to confirm them and provide vitamin D supplementation guidelines for CRC therapy methods. Integrating vitamin D supplementation into cancer care could improve CRC survival rates and benefit public health policies.

Keywords

Colorectal Cancer; Vitamin D; Meta-analysis; Survival Outcomes; RCT

Introduction

Colorectal cancer (CRC) represents a significant global health challenge, ranking as the third most common type of cancer and the second leading cause of cancer-related mortality worldwide (Morgan et al., 2023). This malignant condition is influenced by a complex interplay of genetic, environmental, and nutritional factors, which collectively impact both the incidence and the survival rates of individuals diagnosed with the disease (Keum et al., 2019). Among the numerous factors under investigation for their role in cancer modulation, vitamin D emerges as an important factor. This fat-soluble vitamin, predominantly obtained through sunlight exposure and dietary intake, has been increasingly recognized for its potential effects on cancer prevention, disease progression, and patient survival (Sobhi et al., 2024). The interest in the role of vitamin D in colorectal cancer is driven by its biological plausibility in modulating cell growth and immune function, suggesting a possible therapeutic leverage.

Extensive research over the past decade has sought to clarify the relationship between vitamin D levels and colorectal cancer outcomes. A pivotal meta-analysis has highlighted a negative correlation between serum vitamin D levels and mortality rates in colorectal cancer, suggesting that higher levels of this vitamin might have a protective effect against the disease's progression (Ottaiano et al., 2024). Similarly, another significant study by Boughanem et al. (2021) supported the chemopreventive properties of vitamin D, showing reduced incidence and malignant transformation of colorectal adenomas with vitamin D supplementation. Furthermore, a series of studies have demonstrated an association between higher vitamin D levels at diagnosis and improved survival rates among colorectal cancer patients (Na et al., 2021; Ng et al., 2011; Chandler et al., 2015; Zhang et al., 2019). These findings underscore the potential benefits of vitamin D in enhancing survival, which is further supported by prospective cohort studies and randomized controlled trials (RCTs). Such studies meticulously follow-up participants over time, comparing the outcomes of those receiving vitamin D supplements to those given a placebo, focusing on survival metrics like Recurrence-Free Survival (RFS) and Overall Survival (OS) (Antunac Golubić et al., 2018; Ng et al., 2019; Urashima et al., 2019; Trivedi et al., 2003).

Although the molecular function of Vitamin D in improving colorectal cancer outcomes is increasingly supported, explicit clinical practice is still lacking. While useful, the majority of the data is observational and a few RCTs do not prove causality or the optimal settings for vitamin D administration. This thesis addresses these gaps by doing a systematic review and meta-analysis of prospective and RCTs on vitamin D supplementation in colorectal cancer survivorship. This study will compare vitamin D supplementation to non-supplementation on colorectal cancer relapse rates in people. The key question is: "In adult patients with colorectal cancer, how does supplementation with vitamin D influence the relapse rate of colorectal cancer compared to similar patients who receive no vitamin D supplementation?" . This study could clarify involvement of vitamin D in colorectal cancer treatment. This research could greatly alter patient care and treatment guidelines by revealing how vitamin D affects survival outcomes, especially given the global prevalence of colorectal cancer and its public health implications. Future studies may investigate how vitamin D influences colorectal cancer prognosis and establish integrative cancer management strategies.

Aims and Objectives

This study aims to determine whether vitamin D supplementation improves survival outcomes for patients with colorectal cancer, with an emphasis on relapse rates. The study reviewed current literature on vitamin D supplementation in colorectal cancer patients to achieve this. This analysis encompasses randomized controlled trials and prospective cohort studies to gather comprehensive data. Subsequently, a meta-analysis aggregated data from these randomized studies to assess survival and relapse rates upon vitamin D supplementation. This research aims to offer evidence-based clinical practice guidelines for vitamin D supplementation in colorectal cancer treatment protocols. This strategy ensures a rigorous scientific examination into potential benefits of vitamin D supplementation to guide medical treatment and improve colorectal cancer patient care.

Research Methodology

Study Design and Search Strategy

This comprehensive review and meta-analysis examined how vitamin D supplementation affects colorectal cancer survival. This required a thorough literature search for data on vitamin D administration and survival in this patient population. The PubMed and Web of Science were systematically searched for eligible trials from inception until January 2024. The search strategy used

several keywords to cover a large variety of relevant research. The terms "vitamin D," "25-hydroxyvitamin D," "calcidiol," "cholecalciferol," and "25OHD" were searched. Intervention terms included "supplementation," "intervention," "treatment," "placebo," and "RCT." Patient-related terminology include "CRC," "colorectal cancer," "bowel," "digestive system," "colon," and "rectum." Indicators included "survival," "prognosis," "mortality," and "recurrence." **Supplementary Table 1** details the search approach. Our search included the retrieved papers' bibliographies, relevant reviews, and the clinicaltrials.gov database to ensure thoroughness and relevance. Titles and abstracts were screened for every record found. This was followed by a comprehensive text review for eligibility.

Inclusion and Exclusion Criteria

In order to be included in this review, papers must satisfy specified criteria that are established according to the 'PICO' framework: Eligible participants for this study must be persons who are diagnosed with colorectal cancer and are over the age of 18. The intervention being investigated is the supplementation of vitamin D. The comparators being considered are either a placebo or a lesser dosage of vitamin D. The outcomes should incorporate quantifiable survival parameters, such as progression-free survival, overall survival, and colorectal cancer-specific survival. Only randomized controlled trials (RCTs) were included in order to maintain a high level of evidence by reducing the potential for bias that is present in non-randomized research. The exclusion criteria shall be strictly enforced to uphold the scientific integrity of the meta-analysis. In order to ensure the greatest quality of evidence, we only included primary research and reject non-randomized controlled trials (RCTs), case reports, review papers, and previous meta-analyses.

Data extraction

In order to guarantee a thorough and precise collection of data from the chosen studies, a rigorous data extraction approach was employed for this systematic review and meta-analysis. Two investigators conducted this assignment, extracting data into a pre-designed, standardized database to ensure the consistency and dependability of the obtained information. The extracted data comprised comprehensive information about each trial, including the trial's name, publication year, geographical location, sample size, duration and specific details of the intervention (including dosage and frequency of vitamin D supplementation). The study also documented important information such as the length of treatment, the total length of the follow-up period, the specific primary and secondary outcomes identified by the studies, and the hazard ratios (HRs) that were fully adjusted for factors such as overall survival (OS), progression-free survival (PFS), and colorectal/disease-specific survival (DSS). In cases where hazard ratios were not explicitly provided, we made efforts to obtain this information from the original authors of the studies.

Quality Assessment and Risk of Bias

The methodological quality of each study included in the analysis was thoroughly evaluated using the CONSORT 2010 checklist, which is a widely accepted standard for assessing the accuracy and completeness of reporting in randomized controlled trials. Two reviewers conducted this quality evaluation to reduce subjective bias, resolving any disputes through discussion or consultation with a third, senior reviewer. Every trial was assessed based on a predetermined set of criteria outlined in the CONSORT checklist. These criteria included randomization, blinding, statistical analysis, and the reporting of results. Each study was meticulously scrutinized to ensure the thoroughness of its reporting. Trials that did not follow more than 50% of the CONSORT items were deemed to have a high risk of bias and were therefore eliminated from the quantitative synthesis portion of the meta-analysis.

Synthesis of Evidence and Statistical Analysis

Our systematic review and meta-analysis rigorously analyzed the gathered papers to evaluate the effect of vitamin D supplementation on the survival outcomes of patients with colorectal cancer. The main study consisted of a trial-level meta-analysis of all relevant trials to ascertain the overall impact of vitamin D supplementation on outcomes related to colorectal cancer. In addition, subgroup meta-analyses were conducted to examine outcomes in more specific contexts, such as survival specific to colorectal cancer and freedom from disease. These analyses also distinguished between trials that directly involved colorectal cancer patients and trials in which colorectal cancer outcomes were reported incidentally in the population.

The hazard ratios (HRs) and 95% confidence intervals (CIs) obtained from the studies were utilized to calculate the logHR and standard error. The weighting of each trial in the meta-analysis was established based on the standard errors associated with each hazard ratio (HR) estimate. This approach ensures that trials with more accurate estimates have a stronger impact on the overall results of the meta-analysis. The Hartung-Knapp-Sidik-Jonkman technique was used to determine the combined hazard ratios due to the expected variations among the trials, which could be caused by differences in population demographics, intervention specificity, or methodological approaches. The selection of this method over the DerSimonian and Laird random-effects model was based on its ability to generate more precise confidence intervals in situations where there are a limited number of studies.

The level of diversity among the studies was assessed using the I^2 statistic, which quantifies the fraction of overall variation among studies that is attributable to heterogeneity rather than random chance. Interpreting the strength and validity of the meta-analysis results is essential. In order to evaluate the possibility of publication and selection biases, we analyzed the asymmetry in the funnel plots with trim-and-fill analysis, along with conducting the Egger's regression test. These methods aid in determining whether the findings of the smaller studies in the meta-analysis significantly deviate from those of the bigger studies, which may indicate the presence of publication biases. The statistical analyses were conducted using Stata v18. All the outputs, scripts and data template used for the analysis have been deposited in the following public github depository.

Results

Literature search

The PRISMA flowchart illustrates the systematic review and meta-analysis procedure employed to evaluate the effects of vitamin D supplementation on colorectal cancer outcomes (**Figure 1**). At first, a thorough search of PubMed and Web of Science databases resulted in a total of 5,647 records. Out of these, a total of 1,146 duplicates were eliminated, resulting in 4,501 remaining records for further examination. Following the evaluation of titles and abstracts, a total of 12 papers were identified as potentially relevant and subsequently obtained for a thorough examination of their complete text. After doing a thorough assessment, five of them were eliminated due to several reasons, such as ongoing trials (D2dca trial), absence of relevant colorectal cancer outcomes, incomplete endpoint data, or their concentration on an adenoma population rather than actual instances of colorectal cancer. After filtering, there remained a total of seven papers that were appropriate for qualitative analysis. However, two additional studies were not included in the meta-analysis. One study by Golubic et al (2018), was omitted because it had a high risk of bias, while the RECORD study did not provide hazard ratios (Avenell et al., 2012), which are necessary for conducting a meta-analysis. Therefore, the final meta-analysis consisted of five studies that specifically examined the impact of vitamin D supplementation on the survival outcomes of patients with colorectal cancer. The D-health trial and

the D2dca trial were excluded from the analysis due to their continuing status and lack of published results, respectively. Furthermore, the study conducted by Lappe et al. was excluded due to its focus solely on cancer occurrence, without including data on patient survival, which is essential for evaluating the influence of vitamin D on patient longevity. The study by Baron et al. was not included in our analysis since it specifically examined the incidence of colorectal cancer in a group of individuals with adenomas. This study only had 14 cases of colorectal cancer, which did not fulfill our threshold for significant outcomes related to colorectal cancer.

In addition, we omitted the VIDA trial (Scragg et al., 2019) from our analysis due to its lack of reporting on mortality specifically related to colorectal cancer, and we were unable to receive any further data upon request. In addition, the RECORD trial did not include hazard ratios (HRs), which are necessary for our meta-analysis, and so it was not included in our study. The Golubic et al. study was excluded from the meta-analysis because it was found to have significant biases that could potentially affect the overall analysis results.

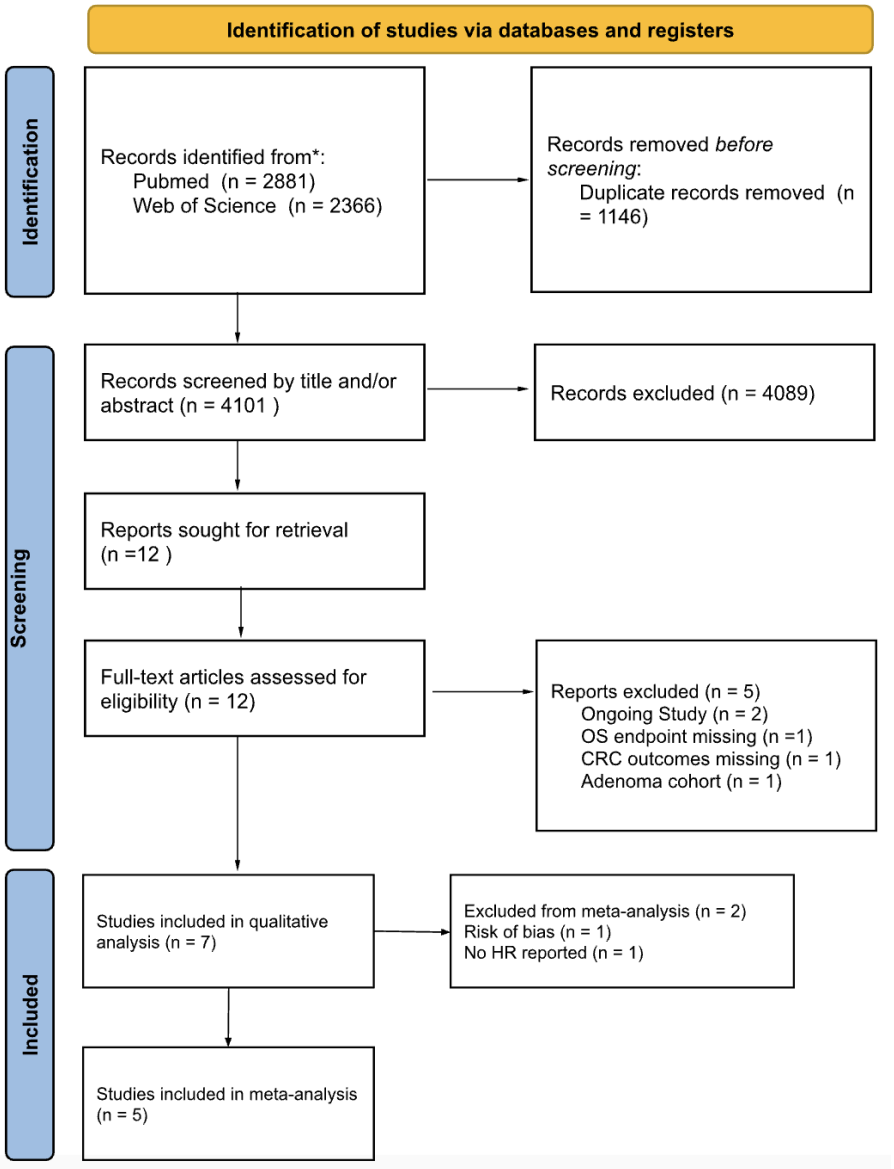

Figure 1: PRISMA flowchart of the trial selection process.

The main characteristics of included trials are summarized in **Table 1**. The SUNSHINE trial (Ng et al., 2019), with an equal number of total and CRC cases (139/139), used a high dosage of 4000 IU/day

of vitamin D3 alongside standard chemotherapy, reporting hazard ratios (HRs) of 0.64 (95% CI 0–0.90) for overall survival (OS) over a 23-month follow-up period, indicating a significant potential benefit in survival. The AMATERASU trial (Urashima et al., 2019) with 201 participants reported a HR of 0.69 (95% CI 0.39–1.24) for progression-free survival (PFS) over a 3.5-year period, suggesting a moderate protective effect of 2000 IU/day of vitamin D3 on CRC progression. In contrast, the Golubic et al. trial, which included 71 participants and also administered 2000 IU/day of vitamin D3, showed no significant benefit in overall survival (HR 1.11, 95% CI 0.69–1.77) over 46 months. The Trivedi et al. trial, notable for its large cohort (2686 participants) but small CRC-specific subgroup (55 cases), utilized a high periodic dosage (100,000 IU every four months) and found an improved colon-specific disease survival (Colon-DSS) with a HR of 0.62 (95% CI 0.24–1.60), although the wide confidence interval suggests variability in the effect. The RECORD and WHI trials, with considerably larger cohorts, provided insights into the effects of lower doses of vitamin D3. The RECORD trial did not provide HR for the CRC-specific outcomes, reporting 20/41 deaths in a large sample over 62 months. The WHI trial (Wactawski-Wende et al., 2006), which administered 400 IU/day combined with calcium carbonate, showed a HR of 0.82 (95% CI 0.52–1.29) for progression-free survival over a seven-year period, suggesting a possible slight improvement in survival outcomes. The VITAL trial (Manson et al., 2019), the largest with 25,871 participants but only 98 CRC cases, combined 2000 IU/day of vitamin D3 with omega-3 fatty acids and reported a HR of 0.79 (95% CI 0.36–1.75) for invasive cancer risk over a 5.3-year follow-up, indicating a potential but not statistically robust protective effect against cancer progression.

Subsequently, we carefully assessed the CONSORT 2010 checklist (Schulz et al., 2011) for compliance of the seven trials found in our literature search. Most studies met the criterion, however the Golubic et al. trial did not. This experiment was not placebo-controlled and did not disclose its random allocation sequence, participant eligibility criteria, or blinding level. These substantial inadequacies suggest a high bias risk, hence the Golubic et al. study was removed from the meta-analysis.

Trial Name, Year	Total/CRC cases	Intervention	Primary outcome	Secondary Outcome	Follow-up	CRC Outcomes
SUNSHINE, 2019[11]	139/139	4000 IU/day vitamin D3 + standard chemotherapy	PFS	OS	23 months	HR = 0.64 (95% CI 0.01–0.90)
AMATERASU, 2019[12]	201/201	2000 IU/day vitamin D3 + standard chemotherapy	PFS	OS	3.5 years	HR = 0.69 (95% CI 0.39–1.24)
Golubic et al, 2018[10]	71/71	2000 IU/day vitamin D3 + standard chemotherapy	OS	PFS	46 months	HR = 1.11 (95% CI 0.69–1.77)
Trivedi et al, 2003[13]	2686/55	100,000 IU/4m vitamin D3	OS	Colon-DSS	NA	HR = 0.62 (95% CI 0.24–1.60)
RECORD, 2012[15]	5292/71	800 IU/day vitamin D3 ± calcium	OS	PFS	62 months	20/41 deaths (No HR reported)
WHI, 2006[19]	36282/322	400 IU/day vitamin D3 + CaCO3	OS	PFS	7 years	HR = 0.82 (95% CI 0.52–1.29)
VITAL, 2019[20]	25871/98	2000 IU/day vitamin D3 + omega-3 fatty acids	Invasive Cancer Risk	OS	5.3 years	HR = 0.79 (95% CI 0.36–1.75)

Table 1: Characteristics of included trials

Vitamin D supplementation and CRC outcomes meta-analysis

The forest plot shows the meta-analysis of five trials on vitamin D supplementation and colorectal cancer survival. The pooled HR of 0.29 (95% CI -0.59, 0.02) suggests a combined effect size. This implies vitamin D supplementation improves survival. Although the confidence interval narrowly crosses the line of no effect, the results are close to statistical significance (Figure 2). The study-specific hazard ratios contribute differently to the combined estimate. The SUNSHINE study, with a weight of 1.84%, reported a hazard ratio (HR) of -0.45 (95% confidence interval -2.70, 1.80), indicating that the effect was not statistically significant. The 27.83% weight AMATERASU study had a better hazard ratio (HR) of -0.37 (95% confidence range -0.95, 0.21). For 10.34% of the data, Trivedi et al. found a hazard ratio (HR) of -0.48 (95% CI -1.43, 0.47). WHI, with the greatest weight of 45.10%, reported an HR of -0.20 (95% CI -0.65, 0.26). With 14.89% of the data, the VITAL study had a hazard ratio (HR) of -0.24 and a 95% CI of -1.03 to 0.55. The analysis showed no heterogeneity among trials, with an I^2 value of 0.00% and a τ^2 value of 0.00. The discrepancies in hazard ratios (HRs) are likely due to sampling variability or intervention differences, not research design or population. The overall test for effect (Z = -1.83, p = 0.07) confirms vitamin D supplementation's favorable effect, although it does not reach statistical significance threshold. This study suggests vitamin D supplementation may increase colorectal cancer survival. More research with larger and more comprehensive trials is needed to prove its efficacy. In addition, the funnel plot and trim and-fill analysis showed publication bias (Effect Size - Observed & Imputed = -0.259, 95% CI -0.548, 0.029) (Figure 3). Egger's regression was non-significant (p = 0.718).

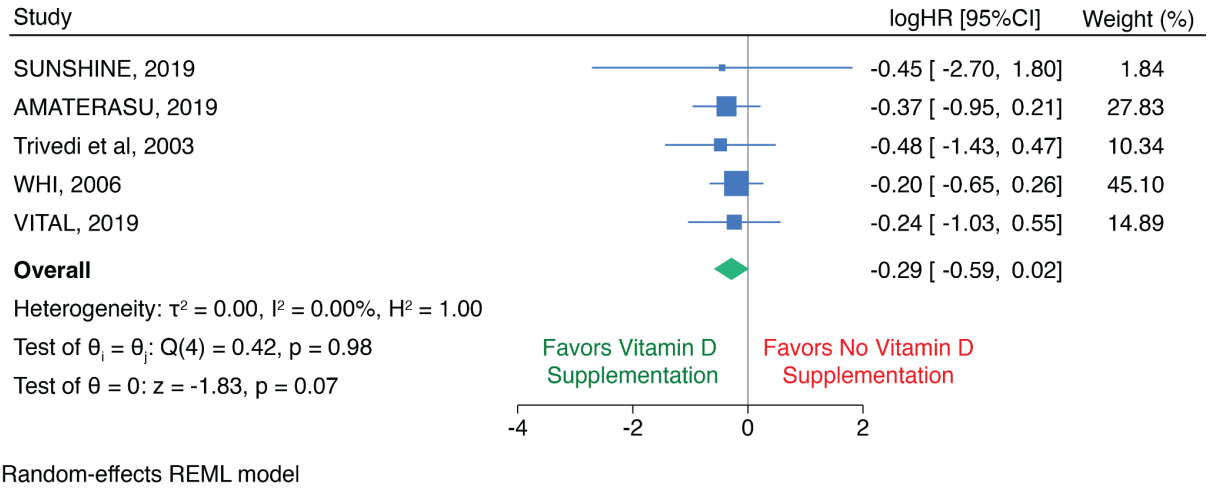

Figure 2: LogHRs are employed for disease (CRC)-specific survival in Trivedi and WHI and progression-free survival in VITAL, SUNSHINE, and AMATERASU. No heterogeneity was found, with $\tau = 0.00$, I2 = 0.00%, and P = 0.98.

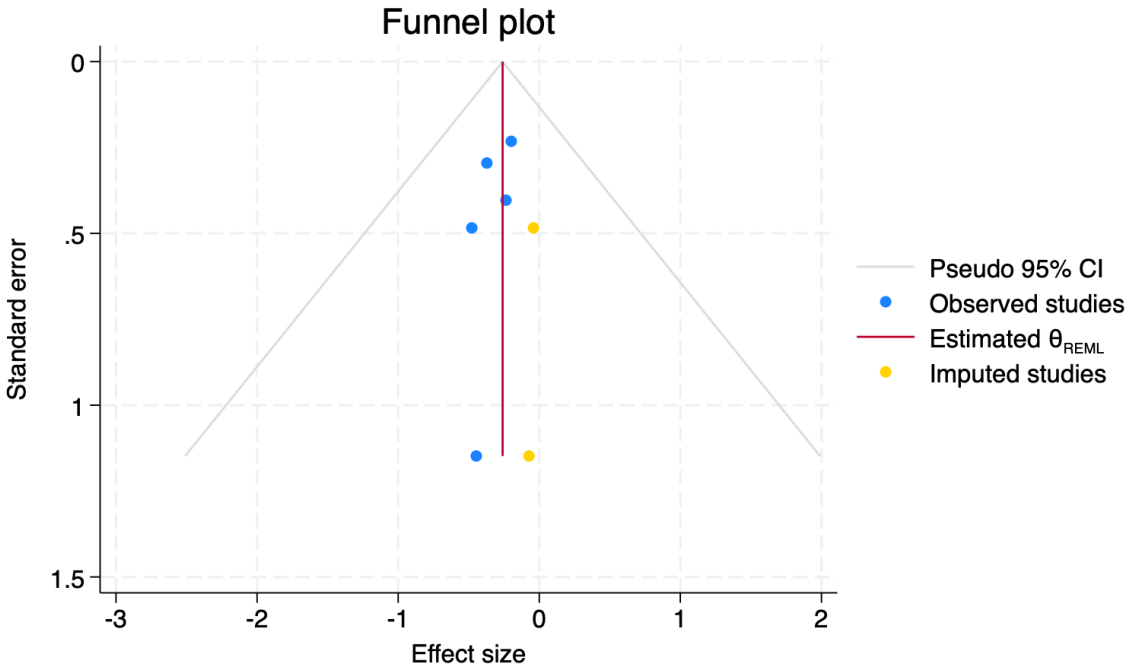

Figure 3: Funnel plot with and trim-and-fill analysis for studies included in overall meta-analysis.

Discussion

The systematic review and meta-analysis in this thesis examined the effects of vitamin D supplementation on colorectal cancer (CRC) survival. A synthesis that suggests vitamin D supplementation may be beneficial was achieved by rigorously analyzing data from multiple randomized controlled trials. However, the statistical results approach but do not reach conventional significance levels. Our findings support the expanding body of research suggesting vitamin D improves cancer prognosis, particularly in CRC. The SUNSHINE and AMATERASU trials showed better survival, supporting the idea that vitamin D's effects on immune response and cell proliferation may affect cancer outcomes. The confidence interval's marginal crossing into the non-significant region warrants cautious interpretation of the data. Vitamin D may decrease tumor development and spread through cell cycle control and apoptosis mechanisms in CRC.

The low variability of included studies suggests that vitamin D supplementation has the same effects across populations and study designs, supporting our findings' generalizability. However, we must admit our analysis's limits. The results may have been affected by vitamin D dosages, duration, and baseline vitamin D status among trials. The majority of included trials did not uniformly describe demographic characteristics including age and sex, which could affect vitamin D metabolism and cancer outcomes, increasing the risk of bias in vitamin D supplementation efficacy studies. Ethical considerations, such as informed consent and the right to withdraw from trials, were followed as per the original studies, but they were not uniformly detailed in the reports, which could limit the study.

Our findings suggest that vitamin D supplementation could be used as an adjuvant therapy in CRC treatment protocols, especially in people with low baseline vitamin D levels. The results were limited and borderline significant, so future research must use larger, more diverse populations with standardized vitamin D exposure and controlled dosing regimens to prove that vitamin D improves CRC survival. This would strengthen the data and assist determine when vitamin D administration is most beneficial.

Conclusions

This comprehensive review and meta-analysis demonstrates that vitamin D supplementation may improve colorectal cancer survival. The results suggest statistical significance, but larger, properly designed trials are needed to determine appropriate dose and demographic specificity. Synthesizing vitamin D's role in cancer survival fills a critical knowledge gap and opens the door for future research that could lead to tailored vitamin D supplementation strategies in oncology protocols, potentially changing public health approaches to cancer treatment and survivorship.

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Supplementary Information

Theme	Terms
Vitamin D	(vitamin D) OR (25-hydroxyvitamin D) OR (25 hydroxyvitamin D) OR (25-hydroxy vitamin D) OR (25 hydroxy vitamin D) OR (calcidiol) OR (cholecalciferol) OR (25OHD) OR (25OH(D)) OR (25(OH)D)
Intervention	(supplement*) OR (intervention) OR (treatment) OR (RCT) OR (randomis *)
Population	((cancer) OR (neoplasm) OR (malignant) OR (malignancy)) AND ((colorectal) OR (bowel) OR (digestive) OR (colon) OR (rectal) OR (rectum) OR (intestine) OR (CRC))
Outcome	(survival) OR (outcome) OR (prognosis) OR (mortality) OR (death)

Supplementary Table 1 Search terms used for literature search