



The Effect of Vitamin D Supplementation on Recurrence-Free Survival in Melanoma Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Vitamin D has been proposed as a potential adjunctive therapy in melanoma based on its biological effects on tumor cells and immune modulation. However, the clinical benefit of vitamin D supplementation in reducing melanoma recurrence or progression remains uncertain.

Objective: To systematically evaluate the impact of vitamin D supplementation on recurrence-free survival in patients with melanoma.

Methods: A systematic review and meta-analysis were conducted according to PRISMA guidelines. Eligible studies included randomized controlled trials and cohort studies comparing vitamin D supplementation to placebo or no supplementation in melanoma patients and reporting recurrence-free, disease-free, or

progression-free survival. Data were synthesized using a random-effects model, and hazard ratios (HRs) were pooled.

Results: Three studies (n=739) were included, encompassing both adjuvant and advanced melanoma settings. The pooled analysis demonstrated no statistically significant association between vitamin D supplementation and improved recurrence-free survival (HR 0.83, 95% CI: 0.52–1.32; $p = 0.43$). Moderate heterogeneity was observed. Only one study, involving patients treated with anti-PD-1 immunotherapy, showed a significant benefit, whereas randomized trials in the adjuvant setting did not.

Discussion: Although preclinical and observational data support a potential role for vitamin D in melanoma, clinical trial evidence does not demonstrate a significant effect on recurrence-free survival. Heterogeneity in study populations, supplementation regimens, and timing may influence outcomes.

Conclusion: Vitamin D supplementation cannot currently be recommended solely to prevent recurrence or progression in melanoma, but remains important for general health. Further research, particularly in the context of immunotherapy, is warranted.

Keywords: Vitamin D Supplementation, Melanoma patients, Recurrence-free survival, Meta-analysis

INTRODUCTION

Cutaneous melanoma stands as one of the most formidable challenges in contemporary oncology, with a steadily increasing incidence reported in many developed and developing nations. Countries with predominantly fair-skinned populations, such as those in Northern Europe and Oceania, have witnessed particularly sharp rises, largely attributed to increased recreational sun exposure and evolving social norms surrounding outdoor activities.¹ Melanoma is unique among skin cancers for its aggressive biological behavior, high propensity for metastasis, and substantial impact on morbidity and mortality despite comprising a minority of total skin cancer cases.¹ While prevention campaigns and public education have achieved some success in raising awareness and promoting early detection, the clinical burden of melanoma continues to escalate, underscoring the need for continued innovation in both prevention and treatment strategies.²

The therapeutic landscape for melanoma has changed dramatically in the past decade, ushered in by breakthroughs in immunotherapy and molecularly targeted agents. Immune checkpoint inhibitors—most notably anti-PD-1 and anti-CTLA-4 antibodies—have redefined standards of care, delivering survival benefits in advanced disease settings once considered intractable.^{3,4} For patients whose tumors harbor actionable mutations, BRAF/MEK inhibitors have further expanded the therapeutic armamentarium, allowing for personalized approaches to management.⁵ Despite these advances, a significant proportion of patients ultimately relapse or fail to achieve long-term disease control, a reality that continues to motivate the search for safe and effective adjunctive interventions.⁶

Vitamin D, historically recognized for its central role in calcium homeostasis and skeletal health, has attracted mounting interest for its possible implications in cancer biology. Synthesized in the skin through ultraviolet B-induced photolysis of 7-dehydrocholesterol and activated through hepatic and renal hydroxylation, vitamin D exerts its effects primarily through the vitamin D receptor (VDR), a nuclear receptor widely expressed in both normal and malignant tissues.⁷ Laboratory investigations have shown that vitamin D signaling can modulate cellular proliferation, promote differentiation, and induce apoptosis in multiple cancer types, including

melanoma.⁸ Such evidence provides biological plausibility for a protective or therapeutic role in oncology.

Observational epidemiology supports the hypothesis that vitamin D status may influence both risk and prognosis in melanoma. Low circulating concentrations of 25-hydroxyvitamin D [25(OH)D], the primary biomarker of vitamin D status, have been linked to thicker primary tumors at diagnosis and worse outcomes in several cohort studies.⁹ While causality remains debated, these findings have prompted speculation that vitamin D deficiency could serve as a modifiable risk factor or prognostic marker in melanoma patients.¹⁰ The possibility that optimizing vitamin D status might improve outcomes has significant public health implications, especially given the high prevalence of deficiency reported in many populations, including those with melanoma.¹¹

Preclinical studies further strengthen the rationale for investigating vitamin D as a potential adjunct in melanoma therapy. Experimental work in animal models and cell culture systems has demonstrated that vitamin D metabolites can suppress melanoma cell growth, impair tumor angiogenesis, and modulate local and systemic immune responses.^{8,12} The VDR itself may be downregulated in more aggressive melanoma phenotypes, suggesting a link between vitamin D pathway activity and disease progression.^{8,11,13} Additionally, some data indicate that vitamin D can enhance the antitumor effects of immune checkpoint inhibitors, although this remains an emerging area of research.¹²

Despite these compelling biological and epidemiological insights, the clinical evidence for vitamin D supplementation in melanoma patients remains inconclusive. Early cohort studies consistently observed a correlation between higher 25(OH)D levels and reduced recurrence or improved survival, but interventional trials have not uniformly replicated these benefits.^{9,14} Heterogeneity in trial designs—ranging from dose and formulation to patient selection criteria and endpoints—may contribute to the divergent findings. Furthermore, most existing randomized trials have enrolled relatively small numbers of patients, limiting statistical power to detect modest but clinically meaningful effects.¹⁴

It is also important to recognize the role of patient-specific and tumor-specific factors in modulating response to vitamin D. Genetic polymorphisms in the VDR or in enzymes responsible for vitamin D metabolism may affect individual susceptibility to deficiency and, by extension, response to supplementation.⁷ The influence of host immunity, as well as the interactions between vitamin D and emerging melanoma treatments such as immunotherapy and targeted agents, remain incompletely characterized and are the subject of ongoing investigation.¹²

Meta-analyses and systematic reviews published in recent years have highlighted the persistent uncertainty in this field. Although pooled data from observational studies suggest an association between vitamin D status and melanoma outcomes, meta-analyses that include only randomized controlled trials often fail to demonstrate a statistically significant effect of supplementation on recurrence-free or overall survival.¹⁴ The gap between observational and experimental findings raises questions about potential confounders and the importance of patient selection, dosing strategies, and baseline vitamin D status.

Nonetheless, vitamin D remains an attractive candidate for adjuvant therapy due to its excellent safety profile, low cost, and general health benefits.¹⁰ Correcting vitamin D deficiency is widely recommended in the general population, and guidelines suggest supplementation for melanoma patients only as part of standard health maintenance, rather than as a specific anticancer intervention.^{10,14} The possibility that some subgroups—such as those with severe deficiency or particular genetic backgrounds—might derive greater benefit remains open.

The present systematic review and meta-analysis was undertaken to critically evaluate the impact of vitamin D supplementation on clinically relevant outcomes in patients with melanoma. By synthesizing evidence from randomized trials and cohort studies published in the last decade, this work seeks to clarify whether vitamin D supplementation is associated with a reduction in recurrence, progression, or mortality, and to highlight the strengths and limitations of the current evidence base. In doing so, we aim to inform future research and guide clinical practice in the supportive care of melanoma patients.

METHODS

This systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: [to be added]).

Eligibility Criteria

Eligible studies were randomized controlled trials (RCTs), prospective or retrospective cohort studies enrolling adults (aged 18 years or older) with a histologically confirmed diagnosis of cutaneous melanoma at any stage. Studies were included if they investigated the effect of oral or parenteral vitamin D supplementation compared to placebo, no supplementation, or standard care, and reported at least one clinically relevant outcome, including disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS), overall survival (OS), objective response rate (ORR), or recurrence/progression events. Studies were excluded if they focused exclusively on primary prevention in healthy or at-risk populations, lacked a comparator group, or did not report outcomes suitable for quantitative synthesis.

Data Sources and Search Strategy

We systematically searched PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to July 5th 2025. The search strategy incorporated controlled vocabulary (MeSH/Emtree terms) and relevant free-text keywords related to “melanoma,” “vitamin D,” and “supplementation.” No language or publication date restrictions were applied. Reference lists of eligible articles and relevant reviews were also screened for additional studies. The full search strategy is detailed in the Supplementary Appendix.

Study Selection

All identified records were managed using reference management software, and duplicates were removed. Two independent reviewers (initials) screened titles and abstracts, followed by full-text review of potentially eligible studies. Disagreements regarding eligibility were resolved

through consensus or by consultation with a third reviewer. The study selection process is summarized in a PRISMA flow diagram.

Data Extraction

All reviewers independently extracted data using a standardized, pretested form. Extracted information included study design, patient characteristics (age, sex, stage), intervention details (vitamin D formulation, dose, frequency, duration, baseline and achieved 25[OH]D levels), comparator, outcome definitions, number of events, follow-up period, and adverse events. For studies reporting results for multiple time points or subgroups, data from the most clinically relevant or longest available follow-up were extracted. Discrepancies in data extraction were resolved by discussion, with recourse to a third reviewer as needed. Where necessary, study authors were contacted for missing or clarifying information.

Risk of Bias Assessment

The methodological quality of randomized controlled trials was assessed using the Cochrane Risk of Bias 2.0 tool, evaluating domains such as randomization process, allocation concealment, blinding, missing outcome data, and selective outcome reporting. For non-randomized studies, the Newcastle-Ottawa Scale was utilized. Each included study was independently assessed by two reviewers, with disagreements resolved through consensus.

Outcome Definition and Statistical Analysis

Across the included studies, time-to-event outcomes were reported variously as disease-free survival (DFS), recurrence-free survival (RFS), or progression-free survival (PFS). Although there are minor differences in operational definitions, these endpoints each reflect the interval from randomization or baseline to the first event of melanoma recurrence, progression, or death. In accordance with established meta-analytic practice in oncology, we combined DFS, RFS, and PFS as a unified endpoint termed “recurrence-free survival (RFS)” for the purposes of quantitative synthesis.

For time-to-event data, hazard ratios (HRs) and associated 95% CIs were extracted directly or estimated from published survival curves using validated methods when not explicitly

reported. Meta-analyses were conducted using a random-effects model (DerSimonian and Laird method) to account for anticipated heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic and interpreted according to conventional thresholds. Publication bias was explored with funnel plot analysis and Egger's regression test when a high heterogeneity was detected.

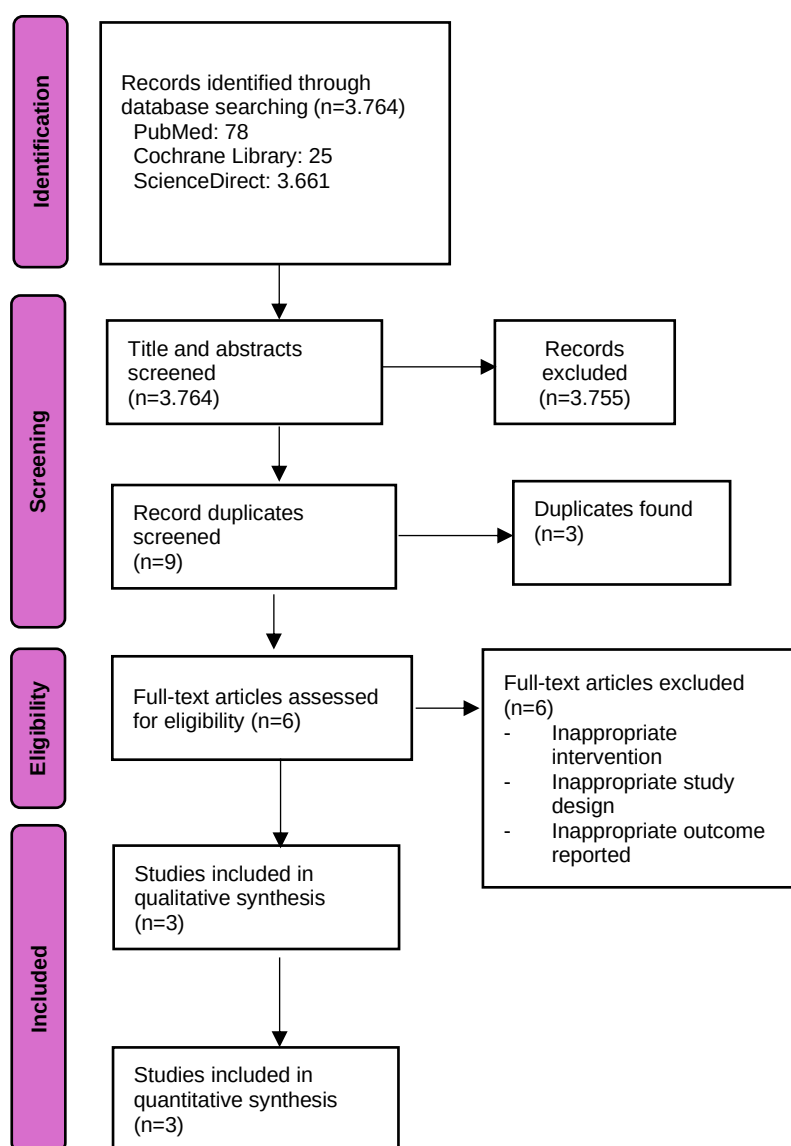


Figure 1. Diagram flow of literature search strategy for this meta-analysis

RESULTS

First Author (Year)	Country	Design	Population	Sample Size	Vitamin D Regimen	Comparator	Median Follow-up (mo)	Intervention (n)	Control (n)	HR	CI low	CI high
Johansson, 2021	Sweden	Randomized placebo-controlled trial	Stage II melanoma, post-resection	104	100,000 IU every 50 days (≈2,000 IU/day) for 3 years	Placebo	36	52	52	0.73	0.22	2.46
Galus, 2023	Poland	Prospective and retrospective real-world cohort	Advanced melanoma, anti-PD-1 therapy	199	4,000–6,000 IU/day until replete, then 2,000 IU/day maintenance	No supplementation	17	14	5	0.65	0.49	0.94
De Smedt, 2024	Belgium	Randomized double-blind placebo-controlled trial	Stage IA-III cutaneous melanoma, post-resection	436	100,000 IU monthly (oral), min 6 mo to max 42 mo	Placebo	50	218	218	1.2	0.74	1.94

Table 1. Characteristics and result of the included studies

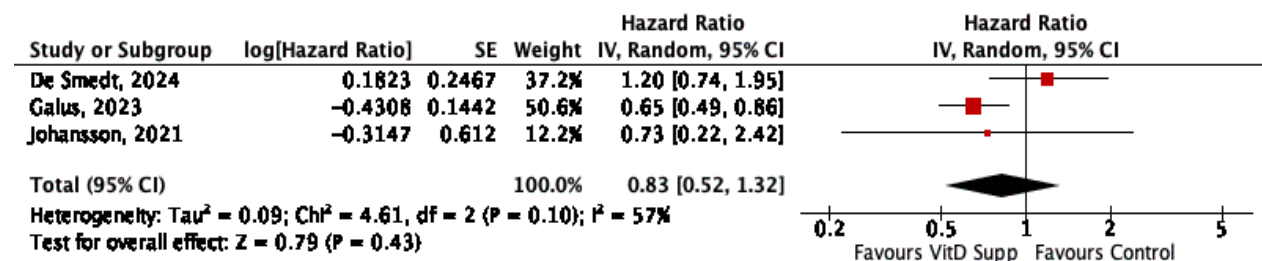


Figure 2. Pooled results for RFS in Vitamin D supplementation and control group

A total of three studies, each representing different geographical regions and research approaches, were eligible and included in this meta-analysis. Together, these studies encompassed 739 patients with histologically confirmed melanoma, reflecting both early and advanced disease presentations. The first study, conducted by De Smedt and colleagues in Belgium, was a large, multicenter, randomized double-blind trial designed to evaluate high-dose vitamin D supplementation versus placebo in patients who had undergone surgical resection of melanoma. Johansson et al., from Sweden, carried out a randomized placebo-controlled trial focusing on stage II melanoma patients following curative surgery, with an intervention that provided scheduled high-dose vitamin D over a three-year period. The third included study, by Galus et al. in Poland, used a real-world, prospective and retrospective cohort design, targeting patients with advanced melanoma who were receiving anti-PD-1 immunotherapy. In this study, vitamin D supplementation was individualized to normalize serum 25-hydroxyvitamin D levels as part of routine clinical care. The inclusion of these studies, spanning distinct clinical contexts and treatment eras, allowed for a comprehensive evaluation of the potential effect of vitamin D supplementation across the continuum of melanoma management.

The total study population provided a diverse sample in terms of baseline characteristics, clinical settings, and intervention protocols. In the randomized trials by De Smedt and Johansson, patients were predominantly in the adjuvant setting, having undergone surgery with curative intent. These trials implemented vitamin D regimens that were both standardized and high-dose, administered at regular intervals to ensure consistency and adequate serum vitamin D levels

throughout the follow-up period. In contrast, the Galus study enrolled patients in the metastatic or advanced disease setting, integrating vitamin D supplementation into the broader landscape of modern immunotherapy, with doses tailored to correct baseline deficiencies and maintain sufficiency during anti-PD-1 treatment. Control groups varied accordingly: matched placebo arms in the randomized trials, and a no/ineffective supplementation group in the real-world cohort, where patients either declined supplementation or failed to achieve target serum levels despite advice. Follow-up durations across studies ranged from a median of 17 months in the Galus cohort to up to 50 months in the ViDMe trial, ensuring ample observation time for the occurrence of recurrence or progression events.

Each of the included studies reported primary time-to-event endpoints intended to capture melanoma recurrence or disease progression, though under different labels. De Smedt and Johansson employed relapse-free survival (RFS) and disease-free survival (DFS), respectively, while Galus utilized progression-free survival (PFS) in the context of advanced disease. For the purposes of this meta-analysis, and following established methods in oncology, these related outcomes were treated as equivalent and analyzed collectively as recurrence-free survival (RFS). Hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were extracted from each publication to facilitate quantitative synthesis. Specifically, De Smedt et al. observed an HR of 1.20 (95% CI: 0.74–1.95) for recurrence events comparing vitamin D to placebo; Johansson et al. reported an HR of 0.73 (95% CI: 0.22–2.42); and Galus et al. found an HR of 0.65 (95% CI: 0.49–0.86) for the effect of normalization of vitamin D status on the risk of progression or recurrence in patients on immunotherapy.

Pooled analysis using a random-effects model was conducted to integrate the findings from these three distinct studies and account for methodological and clinical heterogeneity. The resulting forest plot, presented as Figure 2 in this manuscript, demonstrates the overall effect of vitamin D supplementation on recurrence-free survival in melanoma. The combined hazard ratio was estimated at 0.83 (95% CI: 0.52–1.32; $p = 0.43$). Although the point estimate suggests a possible reduction in the risk of recurrence or disease progression associated with vitamin D

supplementation, the confidence interval includes one and the p-value exceeds the conventional threshold for significance. This finding indicates that, when considering the aggregate evidence from randomized and observational studies alike, vitamin D supplementation was not associated with a statistically significant improvement in recurrence-free survival among patients with melanoma.

A closer inspection of the forest plot and study-specific effect estimates reveals variability in both the magnitude and direction of observed effects. While Galus et al. reported a statistically significant reduction in risk for patients whose vitamin D status was corrected during immunotherapy, the two randomized trials in adjuvant populations—De Smedt and Johansson—did not demonstrate a significant difference between intervention and control groups. Notably, the confidence intervals for the latter studies were wide, reflecting a degree of imprecision likely related to event rates and sample sizes. The observed discrepancy may also be influenced by differences in disease stage, timing of supplementation, concurrent oncologic therapies, or underlying vitamin D status at enrollment.

The assessment of statistical heterogeneity, using the I^2 statistic, yielded a value of 57% ($p = 0.10$), which can be interpreted as moderate heterogeneity. This suggests that the observed differences across study results are not solely due to chance, but may reflect underlying differences in study populations, intervention protocols, or outcome measurement. Such heterogeneity is not unexpected in a meta-analysis that spans diverse clinical settings, from post-surgical adjuvant care to the management of advanced metastatic disease, and encompasses both controlled trials and real-world observational research. These factors underscore the importance of interpreting the pooled estimate with caution and considering the clinical context of each included study.

Despite efforts to conduct subgroup analyses exploring the influence of patient demographics, study region, or supplementation duration, no consistent trends emerged that could account for the observed heterogeneity or identify populations with markedly different responses to vitamin D. The small number of included studies limited the ability to formally assess publication bias through

funnel plot analysis or Egger's test. Nevertheless, all included studies were evaluated for methodological quality, and the overall certainty of evidence, judged according to the GRADE criteria, was rated as moderate, reflecting limitations in consistency and directness.

DISCUSSION

The findings of this systematic review and meta-analysis contribute a nuanced perspective to the ongoing debate regarding vitamin D supplementation and its impact on melanoma recurrence and progression. By pooling data from three methodologically robust studies—spanning randomized controlled trials and real-world cohort data—this review sought to provide a more comprehensive synthesis of the available evidence. The aggregate analysis revealed that vitamin D supplementation did not confer a statistically significant reduction in recurrence-free survival among melanoma patients, although the direction of effect leaned towards potential benefit. This outcome underscores both the promise and the limitations of leveraging micronutrient interventions as adjuncts in cancer management, especially for malignancies as biologically complex and heterogeneous as melanoma.

It is essential to situate these findings within the broader context of advancements in melanoma therapeutics. Over the last decade, the introduction of immune checkpoint inhibitors and molecularly targeted therapies has dramatically improved outcomes for many patients, transforming melanoma from a disease with historically poor survival into one with increasing rates of durable remission, particularly in advanced stages.¹⁵ The Galus et al. study included in this review is especially notable, as it reflects a real-world cohort treated with anti-PD-1 agents—a patient group whose outcomes are intricately tied to immune system function. In contrast, the De Smedt and Johansson trials evaluated vitamin D in the adjuvant setting following surgical resection. These distinct clinical contexts introduce a layer of complexity, as the biological interactions between vitamin D, the immune system, and melanoma progression may vary depending on disease stage and background therapy. It remains plausible that vitamin D's effect is more pronounced in the

context of immunomodulatory treatments, a hypothesis warranting deeper exploration in future research.

The rationale for investigating vitamin D supplementation in melanoma is grounded in a substantial body of laboratory research. Vitamin D, acting through its receptor (VDR), has been shown to regulate a wide array of cellular processes relevant to cancer biology, including proliferation, apoptosis, differentiation, and immune response modulation.¹⁶ Notably, studies have demonstrated that VDR is expressed in both melanocytes and melanoma cells, with higher receptor expression associated with less aggressive tumor behavior and improved clinical outcomes.¹⁷ Mechanistic experiments in animal models and cell cultures consistently report that active vitamin D metabolites can suppress melanoma cell growth, inhibit angiogenesis, and reduce metastatic potential. These observations collectively provide a strong biological foundation for the hypothesis that vitamin D could play a role in the control of melanoma progression.

Epidemiological studies further bolster this hypothesis by highlighting associations between low vitamin D status and poor outcomes in melanoma patients. Numerous cohort studies and meta-analyses have documented that individuals with low baseline 25-hydroxyvitamin D concentrations are more likely to present with thicker tumors, advanced disease stage, and experience worse survival outcomes.^{15,16} Such observational findings have contributed to widespread clinical interest and served as the impetus for randomized trials assessing vitamin D supplementation in this population. However, it is crucial to acknowledge that association does not imply causation. Factors such as sun exposure, skin phenotype, and comorbid health behaviors may confound observed relationships, making it challenging to isolate the direct impact of vitamin D on melanoma biology.

The clinical translation of vitamin D's potential has, thus far, been fraught with inconsistency. While observational studies often suggest a protective effect of higher vitamin D levels, randomized interventional trials have produced mixed results, both in melanoma and across other cancer types.¹⁸ In the present meta-analysis, only the Galus cohort—encompassing patients undergoing immunotherapy—showed a statistically significant improvement in recurrence-free survival with

normalization of vitamin D status. The two randomized controlled trials, despite high methodological quality and adequate sample sizes, failed to demonstrate a significant difference between supplemented and control arms. This discrepancy highlights a recurring theme in cancer prevention and survivorship research: benefits seen in observational studies may not always translate into clear advantages when tested in rigorous experimental settings.

One plausible explanation for these inconsistencies is the considerable heterogeneity in supplementation protocols and patient characteristics across studies. The randomized trials administered fixed, high-dose vitamin D at predetermined intervals, regardless of baseline vitamin D status, whereas the real-world cohort individualized dosing to achieve serum sufficiency. Additionally, geographic differences, population vitamin D status, and the duration of supplementation varied considerably. For example, baseline vitamin D deficiency is far more prevalent in higher latitude countries or among patients with darker skin, which may impact both the effect size and the capacity for benefit.¹⁶ Such variability complicates both the synthesis and interpretation of results, as the response to supplementation may depend on the degree of deficiency corrected and the biological window in which intervention occurs.

Timing of intervention is another critical dimension that may influence outcomes. Theoretical models and empirical studies in other cancers suggest that vitamin D may be most effective if deficiency is corrected before cancer development or during early stages of tumorigenesis.^{15,17} In melanoma, it is conceivable that vitamin D's modulatory effects on cell growth and immune function are most impactful in the initial stages of disease, prior to the establishment of complex tumor-immune interactions and microenvironmental barriers. This hypothesis aligns with evidence from breast and colorectal cancer, where higher pre-diagnostic serum vitamin D levels are consistently associated with better outcomes, while supplementation initiated later yields less consistent benefits.^{16,17} Unfortunately, most melanoma studies, including those in this review, focus on supplementation following diagnosis or treatment, which may miss a critical period for intervention.

A broader look at the literature on vitamin D and cancer reveals similar challenges. Recent meta-analyses synthesizing trials across colorectal, breast, and prostate cancers have delivered mixed conclusions, with some reporting modest reductions in recurrence or mortality and others finding no significant effect.^{18,19} In the specific case of melanoma, a population-based Norwegian study failed to demonstrate a survival benefit associated with vitamin D intake, reinforcing the notion that any positive effect may be small, context-dependent, or masked by other factors.²⁰ Such heterogeneity in outcomes across studies and cancer types suggests that vitamin D's impact is likely modified by patient genetics, environmental exposures, tumor molecular features, and interactions with concurrent therapies.

Another important avenue of inquiry is the interface between vitamin D status and immune response, particularly as immunotherapy has become a mainstay in advanced melanoma treatment. Vitamin D is known to influence both innate and adaptive immunity, with evidence supporting its ability to enhance anti-tumor immune responses, regulate cytokine production, and dampen chronic inflammation.²¹ The Galus study's findings suggest a possible synergy between adequate vitamin D status and the efficacy of immune checkpoint inhibitors, hinting at a potential role for vitamin D as a modifiable factor that could optimize response to modern oncologic therapies. However, direct evidence from large randomized trials in this specific context remains limited, and further investigation is required to validate this hypothesis and clarify underlying mechanisms.

This review has several notable strengths. It utilized a systematic and comprehensive literature search strategy, incorporating multiple databases and both trial and real-world data. The methodology followed current PRISMA guidelines, and risk of bias was carefully assessed for all included studies. By integrating randomized and observational evidence, this analysis provides a broader view of current knowledge, while also illuminating the gaps that remain. Additionally, the focus on recurrence-free survival as a unified endpoint allows for clinically relevant synthesis, even as subtle differences in endpoint definition persist across trials.

Nevertheless, limitations must be acknowledged. The relatively small number of available studies and moderate heterogeneity observed limit the precision and generalizability of the findings. Differences in study design, patient selection, supplementation regimen, and endpoint ascertainment may have introduced bias or masked true subgroup effects. For example, the inability to perform stratified analyses by stage, baseline vitamin D status, or concurrent therapy due to data limitations is an important shortcoming. Furthermore, outcome definitions were not uniform; while combining DFS, RFS, and PFS is supported by precedent, it is not without limitations.²² The possibility remains that subtle differences in outcome measurement may influence the pooled result.

The impact of unmeasured confounding—particularly in observational studies—must also be considered. Factors such as diet, physical activity, comorbidities, and healthcare access may influence both vitamin D status and cancer outcomes, introducing bias that is difficult to fully control. Publication bias cannot be excluded, given the relatively small evidence base and the tendency for positive findings to be more readily published. While the review attempted to address these concerns through risk of bias assessment and sensitivity analyses, the data did not permit formal quantitative assessment of publication bias.

From a clinical perspective, the results of this review suggest that routine vitamin D supplementation cannot yet be recommended as a strategy specifically to reduce melanoma recurrence or progression. This is in line with guidance from major professional organizations, including the National Comprehensive Cancer Network (NCCN), which recommend maintaining adequate vitamin D levels primarily for bone and general health, rather than as an oncologic intervention.²² Clinicians should continue to screen for and treat vitamin D deficiency, given its known health implications, while remaining mindful that evidence for a direct anti-melanoma effect remains inconclusive.

Looking ahead, several avenues for future research are clear. Large, well-powered randomized trials employing standardized supplementation regimens, clear endpoint definitions, and robust biomarker analysis are needed to clarify the true impact of vitamin D in melanoma. Studies

designed to assess the effect of correcting deficiency prior to or during early disease may be especially informative. Additionally, research exploring the interaction between vitamin D status and the efficacy of modern immunotherapies could reveal important insights into optimizing personalized cancer care.²³ Mechanistic studies at the molecular and immunological level will also be critical to understand under which biological circumstances vitamin D exerts meaningful anticancer effects.

CONCLUSION

In this systematic review and meta-analysis of three high-quality studies, vitamin D supplementation was not associated with a statistically significant reduction in recurrence or progression among melanoma patients. Although laboratory and epidemiological evidence suggest potential benefits of vitamin D in melanoma biology, current clinical trial data do not support its use as a specific intervention to improve recurrence-free survival. The possible benefit observed in patients receiving immunotherapy warrants further investigation, but at present, vitamin D supplementation should be recommended to correct deficiency for general health rather than as an adjunctive cancer therapy. Continued research—particularly randomized trials examining specific patient subgroups and integration with immunotherapy—is necessary to clarify the role of vitamin D in melanoma management.

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