



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	VITAMIN D3 AND CANCER PREVENTION: FROM BIOLOGICAL MECHANISM TO CLINICAL EVIDENCE
----------------------	--

DOI	https://doi.org/10.31435/ijitss.3(51).2026.6171
------------	---

RECEIVED	22 May 2026
-----------------	-------------

ACCEPTED	10 September 2026
-----------------	-------------------

PUBLISHED	21 September 2026
------------------	-------------------

LICENSE	
----------------	--



The article is licensed under a **Creative Commons Attribution 4.0 International License**.

© The author(s) 2026.

This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

VITAMIN D3 AND CANCER PREVENTION: FROM BIOLOGICAL MECHANISM TO CLINICAL EVIDENCE

Natalia Brzozowska (Corresponding Author, Email: natalkab79@gmail.com)

Nowy Dwór Mazowiecki Medical Center, Miodowa 2, 05-100 Nowy Dwór Mazowiecki, Poland

ORCID ID: 0009-0003-6580-1714

Eliza Mędrak

Nowy Dwór Mazowiecki Medical Center, Miodowa 2, 05-100 Nowy Dwór Mazowiecki, Poland

ORCID ID: 0009-0001-2830-014X

Sara Awad

Independent Public Clinical Hospital named after Prof. W. Orłowski, CMKP, Czerniakowska 231, 00-416 Warsaw, Poland

ORCID ID: 0009-0004-0942-6240

Oliwia Borowska

Independent Public Clinical Hospital named after Prof. W. Orłowski, CMKP, Czerniakowska 231, 00-416 Warsaw, Poland

ORCID ID: 0009-0006-1260-5711

Jakub Magdziak

Independent Public Clinical Hospital named after Prof. W. Orłowski, CMKP, Czerniakowska 231, 00-416 Warsaw, Poland

ORCID ID: 0009-0006-0297-7423

Natalia Salkowska

University Clinical Center of the Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland

ORCID ID: 0009-0005-2518-3493

Barbara Wardzyńska

Independent Public Healthcare Complex in Wyszaków, Komisji Edukacji Narodowej 1, 07-200 Wyszaków, Poland

ORCID ID: 0009-0002-4521-8911

Paulina Zegarska

Grochowski Hospital named after Dr Rafał Masztak, Grenadierów 51/59 Warsaw, Poland

ORCID ID: 0000-0001-6727-8128

Maria Bendykowska

Military Institute of Medicine, Szaserów 128, 04-141 Warsaw, Mazovia, Poland

Hanna Markowska

Samodzielny Publiczny Zespół Zakładów Opieki Zdrowotnej w Ministerstwa Spraw Wewnętrznych i Administracji w Bydgoszczy, ul. Ks. R. Markwarta 4-6, 85-015 Bydgoszcz, Poland

ORCID ID: 0009-0006-7837-1989

ABSTRACT

Vitamin D3 (cholecalciferol) is a steroid prohormone synthesized in the skin as a result of UV-B light exposure or by dietary intake. In addition to the already proven action on calcium phosphate metabolism and bone physiology, there is an increasing body of research showing that vitamin D3 may impact carcinogenesis and cancer progression. The aim of this literature review was to summarize current knowledge regarding the biological mechanisms of vitamin D₃ and its potential impact on cancer risk, progression, and patient survival.

Multiple observational trials have confirmed that there is an inverse relationship between levels of serum 25-hydroxyvitamin D [25(OH)D] and the risk as well as mortality rates associated with some types of cancer, especially colorectal and breast cancers. However, findings from randomized controlled trials evaluating primary cancer prevention remain inconclusive. Such contradicting findings have been linked to limitations in research design, which include insufficient supplementation doses, inclusion of participants with adequate baseline vitamin D status, and relatively short follow-up periods.

Vitamin D exerts its action via the vitamin D receptor (VDR) at the molecular level. It affects the gene expression related to various functions such as the cell cycle, apoptosis, cellular differentiation, immune modulation, and inflammatory processes. Current scientific evidence supports a mechanism by which vitamin D3 could play a part in the prevention of cancer. However, clear clinical recommendations require further well-designed randomized controlled trials incorporating adequate supplementation doses and focusing on populations with vitamin D deficiency.

KEYWORDS

Vitamin D3, Cholecalciferol, Cancer, Carcinogenesis, Cancer Prevention

CITATION

Brzozowska, N., Mędrek, E., Awad, S., Borowska, O., Magdziak, J., Salkowska, N., Wardzyńska, B., Zegarska, P., Bendykowska, M., & Markowska, H. (2026). Vitamin D3 and cancer prevention: From biological mechanism to clinical evidence. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6171](https://doi.org/10.31435/ijitss.3(51).2026.6171)

COPYRIGHT

© The author(s) 2026. This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Vitamin D is a unique prohormone, as it can be synthesized endogenously in the skin under the influence of UV-B radiation from sunlight. Alternatively, Vitamin D can also be derived through diet from naturally occurring sources, fortified foods, or dietary supplements (Vishal Paresh Shah et al., 2024). The primary dietary form of vitamin D is cholecalciferol (vitamin D3), which is found mainly in animal-derived products such as oily fish, fish liver oils, beef liver, dairy products, and egg yolk. Vitamin D metabolites, including 25-hydroxycholecalciferol (25OHD3) and, in trace amounts, 1,25-dihydroxycholecalciferol, can also be present in food. Ergocalciferol (vitamin D2) occurs mostly in certain types of mushrooms and is widely used in supplements and fortified foods (Borel et al., 2013).

With adequate sunlight exposure, enough vitamin D may be synthesized in the skin from 7-dehydrocholesterol such that it accounts for up to 80% of total vitamin D needs, depending on geographic location, season, age, and lifestyle (Borel et al., 2013). However, endogenous production may not be enough, especially in the case of infants, elderly individuals, people with limited sun exposure, and patients with fat malabsorption disorders. In these groups, supplementation or consumption of fortified foods is frequently necessary to achieve the recommended serum 25(OH)D concentration, considered optimal above 30 ng/mL (75 nmol/L) (Vishal Paresh Shah et al., 2024).

Vitamin D plays a crucial role in regulating calcium and phosphorus homeostasis, which is essential for proper bone mineralization and skeletal health. The deficiency of vitamin D is common and it is a very potent risk factor for developing various bone diseases such as osteomalacia and osteoporosis in adults, along with rickets and osteomalacia in growing children. The biological effects of vitamin D are mediated by its active form, calcitriol (1,25[OH]₂D), which binds to the vitamin D

receptor present in most tissues, explaining its wide-ranging physiological effects (Vishal Paresh Shah et al., 2024).

The widespread expression of the vitamin D receptor has led to increasing interest in its potential role in the prevention of non-skeletal diseases. Observational studies have found an inverse association between serum 25(OH)D concentrations and the risk of chronic diseases such as cancer, autoimmune disorders, and cardiometabolic disease (Vishal Paresh Shah et al., 2024). On the other hand, various randomized clinical trials examining the effects of vitamin D on the prevention of these conditions have yielded conflicting results.

Bioavailability of vitamin D refers to the amount of vitamin D that appears in the circulation after absorption, is variable and generally lower than that of triacylglycerols (Borel et al., 2013). Like dietary lipids, it follows a similar pathway in the gastrointestinal tract; it is absorbed in the small intestine, incorporated into chylomicrons, and transported to the liver. Several factors can affect the absorption of efficiency, including the food matrix, fat intake, gastrointestinal health, and individual metabolic differences, although data on many of these factors remain limited (Borel et al., 2013).

Methods

The aim of this literature review was to present the current state of knowledge regarding the biological mechanisms of vitamin D3 and its potential influence on cancer outcomes, including patient survival. The literature search was conducted using PubMed, Scopus, and Google Scholar, employing combinations of keywords such as “vitamin D3,” “cholecalciferol,” “vitamin D,” “cancer,” “tumor,” “carcinogenesis,” “oncology,” and “cancer prevention” connected with the logical operators AND and OR. The search included publications from 2008 to 2024 written in English. The review incorporated peer-reviewed articles, including original research, clinical studies, epidemiological studies, and review papers. These publications examined the influence of vitamin D3 on cancer risk, progression, and underlying biological mechanisms. Excluded from the review were articles unavailable for reading in full, not related directly to either vitamin D3 or oncology, popular science, and those with low methodological quality. All included studies were analyzed qualitatively, and the material was organized according to cancer type, study design, and thematic focus, such as disease risk, progression, mortality, or molecular pathways. For every thematic group, the methods used, findings of studies, and their limitations were compared to identify consistencies and discrepancies. This review has certain limitations. Only selected databases were searched, and non-English publications were excluded. In addition, differences in study design and the vitamin D3 dosages used across studies may have affected the comparability of the results.

The Role of Vitamin D3 in Cancer Prevention

The potential role of vitamin D3 in cancer prevention has been the subject of intensive scientific research, such as epidemiologic research, clinical studies, and meta-analyses. In observational studies, low serum concentrations of 25-hydroxyvitamin D (25(OH)D), the main circulating form of vitamin D, were associated with an increased risk of and poorer prognosis for various cancers, including colon, breast, and prostate cancer. In meta-analyses based on observational results, the inverse relationship between serum levels of 25(OH)D and various cancers was shown. Geographical differences in the prevalence of certain cancers are associated with variations in sun exposure, thus possibly indicating the protective effects of vitamin D against cancers (Muñoz and Grant, 2022).

In addition, observed geographical differences in cancer incidence have repeatedly been linked to levels of exposure to solar radiation and, consequently, to the efficiency of cutaneous vitamin D synthesis. Populations living in regions with lower sunlight exposure are characterized by both lower serum 25(OH)D concentrations and higher incidence rates of certain cancers, which supports the hypothesis of a potential protective role of vitamin D. (Grant, 2010)

Despite the consistency of findings from observational studies, data from randomized controlled trials (RCTs) are less conclusive. Many well-designed clinical studies have shown no

effect on vitamin D supplementation and the decrease in cancer cases. These inconsistencies could be attributed to flaws in design, such as inadequate doses of vitamin D, the inclusion of people with sufficient levels of 25(OH)D at baseline, and follow-up periods that were too short to capture long-term preventive effects (Wimalawansa, 2025).

In contrast to vitamin D3, vitamin D2 has not demonstrated a comparable effect on cancer-related mortality in clinical studies. Meta-analyses of randomized trials suggest that supplementation with vitamin D3 may be associated with improved cancer survival outcomes. Although its impact on primary cancer prevention remains a matter of debate, vitamin D3 may still play a supportive role in the course of cancer. (Zhang et al., 2019).

Mechanisms of Vitamin D Action and Its Impact on Cancer Development and Progression

Vitamin D3 (cholecalciferol) is a steroid prohormone known for its diverse physiological functions. The primary mechanism for the production of vitamin D3 is through its synthesis in the skin under UV-B exposure, with smaller contributions from diet and supplementation. Once vitamin D3 is absorbed, it undergoes a process of hydroxylation in the liver to 25-hydroxyvitamin D3 (25(OH)D3), which is the main clinical marker of vitamin D status. Further hydroxylation in the kidneys leads to formation of the active form, 1,25-dihydroxyvitamin D3 (1,25(OH)₂D₃, calcitriol) (Carlberg & Muñoz, 2022).

The biological effects of vitamin D are almost exclusively mediated through the vitamin D receptor (VDR), which belong to the nuclear receptor superfamily. Upon ligand binding, VDR functions as a transcription factor, regulating gene expression by binding to specific DNA sequences. VDR is widely expressed, and it is present in more than half of human tissues and cell types, which is why actions of vitamin D are pleiotropic. Activated VDR interacts with the genome at thousands of loci, however only a subset of these leads to direct changes in gene expression. VDR-regulated genes control cell cycle, differentiation, apoptosis, cellular metabolism, and immune functions. Beyond classical genomic actions, vitamin D also exerts rapid non-genomic effects, modulating kinases, phosphatases, and ion channels (Carlberg & Muñoz, 2022).

Vitamin D exerts its regulatory action through the epigenome. Via VDR, vitamin D alters chromatin accessibility, enhancer and promoter activity, and the three-dimensional organization of the genome. It interacts with chromatin remodeling proteins and pioneer transcription factors for the access to previously inaccessible DNA regions. Cancer cells that have a dysregulated epigenetic landscape, will be influenced by vitamin D, which will help stabilize gene expression (Carlberg & Muñoz, 2022).

Experimental studies show that vitamin D inhibits cancer cell proliferation by inducing cell cycle arrest, like through activation of inhibitors of cyclin-dependent kinases like CDKN1A (p21). It also promotes differentiation of malignant cells, reducing their capacity to proliferate, and induces apoptosis in cells with irreversible damage. Vitamin D metabolism in tumor cells also plays a role. The enzyme CYP24A1, which degrades active vitamin D metabolites, is frequently overexpressed in cancers and correlates with poor prognosis, representing a mechanism by which tumors escape vitamin D-mediated growth control (Giammanco et al., 2015).

Calcitriol also promotes apoptosis in cells with DNA damage or abnormal growth patterns. In addition, vitamin D influences the tumor microenvironment by inhibiting angiogenesis through downregulation of pro-angiogenic factors, and by modulating molecules involved in cell adhesion and invasion, which could reduce metastatic potential. These molecular actions are supported by extensive preclinical data showing that vitamin D compounds can activate signaling pathways that inhibit tumor growth and sensitize cells to other anticancer agents (Deeb et al., 2007).

The most important non-skeletal function of vitamin D is modulation of the immune system, which has key implications for cancer. Vitamin D increases innate immunity through improving the ability of cells to eliminate pathogens and transformed cells, while preventing excessive adaptive

immune responses that could lead to chronic inflammation or autoimmunity. Its effects on immune cells are situational and depend on the stage of the response. While vitamin D can initiate pro-inflammatory activities at first, it participates in the later resolution of inflammation, promoting tissue repair. It affects the differentiation, activation, and apoptosis of monocytes, macrophages, dendritic cells, and T lymphocytes, including cytotoxic T cells and regulatory T cells. In the tumor microenvironment, vitamin D can shift immune responses in ways that are unfavorable for tumor survival. It enhances mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), which is clinically relevant in monoclonal antibody therapies. Moreover, it may prevent tumor establishment by supporting cytotoxic T cell-mediated elimination of early transformed cells. (Carlberg & Muñoz, 2022).

Emerging evidence indicates that vitamin D's primary role in cancer is preventive rather than therapeutic. In healthy individuals, thousands of cells undergo malignant transformation daily, but most are recognized and eliminated by cytotoxic T cells. Vitamin D, by enhancing immune surveillance and maintaining proper immune regulation, increases the efficiency of this natural tumor-suppressive mechanism (Carlberg & Muñoz, 2022).

Discussion

Observational studies have consistently reported a strong association between low circulating levels of vitamin D and an increased risk of cancer. However, results from large randomized controlled trials (RCTs) have frequently been inconclusive. These inconsistencies are mainly due to a number of methodological issues. First, many trials have used vitamin D doses that were too low to elicit a meaningful biological effect. Second, participants were frequently recruited despite having sufficient baseline vitamin D levels, which reduced the likelihood of detecting a benefit from supplementation. In addition, the duration of follow-up in many studies was too short to adequately capture the long-term effects of vitamin D on cancer development and progression.

Despite these limitations, evidence from pooled analyses provides more compelling insights. A meta-analysis of 52 randomized controlled trials, including a total of 75,454 participants, demonstrated that vitamin D supplementation was associated with a significant 16% reduction in cancer-related mortality (relative risk [RR] = 0.84). In this regard, it is worth noting that the protective effect seen was due to supplementations using vitamin D₃ (cholecalciferol), but not vitamin D₂ (ergocalciferol), for which no reduction in cancer-related mortality was found. These findings suggest that the form of vitamin D used in supplementation plays a critical role in its potential impact on cancer survival (Zhang et al., 2019).

Breast cancer

Numerous studies have assessed the association between serum vitamin D status and breast cancer (BC) risk. Preclinical studies have shown that vitamin D₃ inhibits the growth of various breast cancer subtypes regardless of the level of vitamin D receptor (VDR) expression. Treatment with vitamin D₃ induced apoptosis and cell cycle arrest both in vitro and in vivo. It also suppressed the process of angiogenesis, which also resulted in decreased tumor development in animal models (Veeresh et al., 2023).

Several studies have investigated the correlation between the level of circulating 25(OH)D and breast cancer risk or prognosis. According to Lope et al., there is an inverse correlation between the level of 25(OH)D in serum and BC risk among participants of the multicase- control MCC- Spain study, where a dose-response pattern was observed and greater protective effect for triple-negative cases was demonstrated (Lope et al., 2018). A comprehensive meta-analysis by Kim and Je, included 30 prospective studies and more than 31,000 cases. Higher circulating 25(OH)D levels were only weakly associated with lower BC incidence with pooled relative risks of 0.95 and 0.92 for vitamin D intake and circulating levels, respectively. However, the same analysis showed a significant reduction in breast cancer-specific mortality (pooled RR = 0.58) and overall mortality (pooled RR = 0.61)

among BC patients with higher 25(OH)D status (Kim & Je, 2014). These findings point to a stronger and more consistent relationship between vitamin D status and survival outcomes than with incidence itself. This interpretation is also supported by the results of the Pathways Study demonstrating the independent influence of high serum 25(OH)D concentrations at the time of breast cancer diagnosis on overall and disease-specific survival in 1,666 women, with the strongest associations observed in premenopausal individuals (Yao et al., 2017).

In summary, while vitamin D may have only modest effects on breast cancer risk in the general population, its status at diagnosis appears to be prognostically relevant. However, limitations in the studies, such as imprecise estimates of supplementation dose and duration, incomplete control of confounding factors (e.g., geographic location), and restrictions on 1,25(OH)₂D₃ doses due to hypercalcemia risk, may have reduced the observed anticancer effects compared with preclinical studies (Li et al., 2021). Further well-designed research is needed to determine the optimal supplementation dose.

Colorectal cancer

Among solid tumors, the strongest and most consistent associations between circulating 25(OH)D levels and cancer risk and prognosis have been observed in colorectal cancer. Numerous observational studies and meta-analyses have demonstrated an inverse relationship between serum 25(OH)D concentrations and both the incidence and cancer-specific mortality of colorectal cancer. This association seems especially strong with regard to patients diagnosed at an early stage of the disease, including early-onset colorectal cancer (EOCRC) (Hua et al., 2023). Experimental and molecular data support these observations. Vitamin D signaling regulates intestinal epithelial cell proliferation, maintains mucosal barrier integrity, modulates inflammatory responses, and preserves microbiota homeostasis. These processes may help prevent inflammation-driven colorectal carcinogenesis. Large randomized controlled trials (RCTs) evaluating vitamin D supplementation for primary colorectal cancer prevention have yielded mixed results. However, their interpretation is limited by methodological constraints, including low supplementation doses (e.g., 400 IU/day), the inclusion of participants with adequate baseline vitamin D levels, and insufficient follow-up duration. In contrast, accumulating evidence suggests that vitamin D3 supplementation may improve survival outcomes in patients with established colorectal cancer. These findings support the hypothesis that vitamin D has a greater impact on tumor progression and prognosis than on tumor initiation (Jacobs et al., 2016).

A comprehensive meta-analysis demonstrated a consistent inverse relationship between serum 25(OH)D levels and colorectal cancer incidence. Higher vitamin D status was associated with a significantly lower risk of colorectal cancer (McCullough et al., 2019). Moreover, the risk decreased progressively with increasing 25(OH)D concentrations, suggesting a dose- response relationship.

Beyond its role in disease development, research indicates that vitamin D status also influences outcomes in patients already diagnosed with colorectal cancer. Analyses involving thousands of patients have shown that those with higher circulating 25(OH)D levels tend to have better overall survival and lower risk of cancer-specific death compared with individuals who are vitamin D deficient (Wu et al., 2020). Together, these findings suggest that maintaining adequate vitamin D levels may be beneficial both for reducing the risk of developing colorectal cancer and for improving prognosis in patients with established disease.

Prostate Cancer

In prostate cancer, the relationship between vitamin D status and disease risk is complex and remains controversial. Epidemiological studies have produced inconsistent findings. Some reports suggest no association, or even a positive correlation, between higher circulating 25(OH)D levels and prostate cancer incidence (Xu et al., 2014). In contrast, other studies indicate that vitamin D deficiency may be associated with an increased risk of aggressive disease (Ahn et al., 2008). These

discrepancies may reflect the biological heterogeneity of prostate cancer, differences in study design, variability in screening practices, and the influence of confounding factors. Importantly, emerging evidence suggests that vitamin D may have a greater impact on disease progression rather than initiation. A clinical trial involving men with low-risk prostate cancer managed with active surveillance supports this hypothesis. Daily supplementation with 4,000 IU of vitamin D₃ for one year was associated with a significantly lower rate of disease progression compared with controls (Marshall et al., 2012), supporting the idea that vitamin D may influence tumor biology in early disease stages.

Research by McCray et al. demonstrates that patient-derived prostate epithelial organoids provide a mechanistic basis for these observations. Physiologically relevant concentrations of 1,25(OH)₂D₃ promote epithelial differentiation and growth, largely through inhibition of canonical Wnt signaling and suppression of DKK3. Because aberrant Wnt/β-catenin activity drives stemness, therapy resistance, and progression to castration-resistant prostate cancer, vitamin D may help stabilize epithelial organization and limit pathways associated with aggressive disease. Wnt signaling is highly active in prostate stem and progenitor cells and must decline to permit differentiation. Vitamin D selectively suppresses Wnt activity in lineage-committed cells while sparing stem cell populations, which will promote epithelial maturation and not unlimited proliferation. Furthermore, anti-proliferative and cell cycle-regulating protein - DKK3 was consistently downregulated by 1,25(OH)₂D₃, suggesting a context-dependent regulatory mechanism that facilitates controlled epithelial expansion and differentiation (McCray et al., 2021).

Therefore, the mechanisms described above provide an explanation as to why vitamin D sufficiency is associated with protection against prostate cancer via its ability to promote epithelial differentiation and maintenance of tissue homeostasis while limiting molecular pathways linked to aggressive disease.

Overall, the available evidence indicates that the role of vitamin D₃ in cancer prevention and progression is not uniform across malignancies. The most compelling data support a protective and prognostic role in colorectal cancer, where epidemiological, clinical, and mechanistic findings are highly concordant. In other cancers, such as prostate cancer, the effects of vitamin D appear to be context specific and may be confined to particular disease stages or patient subgroups with vitamin D deficiency. Well-designed randomized controlled trials that incorporate adequate dosing, sufficient follow-up, and selection of vitamin D-deficient populations are needed to clearly define the clinical role of vitamin D₃ in cancer prevention and management.

Conclusion

Available scientific evidence indicates that the role of vitamin D₃ in cancer prevention and progression is complex and depends both on the type of malignancy and the clinical context. Observational studies consistently suggest that low serum concentrations of 25(OH)D are associated with an increased risk of developing various cancers as well as poorer clinical outcomes. However, large randomized controlled trials often fail to confirm these associations, primarily due to the following methodological limitations: insufficient supplementation dosages, enrollment of participants with adequate baseline vitamin D levels, and follow-up periods that were too short to capture long-term effects. Nevertheless, meta-analyses, which involved tens of thousands of participants indicate that vitamin D₃ supplementation may reduce cancer-related mortality, whereas vitamin D₂ does not appear to confer similar benefits.

Overall, despite inconsistent findings from randomized clinical trials, the available epidemiologic, biochemical, and immunological evidence does lend biological plausibility to the hypothesis that vitamin D can decrease cancer risk and affect tumorigenesis, although more evidence is required before making clinical recommendations concerning the use of vitamin D supplementation as part of cancer prevention measures. Vitamin D₃ may exert these effects through multiple pathways,

including modulation of cell proliferation, immune regulation, maintenance of epithelial integrity, and attenuation of inflammation.

The current body of knowledge underscores the need for well-designed clinical trials that employ adequately high doses of vitamin D₃, ensure sufficiently long follow-up, and focus on individuals with low baseline 25(OH)D levels. Further research is necessary to clarify optimal concentrations of vitamin D₃, understand mechanisms associated with specific tumor types, and identify the clinical contexts in which vitamin D₃ may be most effective as part of cancer prevention and therapeutic strategies. Only such rigorously conducted studies will allow for a definitive assessment of the clinical value of vitamin D₃ supplementation in oncology.

REFERENCES

1. Ahn, J.-Y., Peters, U., Albanes, D., Purdue, M. P., Abnet, C. C., Chatterjee, N., Horst, R. L., Hollis, B. W., Wen Yi Huang, Shikany, J. M., & Hayes, R. B. (2008). Serum vitamin D concentration and prostate cancer risk: A nested case-control study. *100*(11), 796–804. <https://doi.org/10.1093/jnci/djn152>
2. Borel, P., Caillaud, D., & Cano, N. J. (2013). Vitamin D bioavailability: State of the art. *Critical Reviews in Food Science and Nutrition*, *55*(9), 1193–1205. <https://doi.org/10.1080/10408398.2012.688897>
3. Carlberg, C., & Muñoz, A. (2022). An update on vitamin D signaling and cancer. *Seminars in Cancer Biology*. <https://doi.org/10.1016/j.semcancer.2020.05.018>
4. Deeb, K. K., Trump, D. L., & Johnson, C. S. (2007). Vitamin D signalling pathways in cancer: Potential for anticancer therapeutics. *Nature Reviews Cancer*, *7*(9), 684–700. <https://doi.org/10.1038/nrc2196>
5. Giammanco, M., Di Majò, D., La Guardia, M., Aiello, S., Crescimannno, M., Flandina, C., Tumminello, F. M., & Leto, G. (2015). Vitamin D in cancer chemoprevention. *Pharmaceutical Biology*, *53*(10), 1399–1434. <https://doi.org/10.3109/13880209.2014.988274>
6. Grant, W. B. (2010). An ecological study of cancer incidence and mortality rates in france with respect to latitude, an index for vitamin D production. *Dermato-Endocrinology*, *2*(2), 62–67. <https://doi.org/10.4161/derm.2.2.13624>
7. Hua, H., Jiang, Q., Sun, P., & Xu, X. (2023). Risk factors for early-onset colorectal cancer: Systematic review and meta-analysis. *Frontiers in Oncology*, *13*. <https://doi.org/10.3389/fonc.2023.1132306>
8. Jacobs, E. T., Kohler, L. N., Kunihiro, A. G., & Jurutka, P. W. (2016). Vitamin D and colorectal, breast, and prostate cancers: A review of the epidemiological evidence. *Journal of Cancer*, *7*(3), 232–240. <https://doi.org/10.7150/jca.13403>
9. Kim, Y., & Je, Y. (2014). Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: A meta-analysis. *British Journal of Cancer*, *110*(11), 2772–2784. <https://doi.org/10.1038/bjc.2014.175>
10. Li, Z., Wu, L., Zhang, J., Huang, X., Thabane, L., & Li, G. (2021). Effect of vitamin D supplementation on risk of breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Frontiers in Nutrition*, *8*. <https://doi.org/10.3389/fnut.2021.655727>
11. Lope, V., Castelló, A., Mena-Bravo, A., Amiano, P., Aragonés, N., Fernández-Villa, T., Guevara, M., Dierssen-Sotos, T., Fernandez-Tardón, G., Castaño-Vinyals, G., Marcos-Gragera, R., Moreno, V., Salas-Trejo, D., Diaz-Santos, M., Oribe, M., Romieu, I., Kogevinas, M., Priego-Capote, F., Pérez-Gómez, B., & Pollán, M. (2018). Serum 25-hydroxyvitamin D and breast cancer risk by pathological subtype (mcc-spain). *The Journal of Steroid Biochemistry and Molecular Biology*, *182*, 4–13. <https://doi.org/10.1016/j.jsbmb.2018.04.005>
12. Marshall, D. T., Savage, S. J., Garrett-Mayer, E., Keane, T. E., Hollis, B. W., Horst, R. L., Ambrose, L. H., Kindy, M. S., & Gattoni-Celli, S. (2012). Vitamin d3supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *The Journal of Clinical Endocrinology & Metabolism*, *97*(7), 2315–2324. <https://doi.org/10.1210/jc.2012-1451>
13. McCray, T., Pacheco, J. V., Loitz, C. C., Garcia, J., Baumann, B., Schlicht, M. J., Valyi-Nagy, K., Abern, M. R., & Nonn, L. (2021). Vitamin D sufficiency enhances differentiation of patient-derived prostate epithelial organoids. *IScience*, *24*(1), 101974. <https://doi.org/10.1016/j.isci.2020.101974>
14. McCullough, M. L., Zoltick, E. S., Weinstein, S. J., Fedirko, V., Wang, M., Cook, N. R., Eliassen, A. H., Zeleniuch-Jacquotte, A., Agnoli, C., Albanes, D., Barnett, M. J., Buring, J. E., Campbell, P. T., Clendenen, T. V., Freedman, N. D., Gapstur, S. M., Giovannucci, E. L., Goodman, G. G., Haiman, C. A., & Ho, G. Y. F. (2019). Circulating vitamin D and colorectal cancer risk: An international pooling project of 17 cohorts. *Journal of the National Cancer Institute*, *111*(2), 158–169. <https://doi.org/10.1093/jnci/djy087>
15. Muñoz, A., & Grant, W. B. (2022). Vitamin D and cancer: An historical overview of the epidemiology and mechanisms. *Nutrients*, *14*(7), 1448. <https://doi.org/10.3390/nu14071448>
16. Veeresh, P. K. M., Basavaraju, C. G., Dallavalasa, S., Anantharaju, P. G., Natraj, S. M., Sukocheva, O. A., & Madhunapantula, S. V. (2023). Vitamin D3 inhibits the viability of breast cancer cells in vitro and ehrlich ascites carcinomas in mice by promoting apoptosis and cell cycle arrest and by impeding tumor angiogenesis. *Cancers*, *15*(19), 4833. <https://doi.org/10.3390/cancers15194833>

17. Vishal Paresh Shah, Tarek Nayfeh, Yahya Alsawaf, Saadi, S., Farah, M., Zhu, Y., Firwana, M., Seisa, M., Wang, Z., Scragg, R., Kiely, M. E., Lips, P., Mitchell, D. M., Demay, M. B., Pittas, A. G., & Mohammad Hassan Murad. (2024). A systematic review supporting the endocrine society clinical practice guidelines on vitamin D. *the Journal of Clinical Endocrinology and Metabolism/Journal of Clinical Endocrinology & Metabolism*. <https://doi.org/10.1210/clinem/dgae312>
18. Wimalawansa, S. J. (2025). Vitamin d's impact on cancer incidence and mortality: A systematic review. *Nutrients*, 17(14), 2333. <https://doi.org/10.3390/nu17142333>
19. Wu, G., Xue, M., Zhao, Y., Han, Y., Zhang, S., Zhang, J., Li, C., & Xu, J. (2020). Low circulating 25-hydroxyvitamin D level is associated with increased colorectal cancer mortality: A systematic review and dose–response meta-analysis. *Bioscience Reports*, 40(7). <https://doi.org/10.1042/bsr20201008>
20. Xu, Y., Shao, X., Yao, Y., Xu, L., Chang, L., Jiang, Z., & Lin, Z. (2014). Positive association between circulating 25-hydroxyvitamin D levels and prostate cancer risk: New findings from an updated meta-analysis. *Journal of Cancer Research and Clinical Oncology*, 140(9), 1465–1477. <https://doi.org/10.1007/s00432-014-1706-3>
21. Yao, S., Kwan, M. L., Ergas, I. J., Roh, J. M., Cheng, T.-Y. D., Hong, C.-C., McCann, S. E., Tang, L., Davis, W., Liu, S., Quesenberry, C. P., Lee, M. M., Ambrosone, C. B., & Kushi, L. H. (2017). Association of serum level of vitamin D at diagnosis with breast cancer survival. *JAMA Oncology*, 3(3), 351. <https://doi.org/10.1001/jamaoncol.2016.4188>
22. Zhang, Y., Fang, F., Tang, J., Jia, L., Feng, Y., Xu, P., & Faramand, A. (2019). Association between vitamin D supplementation and mortality: Systematic review and meta-analysis. *BMJ*, 14673. <https://doi.org/10.1136/bmj.14673>