

Review

Umbrella Review on the Relationship Between Vitamin D Intake and Cancer

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Abstract

Cancer is a major public health problem and the second leading cause of mortality in the European Union. Vitamin D deficiency has been linked to cancer via several pathways. However, umbrella reviews on the extra-skeletal effects of vitamin D have largely overlooked its connection to cancer. This review presents an overview of the relationship between vitamin D intake (nutritional and/or supplementation) and five major types of cancer (breast, colorectal, lung, pancreatic, and prostate cancer). The findings indicate that vitamin D intake may have a preventive effect on breast, colorectal, and lung cancer and may reduce colorectal cancer mortality. However, results for other cancers were inconsistent, and no data were available on the impact of vitamin D intake on pancreatic and lung cancer mortality. While there is some evidence suggesting potential benefits of vitamin D intake, most reviews are based on observational studies, limiting conclusions about causality. Additionally, methodological challenges related to vitamin D metabolism and study designs contribute to the inconclusive nature of the data. Further research is needed to clarify the role of vitamin D intake in cancer prevention and management.

Keywords: Umbrella review, vitamin D, vitamin D intake, vitamin D supplementation, pancreatic cancer, breast cancer, lung cancer, prostate cancer, colorectal carcinoma, review.

Introduction

Cancer is a major public health problem and the second leading cause of mortality in the countries of the European Union, accounting for 22 percent of all deaths in 2021 (1). Data from the “Global Burden of Disease Project” show a

25 percent increase in global cancer mortality from 2007 to 2017, with certain countries (*e.g.*, Denmark or France) experiencing a transition in which cancer became the leading cause of death (1, 2). This shift is largely attributed to the aging populations in Western countries, as age is one of the most important risk factors for cancer. Furthermore,



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advanced age is not only a major risk factor for cancer but is also associated with a higher prevalence of vitamin D deficiency (3, 4). A substantial body of scientific literature has examined the potential beneficial effects of vitamin D in relation to cancer, with the vitamin D-cancer hypothesis first proposed as early as 1980 (5). Since the seminal work of Garland and Garland (5), ecological studies have shown that elevated 25(OH)D levels or augmented UVB radiation (which leads to increased dermal vitamin D synthesis) are inversely related to cancer incidence and mortality. These observations are supported by findings from *in vitro* and *in vivo* studies, which show several mechanisms by which vitamin D regulates cellular functions implicated in cancer development (cell growth, differentiation, adhesion, and apoptosis). Additionally, Vitamin D plays a role in indirect (*i.e.*, effects on the tumor microenvironment and immunomodulation) tumor suppression mechanisms (6-10). Despite these positive aspects, it is important to note the widespread criticism of recent vitamin D supplementation trials, such as the VIDA- or the VITAL-trials [*e.g.*, Lips *et al.* (11), Sluyter *et al.* (12) or Fassio *et al.* (13)]. In the light of this controversy, it is vital to investigate further the influence of vitamin D, and particularly vitamin D intake, on cancer.

Vitamin D is a fat-soluble vitamin that is synthesized in the epidermis through the energy of ultraviolet radiation B (UV-B). Alternatively, it can be obtained *via* diet or supplements. The dermal synthesis is far more important than the pathway *via* nutrition or supplements. However, several large groups are at risk of vitamin D deficiency due to insufficient exposure to UV-B radiation [*e.g.*, elderly (4) or non-white (14) populations in northern countries]. Therefore, this paper focuses on vitamin D intake as a means to elevate vitamin D levels. Calcidiol [25(OH)D], the circulating form of vitamin D, is hydroxylated in the liver from vitamin D₂ (from food/supplements) or vitamin D₃ (from food/supplements or dermal synthesis). The 25(OH)D level is used as an approximation of the vitamin D level. However, the active form of vitamin D is 1,25(OH)D (calcitriol), which is hydroxylated from calcidiol in the kidneys. Additionally 1,25(OH)D is synthesized locally in

tissues that express CYP27B1-hydroxylase (15). 1,25(OH)D exerts its biological effects by binding to the nuclear vitamin D receptor (VDR). The VDR influences target genes involved in intracellular signaling pathways that are mentioned above (7, 8, 10).

Back in 2011, Linseisen *et al.* (16) provided a comprehensive overview on vitamin D and cancer. Their findings were inconclusive, with results ranging from no influence of vitamin D on prostate carcinoma to a possible beneficial effect of vitamin D on colorectal carcinoma. Since then, research on the extra-skeletal effects of vitamin D has grown, but the most recent umbrella reviews on these effects did not focus on cancer (17-19). Therefore, it is necessary to summarize the current evidence on vitamin D and its relationship with cancer, especially regarding vitamin D intake, as oral vitamin D intake is a simple and cost-effective way to elevate deficient 25(OH)D blood levels to recommended levels (20, 21). Achieving these recommendations might help address the increasing number of cancer cases and related deaths.

This umbrella review aimed to provide an update on the association between vitamin D intake and the incidence and mortality of five of the most important cancers in industrialized countries like Germany (breast, prostate, pancreatic, colorectal, and lung cancer) (22, 23). The results of the umbrella review on the association between 25(OH)D levels and the five cancers mentioned above have been reported elsewhere (24).

Materials and Methods

An umbrella review was drafted to provide an overview of the association between vitamin D and the incidence and mortality of cancer. Umbrella reviews are used to summarize the scientific evidence of a given research area; they are considered as high quality of evidence, as they incorporate the results of several systematic reviews (25-27). The study protocol followed the PRISMA checklist (28). This checklist was developed for conducting systematic reviews (SR), therefore some of the items were modified [PRISMA items 12-15, (28)]. The protocol was registered at the International

Prospective Register of Systematic Reviews database (PROSPERO; registration number CRD42021244758; date of registration: 06/21/21). The literature search for the umbrella review was structured using the PICOS framework (29), focusing on populations at risk for the aforementioned cancers or patients with these cancer; interventions involving vitamin D intake (through food or supplements) and the measurement of 25(OH)D levels (24), and outcomes related to cancer incidence or mortality. Eligible study designs included systematic reviews (with or without meta-analyses) that incorporated at least two randomized controlled trials (RCTs) or cohort studies with prospective designs. Additional inclusion criteria were limited to studies involving adult populations, published in English or German, and dated between 2010 and 2020.

Two databases were searched for eligible studies (PubMed in December 2020 and Cochrane Library in February 2021). A complementary hand search of reference lists of the included reviews and of the excluded narrative reviews was also conducted.

The relevant data were extracted from the eligible reviews and transferred into separate tables for each of the five cancers. The key data were: author(s), publication year, study type, investigation period, study population, exposition(s), outcome(s), calculated effect estimates, estimates for heterogeneity, subgroup analyses, included single studies, estimates for publication bias. The results are presented in qualitative form, as the umbrella review did include not only meta-analyses but also reviews with qualitative statements. Therefore, summary risk estimates were not computed.

The evidence of the results was rated with the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence chart from 2009 (30) and the methodological quality of the included reviews was assessed by using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) checklist (31). This instrument can be utilized to evaluate reviews derived from both RCTs and observational studies, therefore it is appropriate for the present review. The AMSTAR 2 checklist uses 16 items ("domains") to rate systematic reviews. Seven domains are

considered "critical" for the methodological quality of a review. The critical domains are domains 2 ("Protocol registered before commencement of the review"), 4 ("Adequacy of the literature search"), 7 ("Justification for excluding individual studies"), 9 ("Risk of bias from individual studies being included in the review"), 11 ("Appropriateness of meta-analytical methods"), 13 ("Consideration of risk of bias when interpreting the results of the review"), and 15 ("Assessment of presence and likely impact of publication bias"). The methodological quality of a review can be rated by counting the weaknesses in the critical and non-critical domains. AMSTAR 2 describes four categories: "High" quality (no or one non-critical weakness), "Moderate" quality (more than one non-critical weakness), "Low" quality (one critical flaw with or without non-critical weaknesses), or "Critically low" quality (more than one critical flaw with or without non-critical weaknesses) (31).

Results

The search retrieved 182 articles from PubMed and three from the Cochrane Library. In addition, the manual search identified 57 articles. After the screening of titles and abstracts, followed by a review of potentially eligible full texts, 21 articles on vitamin D intake were included in the qualitative synthesis (Table I). Twenty additional reviews focused only on the relation between 25(OH)D level and cancer; these were not included in this article but are presented elsewhere (24).

Breast cancer. The results related to breast cancer are presented in Table II. Six SR with meta-analyses (32-37) were included in this section of the umbrella review.

Just one of five reviews that analyzed the association between vitamin D intake and breast cancer incidence shows significant inverse associations when comparing the lowest vs. highest levels of vitamin D intake with an odds ratio (OR) of 0.91 (95% confidence interval (CI)=0.85-0.97) (32). However, no statement on causality can be made, as this review only included observational

Table I. Summary of literature extraction for selected cancer types.

	Breast cancer	Prostate cancer	Pancreatic cancer	Colorectal cancer	Lung cancer
Articles for screening (after duplicates removed)	90	52	18	69	17
Retrieved full texts (after screening)	40	18	5	40	11
Included in qualitative synthesis	14	11	3	15	10
Reports on vitamin D intake	6	4	3	6	2

Table II. Summary of results on the association between vitamin D intake and breast cancer.

Incidence	Mortality
5 reviews included (32-36) (5 with meta-analyses)	1 review included (37) (1 with meta-analyses)
1 meta-analysis (32) shows significant inverse association	Review (37) reports inconsistent results

Table III. Summary of results on the association between vitamin D intake and prostate cancer.

Incidence	Mortality
1 review included (40) (1 with meta-analysis)	3 reviews included (38, 39, 41) (2 with meta-analyses)
Meta-analysis (40) reports no association	Meta-analyses and review report no association

studies. The four other reviews do not show significant associations, but several of them show trends towards inverse associations, with relative risks or odds ratios below 1 and upper limits of the 95%CI close to 1 (33-36).

For breast cancer mortality and survival only the SR with meta-analysis by Kanellopoulou *et al.* was available (37). This meta-analysis provided inconclusive results. A significant risk reduction was calculated for the highest vs. the lowest vitamin D intake and the overall mortality of patients with breast cancer (RR=0.85; 95%CI=0.72-0.99), but not for cancer specific mortality (RR=0.65; 95%CI=0.30-1.42).

Prostate cancer. The results related to prostate cancer are presented in Table III. Four reviews [3 SR with meta-analyses (38-40), and one SR without meta-analysis (41)] were included in this section of the umbrella review. The only meta-analysis that analyzed the association between vitamin D intake and prostate cancer incidence showed no

significant association for an intake of 1,000 IU/d (40). This was consistent across both case-control studies (OR=0.83; 95%CI=0.28-2.43) and prospective, including nested case-control and cohort studies (RR=1.14; 95%CI=0.99-1.31).

Regarding prostate cancer mortality, all three reviews on vitamin D intake (38, 39, 41) provided inconclusive results about prostate cancer specific mortality and the overall mortality of patients with prostate cancer. This is due to the inconsistent results of the three RCTs (42-44), which are included in all three reviews.

Pancreatic cancer. The results for pancreatic cancer are presented in Table IV. Three reviews (all three with meta-analyses) were included in this section of the umbrella review (45-47). All three meta-analyses about the association between vitamin D intake and pancreatic cancer showed no associations (45-47). Only the subgroup analysis of prospective studies by Liu *et al.* (46) showed an inverse dose-response relationship (RR=0.75 per 10 µg/d,

Table IV. Summary of results on the association between Vitamin D intake and pancreatic cancer.

Incidence	Mortality
3 reviews included (45-47) (3 with meta-analyses)	No reviews included
3 meta-analyses (45-47) report no association, 1 subgroup analysis (46) with trend towards protective dose-response relationship	

Table V. Summary of results on the association between vitamin D intake and colorectal cancer.

Incidence	Mortality
5 reviews included (48-52) (5 with meta-analyses)	1 review included (53) (1 with meta-analysis)
3 meta-analyses (49-51) show significant inverse associations, 2 meta-analyses (48, 52) with inconsistent results	Meta-analysis (53) shows significant inverse association

Table VI. Summary of results on the association between vitamin D intake and lung cancer.

Incidence	Mortality
2 reviews included (54, 55) (2 with meta-analyses)	No reviews included
1 meta-analysis (54) shows significant inverse association	

95%CI=0.60-0.93). No reviews about vitamin D intake and pancreatic cancer mortality met the inclusion criteria of this umbrella review.

Colorectal cancer: The results related to colorectal cancer are presented in Table V. Six reviews with meta-analyses were included in this section of the umbrella review (48-53). Three reviews with meta-analyses reported significant inverse associations between vitamin D intake (overall, nutritional, supplementation) and colorectal cancer incidence (49-51). Huang *et al.* (49) and Ma *et al.* (51) showed a possible risk reduction for overall vitamin D intake [RR=0.81; 95%CI=0.74-0.89 (49); RR=0.87; 95%CI=0.77-0.99 (51)]. Huang *et al.* further showed significant inverse associations for nutritional vitamin D intake (RR=0.88; 95%CI=0.81-0.95) and vitamin D supplementation (RR=0.87; 95%CI=0.77-0.99) (49). Liu *et al.* (50) compared the highest and lowest vitamin D supplementation and showed a significant inverse association regarding colorectal

cancer incidence (RR=0.88; 95%CI=0.80-0.96). However, no statement on causality can be made, as the reviews included predominantly observational studies. The other two meta-analyses showed significant associations only in subgroup analyses: Heine-Bröring *et al.* for supplemental vitamin D intake (significant dose-response relation per 100 mg/d) (48) and Touvier *et al.* for overall vitamin D intake (highest vs. lowest) and nutritional vitamin D intake (significant dose-response relation per 100 IU/d) (52).

The only meta-analysis on vitamin D intake and mortality in this section showed a significant association between vitamin D supplementation and colorectal cancer mortality (overall and cancer specific) (53). This meta-analysis included only RCTs, which results in an evidence level of 1a.

Lung cancer: The results related to lung cancer are presented in Table VI. Two reviews with meta-analyses were included in this section of the umbrella review (54,

55). One review including a meta-analysis reported a significant inverse association between nutritional vitamin D intake and lung cancer incidence (RR=0.854; 95%CI=0.741-0.984) (54). Another review did not show a significant association between overall vitamin D intake and lung cancer (55). No reviews regarding vitamin D intake and lung cancer mortality met the inclusion criteria of this umbrella review.

Methodological quality. The rating of the methodological quality of the included reviews revealed shortcomings in critical domains of the AMSTAR 2 tool for most of the included reviews. Only four reviews were rated as “moderate” (45, 47) or “high” quality (39, 53). The majority of the reviews were rated as “low” (41, 46, 48) or even “critically low” (32-38, 40, 49-52, 54, 55).

Discussion

This umbrella review provides an overview on the broad field of research on vitamin D intake and five of the most important cancer types. The results show that vitamin D intake might help prevent breast, colorectal and lung cancer, and reduce colorectal cancer mortality. However, several aspects require further consideration. It is important to point out that this review distinguishes between different types of cancer and does not treat “cancer” as one disease [as performed, for example, by Sluyter *et al.* (56)]. This distinction is important because there are differences in the evidence regarding the various types of cancer. In particular, significant data gaps exist, as no systematic reviews could be found exploring the connection between vitamin D intake and pancreatic and lung cancer mortality. This umbrella review clearly shows knowledge gaps about the influence of vitamin D intake on cancer. Apart from the two sub-sections without data, other sub-sections are supported by a small number of reviews or reviews with a limited number of included studies (or both), *e.g.*, the only review on mortality and colorectal cancer by Vaughan-Shaw *et al.* (53) includes just 5 RCTs with 815 cases in total. Another problem in assessing the association between

vitamin D intake and cancer arises from the fact that the reviews forming the basis of the umbrella review often have varying focuses on vitamin D intake. Some of these reviews examine dietary intake (33, 34, 45, 49, 52, 54), while others assess supplementation (33, 34, 37-39, 41, 48-50, 52, 53), and still others include both aspects and study vitamin D intake in general (32-36, 40, 46, 47, 49, 51, 52, 55). Moreover, most reviews show inconclusive results regarding vitamin D intake and cancer incidence or mortality. Only six reviews show significant inverse associations (32, 49-51, 53, 54). Even in these cases it is not possible to make statements about a causal relationship between vitamin D intake and cancer because most of the studies included in the various reviews are observational studies [the only exception is the review by Vaughan-Shaw *et al.* (53) that includes only RCTs]. Furthermore, meta-analyses of observational studies are criticized by several authors because of the wide range of epidemiological methods, study designs, different adjustment of confounders, *etc.* (57, 58). The reviews included in the study also encounter these issues, thereby complicating the comparison of their results. This in turn affects the validity of the umbrella review as a whole.

Apart from these problems regarding the different study design(s), studies on vitamin D intake face additional challenges based on the vitamin D metabolism. First, due to the parallelism of cutaneous synthesis by UV-B radiation and the intake of vitamin D *via* food or supplements, it is difficult to determine the exact influence of the exogenous vitamin D intake. For this reason, it is not possible to give recommendations for vitamin D intake to reduce the incidence of cancer or to reduce cancer mortality. In order to obtain information on the level of such recommendations, it would be important to design studies with participants less interfered by sun exposure (such as living in areas at a high latitude) as proposed by Zheng *et al.* (59). Second, as 25(OH)D levels are recommend to be in the range between 50 and 75 nmol/l (20-30 ng/ml) (60, 61), it does not seem necessary to increase 25(OH)D levels to or above the upper threshold of this range to achieve additional health gains. However,

this fact is often ignored in vitamin D supplementation studies and subjects without vitamin D deficiency are regularly included in studies on vitamin D intake. This issue is discussed by several authors (11, 13, 59, 62) and it might be a reason for the weak results regarding vitamin D intake and cancer. Third, a further problem arises from supplementation studies that use low doses of vitamin D [*e.g.* Chlebowski *et al.* used 400 IU/d (63)]. This is criticized by some of the included reviews (32, 33). Mohr *et al.* suggest doses of 1,000 IU/day as appropriate, newer studies like Kralova *et al.* show that a dose of 2,000 IU/day seems to be sufficient to raise and stabilize the 25(OH)D serum level in the recommended range above 75 nmol/l (60, 64).

In regard to the use of the AMSTAR 2 tool (31) it has to be stated, that most reviews were rated as “low” or “critically low”. This further reduces the credibility of the included reviews. Finally, the umbrella review might have missed some relevant reviews as the inclusion criteria did not made specifications on nested case control studies, which are case control studies by name but follow a prospective approach (65). This section shows that the topic of vitamin D intake and cancer drives the umbrella review approach to its limit and that various limitations must be taken into account when interpreting the results of this umbrella review.

Conclusion

The prevention of 25(OH)D deficiency is an important component of health (60, 61). For most of the five cancers studied, adequate 25(OH)D levels imply a protective influence on incidence, and even more so on mortality (24). In contrast to the observations on 25(OH)D levels, this article on vitamin D intake shows various gaps in knowledge and methodological shortcomings. Further research is necessary to draw firmer conclusions about the influence of vitamin D intake on cancer. For example, Zheng *et al.* (59) suggest a framework for future vitamin D trials that could be helpful in obtaining more accurate results on the health benefits of vitamin D intake.

Conflicts of Interest

MSF declares no conflicts of interest in relation to this study. TV The Saarland University, together with Prof. Vogt as one of several responsible group leaders, has received a research grant from the Jörg Wolff Foundation, Stuttgart, Germany. JR is member of the Arnold Rikli-Award Jury of the Jörg Wolff Foundation. The Saarland University, together with Prof. Reichrath as one of several responsible group leaders, has received a research grant from the Jörg Wolff Foundation, Stuttgart, Germany.

Authors' Contributions

Matthias Schömann-Finck: Conceptualization, Investigation, Writing – original draft. Thomas Vogt: Supervision, Writing – review & editing. Jörg Reichrath: Conceptualization, Supervision, Investigation, Writing – review & editing.

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