

Vitamin D and Cancer Mortality: Systematic Review of Prospective Epidemiological Studies

Stefan Pilz^{1,2,#,*}, Katharina Kienreich^{2,#}, Andreas Tomaschitz³, Eberhard Ritz⁴, Elisabeth Lerchbaum², Barbara Obermayer-Pietsch², Veronika Matzi⁵, Joerg Lindenmann⁵, Winfried März⁶⁻⁸, Sara Gandini⁹ and Jacqueline M. Dekker¹

¹Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands; ²Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria; ³Department of Internal Medicine, Division of Cardiology, Medical University of Graz, Graz, Austria; ⁴Division of Nephrology, Department of Medicine, University Hospital Heidelberg, Heidelberg, Germany; ⁵Division of Thoracic and Hyperbaric Surgery, Department of Surgery, Medical University of Graz, Austria; ⁶Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; ⁷Synlab Academy, Synlab Services LLC, Mannheim, Germany; ⁸Mannheim Institute of Public Health, Ruperto Carola University Heidelberg, Medical Faculty Mannheim, Mannheim, Germany; ⁹Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy

Abstract: Accumulating evidence from experimental and epidemiological studies suggests that vitamin D deficiency might be a causal risk factor for cancer and therewith associated mortality. We performed a systematic review in Medline up to February 2012 to identify prospective studies on 25-hydroxyvitamin D (25[OH]D) and cancer mortality as well as on 25(OH)D and survival in cancer patients. Our search retrieved 13 studies on cancer-specific mortality and 20 studies on overall mortality in cancer patients. Data on 25(OH)D and cancer mortality were mainly derived from general populations. The results were inconsistent and yielded either no, inverse or positive associations. By contrast, the majority of studies in cancer patients showed that patients with higher 25(OH)D levels had a decreased risk of mortality. This relationship was particularly evident in cohorts of colorectal cancer patients. In contrast, there was no indication for increased mortality risk with higher vitamin D levels in any cancer cohort. In conclusion, the relationship of vitamin D status and cancer-specific mortality is still unclear and warrants further studies. Our results provide a strong rationale to perform prospective randomized controlled studies to document a potential effect of vitamin D supplementation on survival in cancer patients.

Keywords: Vitamin D, Cancer, Death, Mortality, 25(OH)D, Prospective, Calcidiol, Calcitriol, Randomized controlled trial, Epidemiological, RCT, WHI, Colorectal cancer, Outcome, 1,25(OH)2D, Survival, Follow-up.

INTRODUCTION

Vitamin D is classically known as a major regulator of mineral and bone metabolism [1, 2]. Apart from the crucial role of vitamin D for the maintenance of musculoskeletal health, accumulating evidence suggests that vitamin D might also be involved in the pathogenesis of various extra-skeletal diseases including cardiovascular, renal, infectious and autoimmune diseases as well as cancer [1-12]. These issues are of great public health interest because the worldwide prevalence of vitamin D deficiency is extraordinary high [13]. Such low vitamin D levels are mainly the consequence of reduced sunlight exposure with the resulting decrease of ultraviolet-B (UV-B) induced vitamin D synthesis in the skin [14]. Nutrition is usually only a minor source of vitamin D. Obesity contributes to reduced availability of vitamin D because of vitamin D deposition and sequestration in adipose tissue [15]. Hence, vitamin D deficiency can be considered a significant lifestyle problem.

Beneficial effects of vitamin D on musculoskeletal health have been well documented and are supported by most meta-analyses of randomized controlled trials (RCTs) [16-20]. By contrast, an ongoing debate persists with respect to a potential role of vitamin D in extra-skeletal diseases and particularly in cancer [21-27]. Many experimental studies have documented a crucial role of vitamin D for the genesis and progression of cancer [2, 28-33]. Vitamin D

receptor (VDR) expression is observed in almost all human cells and VDR activation exerts a variety of anti-cancer effects including regulation of cell cycle and differentiation [2, 28-33]. Data from epidemiological studies and some RCTs have partially but not consistently supported the notion that vitamin D deficiency is a causal risk factor for incidence and mortality of cancer [3, 12, 21-27]. In this context, the Institute of Medicine (IOM) in the US and the International Agency of Cancer Research (IARC) have systematically reviewed the literature on vitamin D and cancer [23, 24]. In general, they both concluded that there is evidence supporting a role of vitamin D for cancer but the available data are insufficient to recommend vitamin D for the prevention and treatment of cancer [23, 24]. However, since the IOM and IARC reports have been released in 2010 and 2008, several prospective studies have been published on the association of vitamin D status and cancer mortality. These data are crucial for our picture of 25-hydroxyvitamin D (25[OH]D) and cancer in particular because RCTs on this topic are sparse and have not yet evaluated the effect of vitamin D on cancer as a primary endpoint. This prompted us to perform a systematic review to evaluate the association of vitamin D status, assessed by 25(OH)D serum levels on the one hand, and cancer mortality on the other hand. Our aim was to summarize in this text the data of prospective epidemiological studies (i) on the association of 25(OH)D and overall mortality in cancer patients and (ii) on the association of 25(OH)D with cancer-specific mortality.

This review starts with a brief overview of vitamin D metabolism, skeletal vitamin D effects and a historical perspective of vitamin D and cancer research. Then, we describe our systematic literature search and summarize prospective studies on vitamin D and cancer-specific mortality. In addition, we also present data on

*Address correspondence to this author at the Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands; Tel: ++43 650 9103667; Fax: ++43 316 673216; E-mail: stefan.pilz@meduni-graz.at

#Both authors contributed equally as first authors to the manuscript

the association of vitamin D status and total mortality in cancer patients. Finally, we critically discuss our findings.

Vitamin D Metabolism

Vitamin D exists in two main isoforms, i.e. vitamin D₃ and vitamin D₂, but unless stated otherwise we do not differentiate between these two isoforms and refer to vitamin D (meaning both isoforms) in general [1, 34]. Vitamin D can be endogenously obtained by synthesis in the skin, where sunlight (i.e. UV-B) induces the conversion of the liver derived precursor 7-dehydrocholesterol to vitamin D₃. This is the main vitamin D source accounting for ~80% of vitamin D [1, 14]. Because vitamin D production in the epidermis is mainly the result of UV-B radiation, its production is modulated by various factors such as latitude, time of day, season, weather or air pollution as well as by skin parameters such as melanin content [35]. Natural foods contain relatively minor amounts of vitamin D₃ (e.g. in fish) or vitamin D₂ (plant sources such as mushrooms). For this reason we did not include nutritional vitamin D intake in this review. Further vitamin D sources are vitamin D fortified food (e.g. milk in the US) and vitamin D supplements.

Vitamin D itself does not exert significant biological actions. Two hydroxylation steps are required to form the most active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D). In a first step vitamin D is hydroxylated in the liver to 25(OH)D which is the main circulating vitamin D metabolite that is usually measured to assess and categorize vitamin D status. Subsequently, 25(OH)D is further hydroxylated by the 1- α -hydroxylase to 1,25(OH)₂D in the kidney. The 1- α -hydroxylase activity is tightly regulated by parathyroid hormone (PTH) and by the Fibroblast growth factor-23 (FGF-23)/klotho axis. Apart from such main biosynthesis in the kidney, almost all organs express 1- α -hydroxylase as well. [32, 34, 36]. This extra-renal synthesis of 1,25(OH)₂D seems to be significantly dependent on circulating 25(OH)D levels which underlines that 25(OH)D serum levels are a good parameter of whole-body vitamin D status, whereas circulating 1,25(OH)₂D levels mainly reflect synthesis of 1,25(OH)₂D in the kidney [32, 34, 36]. It should also be acknowledged that serum levels of 25(OH)D are up to 1000 fold higher concentrated compared to 1,25(OH)₂D levels. The affinity of 1,25(OH)₂D to the almost ubiquitously expressed VDR is much higher compared to 25(OH)D. VDR activation finally leads to the regulation of hundreds of genes by binding to so called vitamin D responsive elements (VDRE) on the DNA [2]. Degradation of 1,25(OH)₂D and 25(OH)D is initiated by 24-hydroxylation and subsequent metabolism to less active vitamin D metabolites.

There is almost universal agreement that serum levels of 25(OH)D are the best parameter to assess the vitamin D status, but there is no consensus what is an adequate and what is an inadequate vitamin D status [1, 3, 4, 23, 37, 38]. The rationale for vitamin D cut-off levels was initially based on the fact that in states of low 25(OH)D levels, disturbances in calcium and bone metabolism emerge. Whereas many vitamin D experts consider 25(OH)D levels ≥ 75 nmol/L (divide by 2.496 to convert nmol/L to ng/mL) as sufficient others classify 25(OH)D levels of ≥ 50 nmol/L as a sufficient vitamin D status [1, 3, 4, 23, 37, 38]. Hence, the general consensus seems to be that 25(OH)D levels < 50 nmol/L (divide by 2.496 to convert nmol/L to ng/mL) are below the normal range for 25(OH)D. In this context, large epidemiological studies in general populations showed that almost every second to every third individual suffers from 25(OH)D levels below this threshold of 50 nmol/L. This underscores the significance of vitamin D deficiency as a public health problem [1, 13, 39].

Skeletal Vitamin D Effects

Main features of vitamin D deficiency are disturbances in calcium metabolism leading to low calcium levels which in turn

stimulate an increase of PTH levels. Resulting consequences of vitamin D deficiency are disturbances in bone calcification and bone metabolism that can finally lead to rickets in children and osteomalacia in adults. Vitamin D supplementation is therefore generally recommended for the prevention of rickets in children, for the treatment of osteomalacia and also of osteoporosis because vitamin D intake reduces fractures and falls [16-20]. Based on evidence for these beneficial effects of vitamin D on skeletal health, the IOM in the US released dietary reference intakes (DRI) for vitamin D for the general population [23]. In brief, a daily intake of at least 600 International Units (IU) of vitamin D is recommended for individuals aged 1 to 70 years corresponding to a 25(OH)D level of at least 50 nmol/L [23]. These recommendations are the Recommended Dietary Allowances (RDAs) that should cover the requirements of $\geq 97.5\%$ of the population [23].

Historical Perspective of Vitamin D and Cancer Research

Even a century ago, it had been noticed that measures of sunlight exposure, e.g. solar radiation, and skin cancer were inversely associated with overall cancer incidence and cancer mortality [40-43]. A few decades later, Garland and Garland documented an inverse relation between solar radiation and colon cancer in 1980 [44]. This prompted them to propose that vitamin D is protective against cancer [44]. Meanwhile, in various regions of the world, an inverse relation has been documented between UV-B and cancers at several sites [45-48].

After these observations on UV-B and cancer, several experimental studies confirmed anti-proliferative, pro-differentiating and various other anti-cancer effects of vitamin D [49-56]. In particular the group by Cross and Peterlik has nicely characterized the effects and metabolism of vitamin D in colon cancer cells [53-55]. Currently, compelling evidence from numerous experimental *in vitro* and *in vivo* studies suggests that vitamin D inhibits almost all steps in carcinogenesis [for review see 2, 28-33, 36].

Over the last two decades several studies on VDR polymorphisms have largely but not consistently supported a role of vitamin D genetics for cancer [47, 57, 58]. Observational studies have further supported a link of vitamin D status and cancer with particular convincing data for colorectal cancer as evidenced by the consistent finding of meta-analyses [59-63]. Meta-analyses of observational studies do not clearly support associations of vitamin D with other cancer sites although there exist some promising findings that need to be further evaluated before drawing final conclusions [63-68].

Data on vitamin D therapy and cancer are sparse compared to experimental and observational studies on vitamin D and cancer. Vitamin D therapy can be either done with active vitamin D (i.e. 1,25(OH)₂D or its analogues), which has a relatively narrow therapeutic window before causing hypercalcemia, or with natural vitamin D, which is used to correct low 25(OH)D levels [69-71]. Only few small studies evaluated the effect of active vitamin D treatment either alone or in combination with cytotoxic agents [69-71]. In general, active vitamin D treatment was well tolerated [69-71]. Anti-tumor responses were documented in some but not all studies so that available evidence on anti-cancer effects of active vitamin D is not conclusive so far [69-71]. While there is no study available that evaluated the effect of vitamin D supplementation on cancer incidence or mortality as a primary endpoint, cancer incidence and cancer mortality was reported as a secondary outcome in some randomized control trials [72-77]. In 2006, data of the Women's Health Initiative (WHI) study, a RCT among 36,282 postmenopausal women receiving either 1,000 mg calcium plus 400 IU vitamin D per day or placebo and followed up for 7 years were published [72]. There was no significant effect on incident colorectal cancer but there was a moderate non-significant trend towards reduced cancer deaths that was also observed in other studies [72, 76, 77]. As acknowledged by the WHI investigators, their

data are limited by the low dose of vitamin D, by poor compliance and by concomitant vitamin D intake. Regarding the latter point it is interesting to note that a re-analysis of the WHI trial excluding women who were taking personal calcium or vitamin D supplements at randomization, showed that risk of total, breast, and colorectal cancers decreased in the intervention group [73]. Admittedly, re-analysis of specific subgroups must be interpreted with caution and therefore the WHI trial fails to provide the definite answer. Of interest is also the study by Lappe *et al.*, who performed a RCT among 1179 community-dwelling postmenopausal women [75]. Fifty incident cancer cases were recorded during a 4 year follow-up period. Compared to the placebo group the risk of incident cancer was significantly reduced by 60% in women receiving 1,100 IU vitamin D plus 1,400-1,500 mg calcium per day [75]. Although these results were promising the current opinion by most health authorities is that there is still insufficient evidence from RCT to conclude that vitamin D has any relevant effect against cancer.

In addition to RCTs, an additional valuable approach to look for a potential role of vitamin D on clinical cancer outcomes are well-designed prospective observational studies to assess a potential relation of serum 25(OH)D concentrations and cancer mortality. Until recently, such data were extremely rare, but some large studies [12] had suggested that low 25(OH)D concentrations are an independent risk factor for cancer mortality. Because in the past 2 - 3 years several additional publications have appeared in this field a systematic evaluation to put conclusions on 25(OH)D and cancer mortality on a more solid footing is warranted. This was the rationale for our present work.

SYSTEMATIC LITERATURE SEARCH

We performed a systematic literature search in PubMed for articles in English language published until 16th February 2012. We used the following search terms: “vitamin D” and “cancer” and “mortality”. In addition, we used the search terms “25-hydroxyvitamin D”, “25(OH)D” or “calcidiol” instead of “vitamin D” and the search terms “death” or “survival” instead of “mortality”. We searched for these keywords in the headers and the abstract and expanded the search by using listed references from selected manuscripts. This literature search was independently carried out by two academic researchers and group discussion resolved any disagreement with article selection.

Our literature search retrieved 1,206 articles and full-text reading was performed in 45 of these articles. Of these selected manuscripts, 33 presented data on prospective studies on 25(OH)D levels and cancer-specific mortality (n=13) or on 25(OH)D levels

and mortality in cancer patients (n=20) [78-110]. Studies on cancer-specific mortality among cancer patients were classified as studies on 25(OH)D levels and mortality in cancer patients.

VITAMIN D AND CANCER MORTALITY

Among the 13 prospective studies assessing a potential relation between 25(OH)D and cancer mortality, 11 were performed in the general population, one study was performed in patients referred for coronary angiography and another one in hemodialysis patients [78-90]. In the Health Professionals Follow-up Study (HPFS), 25(OH)D was not actually measured in all study participants but was estimated based on predictors of vitamin D status which were derived from a linear regression analysis that was performed in a subsample (n=1095) of study participants with measured 25(OH)D levels. The predicted 25(OH)D levels for the HPFS are considered a reliable estimate of 25(OH)D levels and we thus included the results of that study [78, 91, 92, 104]. Five reports were derived from the same study population i.e. the Third National Health and Nutrition Examination Survey (NHANES-III) [79-83]. Of these 5 publications the Freedman *et al.*, study in 2010 included the longest follow-up time with the highest number of fatal cancer events [81]. Main results of that latter NHANES-III publication and the remaining 8 study reports are presented in Table 1. In summary, of that 9 studies, 4 did not report on a significant association of 25(OH)D and cancer mortality [81, 84, 85, 90], whereas 3 reported on a significantly increased risk of fatal cancer at low 25(OH)D levels [78, 88, 89]. By contrast, one study reported on significantly decreased cancer mortality in men with 25(OH)D levels below 50 nmol/L [86] and one study observed evidence for a U-shaped association with increased cancer mortality risk at both low and high 25(OH)D concentrations [87]. Hence, prospective studies on vitamin D status and cancer mortality are inconsistent and do therefore not clearly support a role of vitamin D for cancer mortality.

Cancer site-specific mortality was reported in the two largest study cohorts: the HPFS among male health professionals aged 40-75 years and NHANES-III, a population representative study in the US [78-80, 83]. Although it is not a main focus of this review to outline cancer site-specific events it should be noted that digestive cancer mortality was significantly reduced with higher 25(OH)D levels in the HPFS [78]. In detail, the multivariate adjusted hazard ratio per 25 nmol/L increment in 25(OH)D levels was 0.54 (95% CI: 0.39-0.75) [78]. In line with this, NHANES-III data also support an inverse relationship of 25(OH)D levels and colorectal cancer mortality [79, 81, 83]. Whereas there were no meaningful associations of 25(OH)D and other cancer site mortality in the entire NHANES-III cohort, there was a significant increase of lung

Table 1. Prospective Studies on the Association of 25(OH)D with Total Cancer Mortality

First Author	Ref.	Country	Age, yrs	Males (%)	No. of Subjects	Follow-up, yrs	No. of Events	Main Analysis (25[OH]D in nmol/L)	Adjusted Relative Risk* (95% CI)
Giovannucci	[78]	USA	54	100	47,800	14	2,025	increment of 25	0.71 (0.59-0.84)
Freedman	[81]	USA	44	47	16,819	13.4	884	≥100 vs <37.5	1.15 (0.79-1.68)
Eaton	[84]	USA	66	0	2,429	10	62	≤36.5 vs ≥65.39	1.39 (0.88-2.19)
Hutchinson	[85]†	Norway	59	38 41	4,751 2,410	11.8 11.4	273 225	first versus fourth quartile	1.14 (0.80-1.63) 0.82 (0.56-1.21)
Cawthon	[86]	USA	74	100	1,490	7.3	97	<50 vs ≥ 75	0.51 (0.27-0.98)
Michaëlsson	[87]	Sweden	71	100	1,194	12.7	164	<46 vs 46-93 >93 vs 46-93	1.99 (1.29-3.08) 1.56 (0.95-2.56)
Pilz	[88]	Germany	63	70	3,257	7.75	95	>57.5 vs <25.5	0.45 (0.22-0.93)
Krause	[89]	Germany	71	59	6,518	9	289	<31.2 vs ≥75	1.51 (1.09-2.08)
Semba	[90]	Italy	74	75	1,006	6.5	52	<26.2 vs <63.9	not significant‡

*Adjusted risk from the model including the highest number of covariates

†Separate reports for non-smokers (upper line) and smokers (lower line)

‡No relative risks reported

cancer with high 25(OH)D levels in a subgroup analysis of male study participants [81].

VITAMIN D AND MORTALITY IN CANCER PATIENTS

Twenty studies were found that reported on associations of 25(OH)D and total mortality in patients suffering from certain cancer sites [91-110]. Two reports presented data of colorectal

cancer patients, pooling the data of the Nurses Health Study (NHS) and the HPFS [91, 92]. Of these two manuscripts, the publication by Ng *et al.*, in 2009 included significantly more cases and was thus included in Table 2 along with the remaining 18 other publications (see Table 2). In multivariate adjusted analyses, the vast majority of these studies showed either a significant result or a non-significant trend suggesting an association of low 25(OH)D and increased total

Table 2. Prospective Studies on the Association of 25(OH)D and Total Mortality in Cancer Patients

First Author	Ref.	Country	Age, yrs	Males (%)	No. of Subjects	Follow-up, yrs	No. of Events	Main Analysis (25(OH)D in nmol/L)	Adjusted Relative Risk* (95% CI)
Colorectal cancer patients									
Ng	[91]	USA	66	40	1,017	10	283	>74.1 vs <62.2	0.62 (0.42-0.93)
Fedirko	[93]	Europe	62	47	1,202	6	541	>76.8 vs <36.3	0.67 (0.50-0.88)
Tretli	[110]	Norway	59	62	52	NA	36	>81 vs <46	0.40 (0.10-1.60)
Ng	[94]	USA	61	59	515	5	475	>67.6 vs <32.7	0.94 (0.72-1.23)
Mezawa	[95]	Japan	65	64	257	3	39	per 2.5 nmol/L	0.91 (0.84-0.99)
Gastric cancer									
Ren	[96]	China	60	68	197	5	106	≥50 vs <50	0.59 (0.37-0.91)
Breast cancer									
Vrieling	[97]	Germany	63	0	1,295	6	183	<35 vs ≥55	1.55 (1.00-2.39)
Tretli	[110]	Norway	54	0	251	NA	98	>81 vs <46	0.37 (0.21-0.67)
Jacobs	[98]	USA	52	0	500	7	250	<50 vs ≥50	1.13 (0.72-1.79)
Goodwin	[99]	Canada	50	0	512	12	106	<50 vs >72	1.60 (0.96-2.64)
Lung cancer									
Zhou	[100]	USA	69	50	447	6	234	≥53.9 vs <25.5	0.74 (0.50-1.10)
Tretli	[110]	Norway	59	63	210	NA	190	>81 vs <46	0.19 (0.12-0.30)
Heist	[101]	USA	62	48	294	3.5	233	≥69.1 vs 31.5<	1.08 (0.75-1.57)
Melanoma									
Newton-Bishop	[102]	UK	NA	NA	872	5	141	per 20 nmol/L	0.83 (0.68-1.02)
Prostate Cancer									
Tretli	[103]	Norway	65	100	160	4	61	>80 vs <50	0.24 (0.11-0.53)
Fang	[104]	USA	62	100	1,822	10	595	1 st vs 4 th quartile	1.10 (0.87-1.39)
Lymphoma and leukemia									
Drake	[105] [†]	USA	62	55	370 70 71 285 109 78	3	100 29 19 19 8 18	<62.5 vs ≥62.5	1.99 (1.27-3.13) 2.38 (1.04-5.41) 1.35 (0.53-3.39) 1.52 (0.60-3.88) 2.76 (0.58-13.1) 2.08 (0.79-5.49)
Shanafelt	[106] [‡]	USA	63 67 NA	69 71 NA	390 153 543	3 10 NA	34 62 96	<62.5 vs ≥62.5	2.39 (1.21-4.70) 1.63 (0.99-2.69) 1.47 (0.97-2.23)
Tretli	[110]	Norway	56	64	145	NA	75	>81 vs <46	0.33 (0.16-0.69)
Pardanani	[107] [#]	USA	63 72	68 69	247 74	3 2	129 42	<62.5 vs ≥62.5	1.2 (0.8-1.6) 1.4 (0.7-2.7)
Upper aerodigestive tract cancer									
Gugatschka	[108]	Austria	63	89	88	1	29	Not indicated	0.89 (0.83-0.97)
Head and neck cancer									
Meyer	[109]	Canada	63	79	522	8	223	>78 vs <48	0.85 (0.57-1.28)

*Adjusted risk from the model including the highest number of covariates

[†]Separate subgroups for diffuse large B-cell lymphoma (upper line), T-cell lymphoma, mantle cell lymphoma, follicular lymphoma, post-follicular lymphoma and other lymphomas (lowest line)

[‡]Two different cohorts presented in the upper and middle line; pooled analyses of both in the lowest line

[#]Separate subgroups for primary myelofibrosis (upper line) and myelodysplastic syndrome (lower line)

NA, data not available

mortality. Of note, while a few studies reported no meaningful relationship of vitamin D status and mortality, not a single one provided evidence for harmful effects of high 25(OH)D concentrations and its impact on survival.

Cancer site-specific mortality (e.g. mortality from colorectal cancer in patients suffering from colorectal cancer) was documented in some of these publications [91, 95, 103, 105, 109, 110]. Considering that most deaths were attributable to cancer site-specific mortality, these findings were similar when compared to the total mortality results and are thus not further outlined in this review.

DISCUSSION

In this systematic review we identified 13 publications on 25(OH)D and total cancer mortality. In general, the results were inconsistent with most studies reporting on either no or an inverse association of 25(OH)D and cancer mortality. One study, however, documented a positive relationship and another one showed a U shaped association of 25(OH)D and cancer mortality. In 20 studies on 25(OH)D and mortality in cancer patients, findings were not entirely consistent, but at least the majority reported that low 25(OH)D concentrations were an independent risk factor for total mortality. Although some studies showed no significant association, remarkably no reported increased mortality in cancer patients with higher 25(OH)D levels.

Vitamin D and Cancer Mortality

Due to the above mentioned inconsistent results we cannot draw a final conclusion on the relationship between 25(OH)D and total cancer mortality. It is clear that differences in study populations and study designs might have contributed to these above mentioned inconsistent results. It is not really obvious that there exists consistent and significant effect modification by general study parameters such as age, sex, region or length of follow-up. We are well aware that in NHANES-III, some subgroup analyses suggest that higher 25(OH)D levels tend to be rather beneficial in women and rather harmful in men but this indication for a possible gender difference was not supported by the majority of the remaining study cohorts [79-83]. Interestingly, the only two studies that were performed among specific patient groups (i.e. patients referred for coronary angiography and hemodialysis patients) showed a consistent and inverse association of 25(OH)D and cancer mortality [88, 89]. Access to sunlight may be limited in such patients thus comprising vitamin D status. It could be hypothesized that the findings in patient cohorts might have been significantly driven by the very low 25(OH)D levels in these populations or due to the fact that underlying disease status might be a significant confounder for the association of 25(OH)D and cancer mortality. This may well be true but it should also be acknowledged that multivariate adjustments were performed for several possible confounders and that some studies in general populations had similar low 25(OH)D levels when compared to the two above mentioned patient cohorts. Laboratory methods for 25(OH)D may also be considered in particular because some recent assay comparisons revealed a relatively poor comparability [111, 112]. In this context, it should be noted that only two studies used mass spectrometry, the considered gold standard for 25(OH)D measurements [86, 87]. Interestingly, one of these two studies showed an inverse and the other one a U-shaped association of 25(OH)D and cancer mortality [86, 87]. Thus in contrast to several studies based on immuno-assay technique the results based on mass spectrometry were considerably less in support of a beneficial role of 25(OH)D on cancer mortality [78-90]. Another point that is worth mentioning is the possible impact of competing risks in epidemiological studies. This deals with the problem that vitamin D deficiency is, in general, a risk factor for overall mortality as evidenced by meta-analyses in general populations as well as in

patients suffering from chronic kidney diseases [113, 114]. A situation of competing risk must be taken into consideration as a result of the fact that in epidemiological studies patients dying from non-cancer causes are usually considered as controls. This might impact on the association of 25(OH)D and cancer mortality when one assumes that those patients with non-cancer deaths are also prone to low 25(OH)D levels and probably also to cancer that might, however, be unrecognized due to their premature non-cancer mortality. This should therefore be considered in observational studies on 25(OH)D and cancer mortality. Although the studies on vitamin D status and cancer mortality reviewed by us adjusted for various possible confounders including e.g. obesity, disease status or physical activity we cannot exclude residual confounding. One option to avoid significant confounding is the Mendelian Randomization approach, i.e. to evaluate whether the recently described 25(OH)D determining polymorphisms are related to cancer mortality [115]. Future Mendelian Randomization studies may therefore help to address the link between vitamin D and cancer. Definite conclusions with regard to causality can only be drawn, however, from RCTs on vitamin D supplementation. It is beyond the scope of this present work to review in detail previous vitamin D RCTs that reported on cancer incidence and mortality but we wish to acknowledge that no previous RCT was designed or sufficiently powered to address this issue. None of these previous RCTs found a significant effect of vitamin D supplementation on cancer mortality although it should be noted that some study results documented a modest non-significant trend towards total cancer mortality reduction in individuals receiving vitamin D [72-74, 76, 77]. Whereas one study reported on a significant reduction in cancer incidence among postmenopausal women, other RCTs failed to confirm such an association [73, 75, 116]. It should be noted, however, that a significant vitamin D effect on cancer incidence had been reported in a sub-group analysis of the WHI Study in individuals who had not been on vitamin D or calcium supplements at baseline [73].

In this discussion on a potential association of 25(OH)D and cancer mortality it should also be considered that sunlight exposure with subsequent UV-B induced vitamin D synthesis in the skin is the main source of vitamin D. Given that previous publications on sunlight or UV exposure and cancer were a stimulating rationale for studies on 25(OH)D it should be stressed that ecologic studies have, by the majority, supported an inverse association of UV-B exposure and cancer mortality as well as cancer incidence [40-48]. In this context, it should be pointed out that beyond vitamin D synthesis sunlight exposure exerts various other physiologic effects (e.g. immunomodulatory actions) [117]. Hence, when assuming a causal relationship, it might be speculated that the association of UV-B and cancer might be partially driven by effects that are unrelated to vitamin D. On the other hand, it should also be considered that the impact of nutrition on vitamin D status might underlie observed differences between ecologic studies on UV-B exposure and studies on 25(OH)D levels. Simultaneous assessments of sunlight exposure and 25(OH)D levels in randomized trials including treatment arms with either vitamin D or UV-B exposure are therefore warranted. This would offer the opportunity to assess both common pathways as well as differences of potential anticancer effects of UV-B (sunlight) exposure and vitamin D supplementation.

Vitamin D and Mortality Among Cancer Patients

Data among cancer patients have mainly but not consistently confirmed that patients with higher 25(OH)D levels are at decreased risk of mortality. Importantly, none of these studies showed an increased risk of mortality at high 25(OH)D. These data in cancer patients are of particular importance when considering that there are no RCTs available that were adequately designed to assess effects of vitamin D supplementation on mortality in such patients.

Among specific cancer sites most studies were available for colorectal cancer patients. These studies almost consistently indicated higher mortality risk in patients with low 25(OH)D levels. These results are in good agreement with several experimental studies that demonstrated anti-cancer effects of vitamin D on colorectal cancer sites; they are also in line with previous publications and meta-analyses showing that both higher vitamin D intake as well as higher 25(OH)D levels are associated with decreased colorectal cancer risk [59-63]. Whereas there are no sufficient data available on vitamin D RCTs and specific cancer sites, a re-analysis of the WHI Study suggests that vitamin D supplementation may decrease colorectal cancer risk in a subgroup of patients not previously supplemented with vitamin D or calcium [73]. Hence, overall data on colorectal cancer strongly suggest a causal role of vitamin D deficiency for the development, progression and outcome of colorectal cancer.

Three out of four studies on breast cancer patients showed either a significant result or at least a strong non-significant trend for mortality reduction with higher vitamin D levels. Studies on breast cancer incidence point to a decreased risk with higher 25(OH)D levels but meta-analyses on this topic could not consistently support this notion [63-65]. Although we should be cautious with interpreting subgroup analyses of RCTs it should be mentioned that in the WHI study breast cancer incidence was significantly decreased by vitamin D supplementation in women without additional calcium or vitamin D intake at baseline [73]. On a molecular level it has been shown that deregulation of VDR and 1-alpha-hydroxylase participates in the development of breast cancer [118]. Hence accumulating findings argue for a beneficial role of vitamin D for breast cancer pointing to the urgent need for further studies to clarify whether these associations are of causal nature.

Our data further indicate that in three out of four studies among patients with lymphoma and/or leukemia survival was significantly reduced in patients with lower 25(OH)D levels. Potential effects of vitamin D on immune cells are greatly supported by various experimental studies and are therefore a good rationale to hypothesize that vitamin D metabolism may play a role in hematological disorders [10, 11].

Regarding lung cancer and prostate cancer patients there was one study for each cancer site that indicates a significantly decreased risk of mortality with higher 25(OH)D levels but other studies in these patients did not clearly support this association. The current literature is still insufficient to draw final conclusions regarding vitamin D, prostate and lung cancer [63, 66, 67, 119]. Meta-analyses on 25(OH)D and prostate cancer incidence argue against a significant effect of vitamin D status on prostate cancer risk [63, 66, 67]. In this context we want to underline that observational studies and a small trial of vitamin D supplementation in obese men suggest that vitamin D might increase testosterone levels [120-122]. This might be relevant for prostate cancer patients, who are frequently on antiandrogen therapy [120-122].

With respect to patients suffering from other cancer sites there was one study on upper aerodigestive tract cancer and one on gastric cancer that both showed improved survival in patients with higher 25(OH)D levels [96, 108]. A study in patients with head and neck cancer indicated no significant association of vitamin D status and fatal events [109]. In contrast, a study in melanoma patients showed a strong non-significant trend for mortality reduction with higher 25(OH)D levels [102]. These latter data are well in line with other studies on melanoma suggesting that vitamin D exerts tumor suppressive effects on this cancer site and prevent UV induced carcinogenesis [123, 124].

Most studies on expression of VDR and 24-hydroxylase, the enzyme that initiates degradation of vitamin D metabolites, have shown that both low VDR expression as well as high

24-hydroxylase expression in cancer cells are associated with reduced survival [125-130]. Prospective studies in cancer patients have largely but not consistently shown that VDR polymorphisms and polymorphisms for vitamin D metabolizing enzymes are related to prognosis including survival of these patients [93, 102, 131-139]. Hence, the majority of these above mentioned studies support the notion that disturbed vitamin D metabolism may be associated with poor outcome in cancer patients [93, 102, 125-139].

Our results of increased mortality risk in vitamin D deficient cancer patients should also be viewed in light of observations that vitamin D deficiency is particularly prevalent in cancer patients with chemotherapy, further increasing the risk of low 25(OH)D levels [140, 141]. Furthermore, compared to healthy controls, vitamin D supplementation seems to be less effective in raising vitamin D status of cancer patients [141, 142].

The finding that low 25(OH)D levels predict mortality in cancer patients is also well in line with observations in several other cohorts including general populations, patients with chronic kidney diseases, liver diseases or nursing home residents [113, 114, 143-148]. While we do not have sufficient evidence that this relationship is of causal nature in cancer patients, a recent meta-analysis of RCTs mainly performed among frail elderly patients found that vitamin D supplementation significantly decreases all-cause mortality [149]. We therefore wish to point to the urgent need for further RCTs to evaluate the impact of vitamin D supplementation on survival in cancer patients. In this context, it should also be mentioned that some large RCTs in general populations are already ongoing to address the question whether there is an effect of vitamin D on various health outcomes including cancer [150]. The largest study in this field is the VITAL Study (VITamin D and Omega-3 Trial) among 20,000 older study participants but it will take several years from now (between ~2015 to 2017) until one can expect the publication of the results of these trials [150].

CONCLUSIONS

In this systematic review we found inconsistent results on the association of vitamin D status and cancer mortality. Further data are therefore needed before drawing final conclusions on this topic. Nevertheless, most studies in cancer patients documented that patients with higher 25(OH)D levels are at decreased risk of mortality. Such data support a role of vitamin D for survival of cancer patients and are a good rationale for RCTs to evaluate the effect of vitamin D supplementation on mortality in these patients.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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ABBREVIATIONS

25(OH)D	=	25-hydroxyvitamin D
UV-B	=	Ultraviolet-B
RCTs	=	Randomized controlled trials
VDR	=	Vitamin D receptor
IOM	=	Institute of Medicine
IARC	=	International Agency of Cancer Research
1,25(OH) ₂ D	=	1,25-dihydroxyvitamin D
PTH	=	Parathyroid hormone
FGF-23	=	Fibroblast growth factor-23
VDRE	=	Vitamin D responsive elements

DRI	=	Dietary reference intakes
RDAs	=	Recommended Dietary Allowances
WHI	=	Women's Health Initiative
HPFS	=	Health Professionals Follow-up Study
NHANES-III	=	Third National Health and Nutrition Examination Survey
NHS	=	Nurses Health Study

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