

Prognostic Role of Vitamin D Status and Efficacy of Vitamin D Supplementation in Cancer Patients: A Systematic Review

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ABSTRACT

Background. Whether or not hypovitaminosis D can influence the prognosis of cancer patients and whether or not vitamin D (vitD) supplementation improves outcome remain controversial.

Design. Studies evaluating the prognostic role of vitD and vitD receptor (VDR) in cancer patients and trials evaluating the efficacy of vitD administration on patient outcome were identified by a search of MEDLINE, EMBASE, ISI Web of Knowledge, and the Cochrane Library through June 2010.

Results. Twenty-five studies were included. A negative prognostic role for low serum vitD level was observed in five cohort studies including patients with breast cancer (one study), colon cancer (two studies), prostate cancer (one study), and melanoma (one study), but not in two studies on non-small cell lung cancer and one study on breast cancer. Three of four studies showed that VDR⁺ tu-

mors carry a better prognosis than VDR⁻ tumors, whereas VDR polymorphisms were significantly associated with prognosis in five of 10 studies. A significant interaction between serum vitD level and VDR polymorphism was observed in one study. Three randomized trials involving advanced prostate cancer patients explored the prognostic role of vitD supplementation. A meta-analysis of these trials showed no effect on survival (pooled risk ratio, 1.07; 95% confidence interval, CI, 0.93–1.23), with strong heterogeneity among studies.

Conclusion. Hypovitaminosis D seems to be associated with a worse prognosis in some cancers, but vitD supplementation failed to demonstrate a benefit in prostate cancer patients. The currently available evidence is insufficient to recommend vitD supplementation in cancer patients in clinical practice. *The Oncologist* 2011;16:1215–1227

INTRODUCTION

Vitamin D (vitD) has an important role in regulating body levels of calcium and bone mineralization. The hormonal

activity of vitD is mediated by its binding with vitD receptor (VDR) within the cell nuclei [1]. Because VDR is expressed in all body tissues, vitD also has extraskeletal

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effects. The degree of expression of VDR and its genetic variants may be important factors influencing the activity of serum vitD [2]. Hypovitaminosis D is associated with muscle weakness and a greater risk for type I diabetes, multiple sclerosis, rheumatoid arthritis, cardiovascular disease, and infectious diseases [3]. In cancer, vitD decreases cellular proliferation of cancer cells *in vitro* and induces their terminal differentiation. More than 50 genes have been shown to be involved, including those encoding the cell cycle regulators p21, p27, c-fos, and c-myc [4].

Blood levels of 25-hydroxyvitamin D (25(OH)D), but not calcitriol, correlate with vitD health benefits [3]. There is no consensus on optimal levels of 25(OH)D in serum. Many authors define vitD deficiency as a 25(OH)D level <10 ng/mL, insufficiency as a level of 10–35 ng/mL, and sufficiency as a level of 35–80 ng/mL; vitD toxicity is defined as a 25(OH)D level >80 ng/mL [5]. Other experts define vitD deficiency as a 25(OH)D level <20 ng/mL [3]. The currently available evidence supports the hypothesis that hypovitaminosis D could potentially negatively influence outcome in cancer patients [6].

In this paper, we systematically reviewed observational studies on cancer patients in which the predictive role of vitD or the VDR status was analyzed in relation to major clinical outcomes, as well as randomized controlled trials (RCTs) in which vitD was administered to improve prognosis. Our key questions concern whether or not hypovitaminosis D is associated with a poor prognosis and whether or not vitD repletion improves the prognosis of cancer patients.

METHODS

Prospective studies evaluating the prognostic role of baseline vitD and VDR status in cancer patients and randomized trials evaluating the efficacy of vitD administration in patient outcome were searched. The primary outcome of interest was overall survival (OS); secondary outcomes were time to progression (i.e., the time elapsing between the diagnosis of metastatic disease and disease progression or death, whichever occurred first), disease-free survival (DFS) (i.e., the time elapsing from radical operation to any event, irrespective of cause), recurrence-free survival (RFS) (i.e., the time elapsing from radical operation to any event, except for any second primary cancer).

The following databases were queried using a combination of search terms: MEDLINE, EMBASE, ISI Web of Knowledge, and The Cochrane Library through June 2010. Searches were limited to English language studies including humans. The search terms included combinations of: “Vitamin D” [MeSH], “Receptor, Calcitriol”

[MeSH], “Neoplasms” [MeSH], “Disease-Free Survival” [MeSH], “Recurrence” [MeSH], “Survival Rate” [MeSH], “Mortality” [MeSH], “Survival analysis” [MeSH], “Prognosis” [MeSH], cholecalciferol, ergocalciferol, dihydrotachysterol, hydroxyvitamin D, calcitriol, calcidiol, calcifediol. Figure 1 illustrates the search strategy used for MEDLINE. This strategy was slightly modified for use with EMBASE, The Cochrane Library, and the other databases.

Titles and abstracts of all identified records were scanned for relevancy, and original publications were retrieved when appropriate. Additionally, the reference list of each identified article was manually reviewed to identify other works of interest. Finally, the websites of the American Society of Clinical Oncology (<http://www.asco.org>) and the San Antonio Breast Cancer Symposium (<http://www.sabcs.org>) were visited to search for abstracts and congress proceedings, and the National Cancer Institute clinical trial registry (<http://www.clinicaltrials.gov>) was visited to search for ongoing clinical trials on vitD supplementation. Articles reporting directly or indirectly on the prognostic role of vitD status or VDR in cancer patients were included if they reported data from RCTs, cohort studies, or case-control studies. Articles reporting on the effect of vitD supplementation on patient survival were included if they reported data from RCTs. All selected papers were retrieved as full text.

Each study was analyzed to extract a set of relevant data using a standardized form. The extracted data were: type of study, type of tumor, number of patients, number of events, length of follow-up, and relationship between vitD status and cancer prognosis. The risk for bias in individual observational studies was assessed according to the Newcastle–Ottawa scale [7]; RCTs were assessed using the Cochrane Collaboration tool [8]. Data extraction and critical appraisal of included studies were done by two reviewers; disagreements were resolved by discussion within the group of authors.

We did not perform a meta-analysis of the observational studies because of excessive heterogeneity in study design, cancer type, vitD categories, and statistical measures available from individual studies.

The results of the RCTs evaluating the efficacy of vitD administration on OS were combined in a meta-analysis using the risk ratio (RR) as a measure of effect and a fixed-effects model, with weights calculated with the Mantel–Haenszel method. Heterogeneity was evaluated with the χ^2 approach. As a sensitivity analysis, a random-effects meta-analysis was also performed. STATA, version 9.2 (StataCorp., College Station, TX) was used for all calculations.

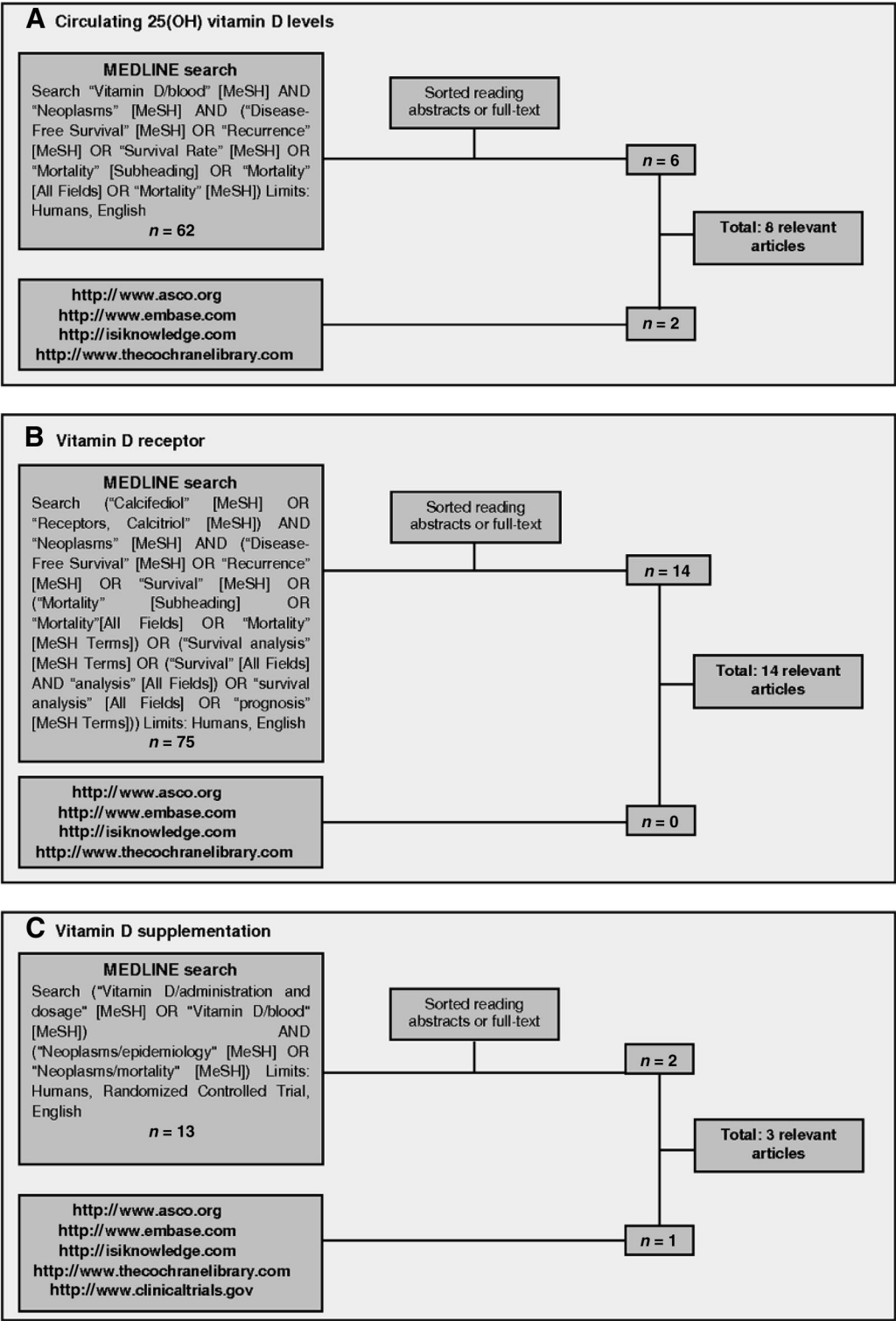


Figure 1. Study selection.
Abbreviation: MeSH, medical subject heading.

Because of the small number of studies and the high level of heterogeneity, no formal assessment of publication bias was performed.

RESULTS
Our search identified 132 independent references, which were sorted using abstracts or full-text publications (Fig. 1). In total,

25 relevant studies were identified and retrieved for analysis. The studies were divided into three groups: (a) circulating 25(OH)D levels (eight studies), (b) VDR expression (14 studies), and (c) vitD supplementation during cancer treatment (three studies). Two studies were included in both group (a) and (b).

Circulating 25(OH)D Levels

Eight studies related serum vitD level with cancer prognosis (Table 1).

In a cohort study [9] including patients with stage IA–IIB non-small cell lung cancer (NSCLC), circulating 25(OH)D levels assessed at diagnosis did not correlate with RFS, whereas patients with serum vitD levels in the highest two quartiles had a lower risk for death (adjusted hazard ratio [AHR], 0.80 and 0.74) than patients in the first quartile, which barely missed attaining statistical significance (p for trend = .07). However, when the patients were stratified by disease stage, a significant association was observed for stage IB–IIB patients (AHR, 0.45; 95% confidence interval [CI], 0.24–0.82; highest versus lowest quartile; p for trend = .002) but not for stage IA patients (HR, 1.10; 95% CI, 0.62–1.96; p = .53) (interaction test p = .046).

In a later paper involving patients with advanced NSCLC [10], no difference in survival by circulating vitD level was observed. Taken together these data suggest that serum vitD is not prognostic in patients with NSCLC and the statistical significance attained in a patient subset only cannot be generalized.

Conversely, a significant association between serum vitD and prognosis was observed in two studies involving colon cancer patients. In the 304 participants of the Nurses' Health Study and the Health Professionals Follow-Up Study diagnosed with colorectal cancer [11], patients in the highest quartile of serum 25(OH)D level had an AHR for overall mortality of 0.52 (95% CI, 0.29–0.94), compared with those in the lowest quartile. More recently, Wesa et al. [12] evaluated the prognostic role of serum vitD measured at diagnosis in 250 colon cancer patients. On univariate analysis, serum vitD was significantly associated with better survival (p = .036). Patients with vitD deficiency had a survival outcome approximately 1.5× worse than those with normal levels.

As far as breast cancer patients are concerned, published data led to controversial results. A prospective cohort study [13] evaluated the association between hypovitaminosis D at diagnosis and the risk for distant recurrence and death in 512 patients with early breast cancer. The DFS interval was worse in women with deficient vitD status than in those with adequate vitD status (AHR, 1.71; 95% CI, 1.02–2.86), as was the OS time, with the latter just failing to attain sta-

tistical significance. According to quintile distribution, a progressive stepwise decrease in the HR for death was observed from the first to the fourth quintile, compared with the reference fifth quintile, considering either DFS or OS. Interestingly, the authors also fitted a model with vitD entered as a continuous linear term. The functional form of vitD in the Cox model was explored using a smoothing spline with three degrees of freedom, and the resulting log hazard for vitD was depicted graphically. The results provided some evidence that maximum benefit in terms of survival occurred with vitD levels in the range of 32–44 ng/mL. Above this range, a further increase in serum vitD seemed to be associated with a trend for a higher risk for death, although this was not statistically significant.

In contrast, another study [14] found no association between serum VitD and RFS among 607 postmenopausal patients with nonmetastatic breast cancer enrolled in the phase III National Cancer Institute of Canada Clinical Trials Group MA.14 trial of adjuvant tamoxifen (20 mg/day orally for 5 years) with or without octreotide (90 mg/month depot injection for 2 years). Continuous vitD was not associated with the RFS interval for any relapse (p = .57), for bone only relapse (p = .19), or for bone plus another site of relapse (p = .73).

The effect of vitD on outcome was also explored in two studies involving prostate cancer and melanoma patients. In the prostate cancer study involving 160 patients [15], a high serum vitD level was significantly related to a better prognosis (AHR, 0.16; 95% CI, 0.05–0.43), compared with a low serum vitD level.

The melanoma cohort study [16], enrolling 872 patients, showed that higher vitD levels were inversely associated with relapse and death. The AHRs across seasons were 0.79 (95% CI, 0.64–0.96) and 0.83 (95% CI, 0.68–1.02), respectively, per 8 ng/mL increase in serum vitD level. The inverse association with higher serum vitD level, stratified by season, persisted through the range of levels detected based on tertile analysis.

VDR EXPRESSION AND RELEVANT POLYMORPHISMS

The activity of vitD is influenced by its receptor expression and relevant genetic variants. VDR polymorphisms comprise a cluster of tightly linked polymorphisms at the 30-end (*Apal*, *BsmI*, *TaqI*, and a length polymorphism of a polyadenyl microsatellite in the 30-untranslated region) and the 50-end of the gene (*FokI* and *Cdx-2*) [17, 18].

VDR polymorphisms reflect an individual's susceptibility to vitD function. Fourteen papers evaluated the relationship with prognosis of either VDR or VDR polymorphism in cancer patients (Table 2). VDR expression was assessed

Table 1. Studies on the prognostic role of circulating vitamin D levels

Study	Cancer type and <i>n</i> of patients	Time of vitamin D assessment and assay used	Follow-up duration	<i>n</i> of events	Categorization	DFS/EFS	OS/CSS	Adjustments	Quality assessment (Newcastle–Ottawa scale) ^a (<i>n</i> of stars)
Zhou et al. (2007) [9]	Early-stage NSCLC (IA–IIIB), <i>n</i> = 447	At initial diagnosis, RIA	Median, 72 mos; range, 0.2–141 mos	161 recurrences, 234 cancer deaths	Quartiles: 1st, <10.2 ng/mL (<25.5 nM/L); 2nd, 10.2–15.7 ng/mL (25.5–39.25 nM/L); 3rd, 15.8–21.5 ng/mL (39.5–53.75 nM/L); 4th, ≥21.6 ng/mL (≥54 nM/L)	AHR: 1st, reference; 2nd, 1.21 (95% CI, 0.86–0.71); 3rd, 0.90 (95% CI, 0.62–1.29); 4th, 0.92 (95% CI, 0.64–1.33)	OS AHR: 1st, reference; 2nd, 1.07 (95% CI, 0.74–1.53); 3rd, 0.80 (95% CI, 0.55–1.18); 4th, 0.74 (95% CI, 0.50–1.10)	Age, sex, stage, smoking habit, chemotherapy, radiation therapy, and surgery season	Selection, 4; comparability, 2; outcome, 3
Heist et al. (2008) [10]	Locally advanced/metastatic NSCLC, <i>n</i> = 294	Within 2 mos of initial diagnosis, RIA	Median, 42 mos; range, 2–146 mos	233 deaths	Quartiles: 1st, <12.6 ng/mL (<31.5 nM/L); 2nd, 12.6–20.2 ng/mL (31.5–50.5 nM/L); 3rd, 20.3–27.6 ng/mL (50.75–69 nM/L); 4th, ≥27.7 ng/mL (≥69.25 nM/L)		OS AHR: 1st, reference; 2nd, 1.09 (95% CI, 0.75–1.57); 3rd, 1.03 (95% CI, 0.71–1.50); 4th, 1.08 (95% CI, 0.75–1.57)	Sex, stage, performance status	Selection, 4; comparability, 2; outcome, 3
Ng et al. (2008) [11]	All stages colorectal cancer, <i>n</i> = 304	Median, 72 mos before cancer diagnosis; range, 25–128 mos, RIA	Median, 78 mos; range, 36–162 mos	123 overall deaths, 96 cancer-specific deaths	Quartiles (mean): 1st, 16.5 ng/mL (41.25 nM/L); 2nd, 23.6 ng/mL (59 nM/L); 3rd, 28.9 ng/mL (72.25 nM/L); 4th, 40.0 ng/mL (100 nM/L)		OS AHR: 1st, reference; 2nd, 0.81 (95% CI, 0.49–1.35); 3rd, 0.81 (95% CI, 0.47–1.37); 4th, 0.52 (95% CI, 0.29–0.94)	Age, season, sex, stage, tumor grade, location of primary tumor, year of diagnosis, BMI, physical activity	Selection, 3; comparability, 2; outcome, 2
Wesa et al. (2010) [12]	Colorectal cancer (stage IV), <i>n</i> = 250	± 30 days after diagnosis		153 deaths	Deficient, <30 ng/mL (<75 nM/L); normal ≥30 ng/mL (≥75 nM/L)		Patients with vitamin D deficiency (<30 ng/mL) had survival outcomes 1.5 times worse than those with normal levels	Nonadjusted	Not assessed
Goodwin et al. (2009) [13]	Early breast cancer (T1–3, N0–1, M0), <i>n</i> = 512	Mean ± SD, 58.1 ± 23.4 days after diagnosis, RIA (DiaSorin, Stillwater MN)	Median, 11.6 yrs	116 distant recurrences, 106 deaths	Deficient, <50 nM/L (<20 ng/mL); insufficient, 50–72 nM/L (20–28.8 ng/mL); sufficient >72 nM/L (>28.8 ng/mL) Quintiles: 1st, 8–38 nM/L (3.2–15.2 ng/mL); 2nd, 39–50 nM/L (15.6–20 ng/mL); 3rd, 51–61 nM/L (20.4–24.4 ng/mL); 4th, 62–76 nM/L (24.8–30.4 ng/mL); 5th, 77–177 nM/L (30.8–70.8 ng/mL)	AHR: deficient, 1.71 (95% CI, 1.02–2.86); insufficient 1.25 (95% CI, 0.73–2.14) Sufficient, reference; 1st, 1.84 (95% CI, 1.18–2.88); 2nd, 1.54 (95% CI, 1.13–2.11); 3rd, 1.35 (95% CI, 1.04–1.67); 4th, 1.19 (95% CI, 1.05–1.35); 5th, reference	OS AHR: deficient, 1.60 (95% CI, 0.96–2.64); insufficient, 0.98 (95% CI, 0.567–1.69) Sufficient, reference; 1st, 1.73 (95% CI, 1.09–2.74); 2nd, 1.47 (95% CI, 1.07–2.04); 3rd, 1.30 (95% CI, 1.04–1.63); 4th, 1.17 (95% CI, 1.03–1.33); 5th, reference	Age, tumor stage, nodal stage, estrogen receptor, grade	Selection, 4; comparability, 2; outcome, 2
Piura et al. (2009) [14]	Early-stage breast cancer, <i>n</i> = 607	At initial diagnosis	Median, 7.9 yrs		Serum vitamin D level considered a continuous variable	EFS for any relapse, <i>p</i> = .57; EFS for bone only relapse, <i>p</i> = .19; EFS for bone plus another site of relapse, <i>p</i> = .73; EFS for all bone relapse types, <i>p</i> = .66		Adjuvant chemotherapy, axillary lymph node status, hormone receptor status, season, age, BMI	Not assessed

(continued)

Table 1. (Continued)

Study	Cancer type and n of patients	Time of vitamin D assessment and assay used	Follow-up duration	n of events	Categorization	DFS/EFS	OS/CSS	Adjustments	Quality assessment (Newcastle-Ottawa scale) ^a (n of stars)
Tretli et al. (2009) [15]	Prostate cancer, n = 160	123 patients at baseline, 37 patients after hormone therapy, RIA (DiaSorin, Stillwater MN)	Median, 44 mos; range, 1.2–154.6 mos	61 overall deaths, 52 cancer-specific deaths	Low, <50 nM/L (<20 ng/mL); moderate, 50–80 nM/L (20–32 ng/mL); high, >80 nM/L (>32 ng/mL)	AHR, 0.79 (95% CI, 0.64–0.96) for each 20-nM/L (8 ng/mL) increase in serum level	OS AHR, low, reference; moderate, 0.33 (95% CI, 0.14–0.77); high, 0.16 (95% CI, 0.05–0.43)	Tumor grade and patient functional status	Selection, 4; comparability, 2; outcome, 2
Newton-Bishop et al. (2009) [16]	Melanoma (stages I–IIIA), n = 872	3–6 mos after diagnosis, liquid chromatography tandem mass spectrometry	Median, 4.7 yrs	173 relapses, 141 deaths		AHR, 0.79 (95% CI, 0.64–0.96) for each 20-nM/L (8 ng/mL) increase in serum level	OS AHR, 0.83 (95% CI, 0.68–1.02) for each 20-nM/L increase in serum level	Age, sex, Townsend score, tumor site, Breslow thickness, BMI, season	Selection, 4; comparability, 2; outcome, 2

^aThe number of stars attributed to each domain is a measure of study validity. For cohort studies, the maximum number of stars is: 4 for selection, 2 for comparability, 3 for outcome. For case control studies, the maximum number of stars is: 4 for selection, 2 for comparability, 3 for exposure [7]. Abbreviations: AHR, adjusted hazard ratio; BMI, body mass index; CSS, cancer-specific survival; DFS, disease-free survival; EFS, event-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; RIA, radioimmunoassay.

in tumor samples in all studies. *VDR* polymorphisms were assessed in blood in four studies and in tumor tissues in six studies.

VDR expression or retinoid X receptor was associated with longer survival on multivariate analysis in three studies involving patients with colorectal cancer, cholangiocarcinoma, and renal cancer, respectively [19–21]. In contrast, in one study including patients with superficial urothelial carcinoma [22], *VDR* expression was predictive of a poor prognosis on univariate analysis.

In regard to *VDR* polymorphisms, a significant association with prognosis was found in five of 10 studies. In two studies involving prostate cancer patients who underwent radical prostatectomy, either the *FokI* polymorphism [23] or the *BsmI* and *TaqI* polymorphisms [24] failed to be predictive of prostate-specific antigen (PSA) failure. Two studies involved patients with malignant melanoma. In one of them [25], *A-1012G* (*A* allele) (*AA* genotype), but not the *FokI* and *TaqI* polymorphisms, was associated with a greater risk for metastasis than the *GG/AG* genotype (HR, 2.9; 95% CI, 1.1–7.5). In the second study [16], there was no clear effect of several *VDR* polymorphisms on outcome, apart from weak evidence that inheritance of the *BsmI A* allele was adversely associated with RFS (HR, 1.44; 95% CI, 1.02–2.03). However, stratifying patients according to vitD status, inheritance of the *BsmI A*, *Apal A*, and *TaqI C* alleles was associated with a higher risk for relapse from melanoma in patients with low vitD levels, but not in those with normal/elevated vitD levels (interaction test, $p = .02$).

The *Apal*, but not *BsmI* and *TaqI*, polymorphism was significantly associated with cancer-related death (HR for *AA* versus *Aa+aa*, 3.3; 95% CI, 1.01–10.6) in renal cancer patients [26]. In breast cancer patients, neither the *TaqI* [27] nor *BsmI* [28] polymorphism showed prognostic significance.

In the two studies involving NSCLC patients, there was no association between *Cdx-2*, *FokI*, or *BsmI VDR* polymorphism and RFS or survival in one of them, involving patients with early-stage disease [29], whereas in the second study [17], the *FokI* genotype *T* was associated with a poor prognosis. The HR for death was 1.32 (95% CI, 0.98–1.77) for *C/T* and 1.41 (95% CI, 0.96–2.07) for *T/T* (p for trend = .04), compared with the *C/C* reference group in patients with advanced or metastatic NSCLC. However, *Cdx-2* and *BsmI* polymorphisms were not prognostic.

In one study involving ovarian cancer patients, the *FokI C/C* genotype was associated with a better prognosis than with the *C/T* and *T/T* genotypes (HR, 0.18; 95% CI, 0.05–0.61) [30].

Table 2. Studies on the prognostic role of VDR expression and VDR polymorphism

Study	VDR expression and VDR polymorphism	Cancer type and <i>n</i> of patients	Follow-up	DFS	OS	Adjustment	Quality assessment (Newcastle-Ottawa scale)* (<i>n</i> of stars); cohort/case-control study
VDR expression							
Evans et al. (1998) [19]	VDR expression (tissue), % not reported, Rnase protection assay	Colorectal cancer, <i>n</i> = 75	Median, 23 mos		Survival benefit for ratio of VDR expression in tumor versus normal tissue: HR, 0.22; 95% CI, 0.06–0.90; <i>p</i> = .04	Dukes' stage, age at operation, sex, tumor differentiation	Selection, 4; comparability, 2; outcome, 2; cohort study
Seubwai et al. (2007) [20]	VDR expression (tissue), 74% of tumor samples, IHC	Cholangiocarcinoma, <i>n</i> = 111			Survival of patients with VDR ⁺ tumor better than in those with VDR [−] tumor: HR, 0.50; 95% CI, 0.27–0.93	Age, postoperative chemotherapy, sex, tumor differentiation, tumor type, disease stage, metastasis	Selection, 3; comparability, 1; outcome, 1; cohort study
Obara et al. (2007) [21]	VDR expression (tissue), 29.4% of tumor samples, IHC	Renal cell carcinoma, <i>n</i> = 68	Mean, 68.2 mos		Retinoid X receptor γ expression (but not VDR expression) significantly associated with lower risk for death: HR, 0.35; 95% CI, 0.13–0.98	T status, lymph node status, M status	Selection, 3; comparability, 2; outcome, 3; cohort study
Sahin et al. (2005) [22]	VDR expression (tissue), 85.7% of tumor samples, IHC	Superficial transitional cell carcinoma of the bladder, <i>n</i> = 105 patients, <i>n</i> = 30 controls	Median, 40 mos	Patients with high (++++) VDR expression had significantly shorter DFS interval than those with lower or no expression (<i>p</i> = .02)	No effect of VDR expression on OS (<i>p</i> = .39)		Selection, 2; comparability, 1; exposure, 1; case-control study
VDR polymorphisms							
Xu et al. (2003) [23]	<i>FokI</i> (F allele) (tissue), PCR	Prostate cancer after radical prostatectomy, <i>n</i> = 191	Median, 54.7 mos	No correlation between <i>FokI</i> polymorphism and PSA failure: HR, 1.03; 95% CI, 0.58–1.85		Age, Gleason score, cancer volume, serum PSA	Selection, 3; comparability, 2; outcome, 3; cohort study
Williams et al. (2004) [24]	<i>BsmI</i> (B allele) and <i>TaqI</i> (T allele) (tissue), PCR	Prostate cancer after radical prostatectomy; white men, <i>n</i> = 428; African-American men, <i>n</i> = 310	5–10 yrs	Nonsignificant effect of <i>BsmI</i> and <i>TaqI</i> polymorphism for PSA progression in both populations: opposite effect of <i>bb</i> versus <i>BB</i> genotype in white men with organ-confined (HR, 4.59; 95% CI, 0.39–53.69) versus locally advanced (HR, 0.50; 95% CI, 0.24–1.03) disease (interaction test <i>p</i> = .03)		Age, Gleason score, pathological stage, serum PSA	Selection, 4; comparability, 2; outcome, 2; cohort study
Halsall et al. (2004) [25]	<i>A-1012G</i> (A allele), <i>FokI</i> (F allele), and <i>TaqI</i> (T allele) (tissue), PCR	Melanoma, <i>n</i> = 191	Mean, 75 mos	<i>A-1012G</i> (A allele) associated with greater risk of metastasis than <i>GG/AG</i> genotype (HR = 2.9, 95% CI, 1.1–7.5); no effect of <i>FokI</i> or <i>TaqI</i> genotypes on prognosis; <i>A-1012G-FokI</i> combination (<i>AA/ff</i>) enhanced effect of <i>A-1012G</i> polymorphism on risk for metastasis (HR, 8.6; 95% CI, 2.5–29.6)		Adjustment for covariates (age at onset, male gender, skin type, eye and hair color, lesion site) had no significant impact on results (data not shown)	Selection, 4; comparability, 2; exposure, 2; case-control study
Newton-Bishop et al. (2009) [16]	<i>Cdx-2</i> , <i>GATA</i> , <i>FokI</i> , <i>BsmI</i> , <i>ApaI</i> , <i>TaqI</i> (blood)	Melanoma, <i>n</i> = 872	Median, 4.7 yrs	In overall population, no significant effect of VDR genotype on DFS, except for weak association between <i>BsmI</i> A allele and shorter RFS (HR, 1.44; 95% CI, 1.02–2.03), when sample divided by vitamin D status, <i>BsmI</i> A, <i>ApaI</i> A, and <i>TaqI</i> C alleles associated with poorer outcome in patients with low vitamin D levels but not in those with high vitamin D levels (interaction tests, <i>p</i> = .02)		Age, sex, site, Breslow thickness	Selection, 4; comparability, 2; outcome, 2; cohort study

(continued)

Table 2. (Continued)

Study	VDR expression and VDR polymorphism	Cancer type and n of patients	Follow-up	DFS	OS	Adjustment	Quality assessment (Newcastle-Ottawa scale)* (n of stars); cohort/case-control study
Obara et al. (2007) [26]	<i>BsmI</i> , <i>ApaI</i> , and <i>TaqI</i> (blood), PCR-RFLP	Renal carcinoma, n = 135 patients; n = 150 controls	1991–2000		No prognostic effect of <i>BsmI</i> or <i>TaqI</i> polymorphism; independent prognostic role for cause-specific survival of AA genotype in <i>ApaI</i> polymorphism, versus <i>Aa + aa</i> genotype (HR, 3.3; 95% CI, 1.01–10.6; p = .038)	T stage (T1–2 versus T3–4), lymph node status (≤1 versus no positive lymph nodes), tumor grade (1–2 versus 3), histological subtype (clear cell versus others)	Selection, 2; comparability, 1; exposure, 2; case-control study
Lundin et al. (1999) [27]	<i>TaqI</i> (T allele) (tissue), PCR-RFLP	Breast cancer, n = 111	Median, 67 mos		No relationship between <i>TaqI</i> polymorphism and mortality (HR, 1.1 for <i>TT</i> versus <i>tt + Tt</i> ; 95% CI, 0.65–1.7)		Selection, 2; comparability, 1; exposure, 2; case-control study
Zhou et al. (2006) [29]	<i>Cdx-2</i> , <i>FokI</i> , <i>BsmI</i> (blood), ABI Prism 1900 HT Sequence Detection System	Early-stage NSCLC, n = 373; adenocarcinoma, n = 180; SCC, n = 108; others, n = 85	Median, 71 mos	No association between VDR polymorphisms and DFS in overall population. Among SCC patients, G/A + A/A genotype group of <i>Cdx-2</i> polymorphism associated with better DFS (HR = 0.57, 95% CI, 0.34–0.94)		Age, gender, smoking status, surgery season	Selection, 4; comparability, 2; outcome, 3; cohort study
Heist et al. (2008) [10]	<i>Cdx-2</i> , <i>FokI</i> , <i>BsmI</i> (blood), ABI Prism 1900 HT Sequence Detection System	Advanced NSCLC, n = 294	42 mo. (median)		<i>FokI</i> genotype associated with prognosis (HR, 1.41 for CC versus TT; 95% CI, 0.96–2.07; p = .04); in haplotype analysis, <i>G-T-C</i> (<i>Cdx-2-FokI-BsmI</i>) haplotype associated with worse survival than for <i>G-C-T</i> genotype (HR, 1.61; 95% CI, 1.21–2.14; p = .001)	Sex, stage, performance status	Selection, 4; comparability, 2; outcome, 3; cohort study
Yagmurdu et al. (2009) [28]	<i>BsmI</i> (tumor tissue), PCR-RFLP	Invasive ductal breast carcinoma (T1–2N0M0), n = 56	NA	5-yr DFS rate, 97% in <i>B/b</i> group and 86% in <i>B/B</i> group (p > .05)			Selection, 4; comparability, 0; outcome, 1; cohort study
Tamez et al. (2009) [30]	<i>FokI</i> (tissue), ABI PRISM 3700 Genetic Analyzer	Epithelial ovarian cancer, n = 101	Median, 85 mos		<i>FokI C/C</i> genotype associated with better prognosis (AHR, 0.18 for <i>C/C</i> versus <i>C/T + T/T</i> ; 95% CI, 0.05–0.61; p = 0.006)	Postoperative stage, postoperative chemotherapy, histology, residual tumor	Selection, 3; comparability, 1; outcome, 2; cohort study

^aThe number of stars attributed to each domain is a measure of study validity. For cohort studies, the maximum number of stars is: 4 for selection, 2 for comparability, 3 for outcome. For case control studies, the maximum number of stars is: 4 for selection, 2 for comparability, 3 for exposure [7]. Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; NA, not available; NSCLC, non-small cell lung cancer; OS, overall survival; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PSA, prostate-specific antigen; SCC, squamous cell carcinoma; vitD, vitamin D; VDR, vitamin D receptor.

Table 3. Efficacy of vitamin D supplementation: Randomized clinical trials

Study	Cancer type and <i>n</i> of patients	Study arms	Follow-up duration (median)	<i>n</i> of events	Overall survival (OS), cancer specific survival (CSS)	Other outcomes	Risk for bias (for OS) [8]
Beer et al. (2007) [32]	Progressive metastatic androgen-independent prostate cancer, <i>n</i> = 250	Weekly docetaxel, 36 mg/m ² i.v., for 3 wks of a 4-wk cycle combined with either 45 µg DN-101 or placebo taken orally 1 day before docetaxel	18.32 mos	Deaths: 122 in total (not specified by arm)	DN-101 versus placebo: AHR, 0.67; 95% CI, 0.45–0.97; <i>p</i> = .07	PSA response: 52% of placebo-treated patients and 49% of DN-101-treated patients (<i>p</i> = 0.07). Skeletal morbidity-free survival: HR, 0.78; 95% CI, 0.57–1.074; <i>p</i> = .13	Adequate sequence generation, unclear; allocation concealment, unclear; blinding, yes; incomplete outcome data addressed, yes; free of selective reporting, yes; free of other bias, yes
Scher et al. (2010) [33]	Progressive metastatic androgen-independent prostate cancer, <i>n</i> = 953	ASCENT DN-101 arm: DN-101, 45 µg; docetaxel, 36 mg/m ² ; dexamethasone, 24 mg/wk for 3 of every 4 wks. Control arm: prednisone, 5 mg twice a day; docetaxel, 75 mg/m ² ; dexamethasone, 24 mg every 3 wks	11.7 mos	Deaths: 138 of 476 in placebo arm; 174 of 477 in DN-101 arm	Median OS, 16.8 mos in DN-101 arm, 19.9 mos in control arm; DN-101 vs placebo arm AHR, 1.33; <i>p</i> = .019	Not reported	Adequate sequence generation, unclear; allocation concealment, unclear; blinding, no, but low risk for bias; incomplete outcome data addressed, yes; free of selective reporting, yes; free of other bias, no, because (a) trial stopped early because of the results of an interim analysis, (b) docetaxel administered with different schedules in experimental and control arm, and (c) preliminary results available only in abstract
Attia et al. (2008) [31]	Progressive metastatic androgen-independent prostate cancer, <i>n</i> = 70	Weekly docetaxel, 35 mg/m ² i.v. for 3 wks of a 4-wk cycle, combined with either doxercalciferol or placebo (10 µg orally, days 1–28)	17.6 mos	Deaths: 25 of 33 in placebo arm; 31 of 37 in DN-101 arm	Median OS, 17.8 mos in doxercalciferol arm, 16.4 mos in control arm (<i>p</i> = .383)	PSA response, 39.4% of placebo-treated patients and 46.7% of doxercalciferol-treated patients (<i>p</i> = .560); median progression-free survival time of 6.20 mos in placebo-treated patients and 6.17 mos in doxercalciferol-treated patients (<i>p</i> = .764)	Adequate sequence generation, unclear; allocation concealment, unclear; blinding, yes; incomplete outcome data addressed, yes; free of selective reporting, yes; free of other bias, no, trial stopped early (53% of total sample size) because of the results of an interim analysis and a change in sponsor's interest

Abbreviations: AHR, adjusted hazard ratio; ASCENT, Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen.

VitD Supplementation

The impact of vitD supplementation on cancer mortality was evaluated in three randomized trials involving advanced prostate cancer patients (Table 3).

A randomized, placebo-controlled, double-blinded phase II study [31] explored whether or not the activity of docetaxel in terms of PSA response was enhanced with the concomitant administration of doxercalciferol (1α-dihydroxyvitamin D₂, Hectorol®; Genzyme Corp., Cambridge, MA), an inactive prohormone that undergoes hepatic conversion to its active metabolites 1,25-dihydroxyvitamin D₂ and 1,24-dihydroxyvitamin D₂. Seventy castration-resistant, chemotherapy-naïve prostate cancer patients were randomized to treatment. The median follow-up was 17.6 months. The response rate was 46.7% (95% CI, 30%–64%) in the doxercalciferol arm and 39.4% (95% CI, 25%–56%) in the placebo arm (*p* = .560). The median progression-free survival interval in the doxercalciferol arm was 6.17 months (95% CI, 4.20–10.7 months) versus 6.20 months (95% CI, 4.83–9.07 months) in the placebo arm (*p* = .764). The median OS time in the doxercalciferol arm was 17.8 months (95% CI, 14.9–23.6 months) versus 16.4 months (95% CI, 11.9–23.8 months) in the placebo arm (*p* = .383).

In a double-blinded, randomized phase II study (Andro-

gen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere [ASCENT] trial) [32], the antineoplastic activity of the combination of DN-101, a high-dose oral formulation of calcitriol, and docetaxel was tested against docetaxel alone in 250 patients with advanced castration-resistant prostate cancer. The administration of DN-101 failed to be associated with a significantly higher PSA response rate—58% for DN-101 patients and 49% for placebo patients (*p* = 0.16)—or a significantly longer skeletal morbidity-free survival duration (HR, 0.78; 95% CI, 0.57–1.074; *p* = .13). Despite this, patients in the DN-101 group had a longer survival time than their counterparts not treated with DN-101 (HR, 0.67; 95% CI, 0.45–0.97; *p* = .04) on multivariate analysis.

Following on these encouraging results, an open-label, phase III trial with the same design was subsequently planned to enroll 900 patients with advanced castration-resistant prostate cancer (ASCENT-II trial). However, that trial was prematurely interrupted after an interim analysis showed an unexpectedly greater mortality rate in the DN-101 arm [33]. At the last available analysis, with a median follow-up of 11.7 months, 174 of 477 men in the calcitriol arm had died (36.5%), compared with 138 of the 476 docetaxel-treated patients (29%).

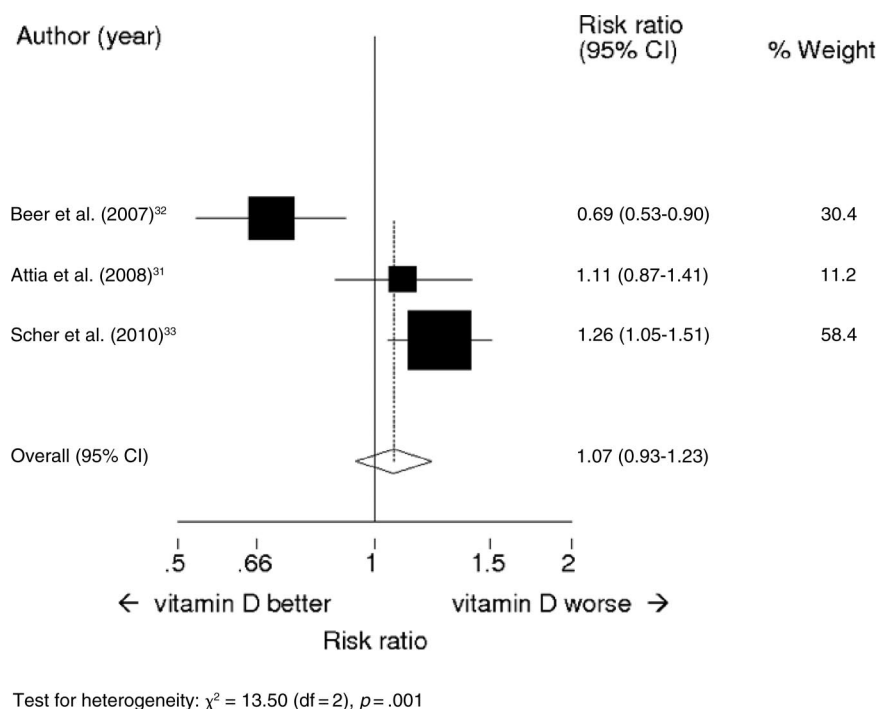


Figure 2. Meta-analysis of three randomized trials evaluating the effect of vitamin D supplementation on overall survival in advanced prostate cancer patients. Risk ratios estimated with a fixed-effects model.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval.

A meta-analysis of these three randomized trials, based on the number of deaths reported or extrapolated from the original papers, confirms a strong heterogeneity among studies (p for heterogeneity test = .001), without any pooled effect of vitD supplementation on survival, both with a fixed-effects model (RR, 1.07; 95% CI, 0.93–1.23) and with a random-effects model (RR, 1.00; 95% CI, 0.71–1.40) (Fig. 2).

DISCUSSION

Questions as to whether or not the prognosis of cancer patients is influenced by hypovitaminosis D status and whether or not vitD supplementation can improve outcomes are attracting increasing interest from clinical investigators.

The published data on circulating vitD levels are generally very sparse and of rather low quality, with eight studies involving patients with different diagnoses or disease stages. Of these studies, five showed a significant negative prognostic role for low serum vitD level, whereas three did not. As a whole, serum vitD level had a prognostic role in two different studies for colon cancer patients; data on breast cancer were conflicting, with one study showing a positive result and one study showing a negative result; and two studies involving NSCLC patients were both negative. The two positive studies involving prostate cancer patients

and melanoma patients had no confirmation in an additional case series.

With the exception of colon cancer patients, these results fail to provide support for a large amount of data from ecologic studies showing a prognostic benefit in cancer patients after sun exposure indirectly assessed either by season or latitude [34, 35].

These studies suffer from several limitations. First, 25(OH)D levels were determined in blood samples obtained only at one time point, and because circulating 25(OH)D has a half-life of approximately 2 weeks [36], they are not representative of long-term chronic 25(OH)D levels nor do they reflect the nadir of 25(OH)D reached during the year. In addition, there are no data on whether a change in 25(OH)D level over time influences clinical outcomes in cancer patients. Second, not all trials adjusted for age, race, body mass index, physical activity, and season, which can influence 25(OH)D levels as well as clinical outcomes. Third, hypovitaminosis D is associated with secondary hyperparathyroidism, which could have contributed to the negative prognostic role observed. Parathyroid hormone (PTH) is similar to parathyroid hormone-related peptide, which is a potent growth factor [37], and both molecules interact with the same receptor that is expressed in several neoplastic cells [38]. None of the studies assessing circulating vitD levels concomitantly assessed serum

PTH. Fourth, different assays were used to determine circulating vitD levels. The assay to determine vitD is not standardized and large variability in 25(OH)D results, both between methods and between laboratories, has been published [39]. This makes the study results difficult to reproduce in routine clinical practice.

Another important consideration is that not all tumor cells express VDR [19–22], and the presence of *VDR* polymorphism implies individual susceptibility to vitD biological activity [40]. These issues further complicate the relationship between circulating vitD level and cancer outcome.

VDR polymorphisms were associated with prognosis in five of 10 papers. These studies suffer several drawbacks: (a) the statistical power is relatively poor; (b) the panel of polymorphisms tested varies among the studies; (c) polymorphisms were tested in blood in some studies and in tumor tissues in others, leading to different interpretations of the results; and (d) some discrepancies between studies involving the same tumor histologies were recorded. That is, *FokI* polymorphism showed prognostic significance in patients with advanced NSCLC [10] but not in NSCLC patients with early disease [29].

Surprisingly, most studies did not measure circulating vitD levels, rendering interpretation of the results difficult. Of the two studies [10, 16] that assessed both vitD and VDR, only one [16] explored their prognostic interaction. However, the prognostic significance of several *VDR* polymorphisms was limited to patients with very low serum vitD levels. These data suggest that the greater functional activity of some *VDR* polymorphisms could protect patients against the negative effects of low vitD levels, but there is no effect in patients with higher vitD levels.

Association does not mean causality, and the serum vitD level might merely be a marker for another causal relationship [41]. The key question is to understand whether low vitD status increases the risk for death from cancer or is simply a consequence of poor health resulting from neoplastic disease. If the first hypothesis is true, then supplementation with vitD is likely to improve the prognosis for cancer patients.

Three prospective RCTs explored the prognostic role of vitD supplementation in prostate cancer patients with advanced castration-resistant disease. In the two randomized phase II studies, vitD supplementation was found to lead to a significantly longer OS time in one, and essentially superimposable survival results were obtained in the other. Following on the encouraging results from the positive study, a prospective phase III trial was designed but then was prematurely discontinued because of an excessively high mortality rate in the control arm.

The most interesting finding to emerge from the meta-analysis was the striking heterogeneity in trial results. How are we to interpret these contradictory data? These clinical trials used either a synthetic vitD analog (Hectoral®) or activated vitD (DN-101), rather than parent vitD (cholecalciferol), which would influence serum 25(OH)D levels.

Moreover, if we look at the prognostic role of serum vitD and classify patients by the percentile distribution of values (Table 1), it appears that prognosis progressively improves with increasing serum levels: the greater the vitD serum level attained, the better the prognosis. This relationship may not necessarily hold true, however. A study by Goodwin et al. [13] explored the prognostic role of vitD considering the serum level as a continuous variable. The results showed that the relationship between vitD serum level and cancer prognosis may not be linear, but may be U-shaped instead, with a greater hazard for death both at a serum vitD level <32 ng/mL and at a serum vitD level >44 ng/mL. Of note is the fact that a similar nonlinear relationship was found between vitD status and cardiovascular events [42]. Accordingly, not only hypovitaminosis D but also hypervitaminosis D could have a negative effect on prognosis. The finding that both low and high vitD levels are associated with a higher prostate cancer risk [43] suggests a stimulatory role of cancer growth in both conditions.

Finally, because the efficiency of the biological activity of vitD is mediated by the inheritance of *VDR* polymorphisms, the alleles associated with better vitD function can be protective against poor prognosis in cases of hypovitaminosis D, but they may have an opposite effect when high vitD levels result from supplementation.

In summary, the heterogeneity in *VDR* expression in prostate cancer patients, the nonlinear relationship between the serum vitD level and prognosis, together with an individual's susceptibility to vitD biological effects linked to *VDR* polymorphisms could account for the higher mortality observed in the ASCENT-II prospective trial in vitD-treated patients than in their non-vitD-treated counterparts.

Unfortunately, neither serum vitD nor *VDR* polymorphism was measured in patients enrolled in the prospective trials, precluding any exploratory prognostic analysis in the populations of supplemented and nonsupplemented patients.

From a methodological perspective, several potential limitations should be considered when interpreting the results of our systematic review of observational studies. Of particular relevance are the problems we encountered with identifying all studies, with assessing the risk for bias in each study because of poor reporting, and with determining the presence of residual confounding. Even more importantly, we needed to take into account multiplicity of anal-

yses and selective reporting and publication, because most of the studies were exploratory in nature and without confirmatory results.

Also, the three RCTs evaluating the potential benefit of vitD administration in advanced prostate cancer patients suffered from some limitations. Two of them were phase II studies with biochemical response as the primary endpoint [31, 32] and the third used different schedules of docetaxel in the two arms [33]. Moreover, these clinical trials used either a synthetic vitD analog (Hectoral®) or activated vitD (DN-101), which are not the standard replacement therapy for low vitD.

CONCLUSION

In conclusion, low vitD levels may have a negative prognostic role in some primary tumors; however, it is still too early to prescribe vitD supplementation in routine clinical practice. The cutoff levels of vitD potentially associated

with a greater hazard for death or progression in cancer patients, together with the interaction of *VDR* polymorphisms, need to be better investigated by future research.

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