Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Cancer Epidemiology, Biomarkers & Prevention

Review

Circulating 25-hydroxyvitamin D Levels and Prognosis among Cancer Patients: A Systematic Review

Adetunji T. Toriola, Nhi Nguyen, Kristen Scheitler-Ring, and Graham A. Colditz

Abstract

Circulating 25-hydroxyvitamin D (25-OHD) is associated with a reduction in risk of some cancers, but its association with prognosis among patients with cancer is poorly understood. In view of the increasing number of cancer survivors in the United States and the high prevalence of vitamin D deficiency among patients with cancer, an evaluation of the role of circulating 25-OHD in prognosis among patients with cancer is essential. We conducted a systematic review of studies published in the following databases—PubMed, OvidSP, BioMed Central, EMBASE, and Scopus till September 2013 using the following search terms: "vitamin D," "25-hydroxyvitamin D," "calcidiol," "cancer," "survival," "mortality," and "prognosis." Our search yielded 1,397 articles. From the 1,397 articles, we identified 26 studies that evaluated the associations of circulating 25-OHD with prognosis among patients with cancer. Evidence suggests that circulating 25-OHD levels may be associated with better prognosis in patients with breast and colorectal cancer, but there is a paucity of information on its association with prognosis in other cancers. This review highlights the need for further studies evaluating the role of vitamin D in prognosis among patients with cancer. *Cancer Epidemiol Biomarkers Prev; 23(6); 917–33. ©2014 AACR.*

Introduction

There is robust evidence that vitamin D is associated with a reduction in cancer risk, particularly breast and colorectal cancers (1–3). Less well known, however, is the impact of vitamin D on prognosis in patients with cancer. Experimental studies have demonstrated that vitamin D can suppress tumor progression and metastasis, via its effect on cellular proliferation, differentiation, and angiogenesis (4)—biologic properties that might be relevant to, and mediate its impact on prognosis in patients with cancer. Vitamin D is converted to 25-hydroxyvitamin D (25-OHD) by cytochrome P450 R21 in the liver (4, 5). Further hydroxylation of 25-OHD to the active form, 1,25-dihydroxyvitamin [1,25-$(OH)_2$D] by cytochrome P450 27B1 occurs in the kidney (4–7). The 1,25-$(OH)_2$D generated in the kidney is secreted into the circulation, bound to vitamin D binding protein (VDBP), and then transported to target organs, where it induces genomic and nongenomic responses through its interaction with the vitamin D receptor (VDR; ref. 4). Many cells and tissues express cytochrome P450 27B1 as well as VDR, which implies that local conversion of 25-OHD to 1,25-$(OH)_2$D, the active form, can take place in such tissues (4).

Nevertheless, experience from the associations of folate with colorectal cancer suggests that bioactive nutrients may have differential effects on tumor initiation and progression, hence, differential effects on cancer incidence and survival (8). Whereas folate deficiency may predispose to colorectal carcinogenesis in normal colorectal epithelial cells, high folate levels seem to promote the growth of an existing cancer (8–10). Hence, understanding the relationship between vitamin and prognosis among patients with cancer is essential, as the impact of vitamin D on cancer risk may differ from its impact on cancer prognosis.

Initial ecological studies indicate a potential inverse association between measures of ultraviolet B (UVB) radiation and cancer mortality (11, 12). Although exposure to UVB is a strong determinant of vitamin D status, it fails to account for differences in vitamin D intake, adiposity, physical activity, and skin pigmentation, which are also important determinants of vitamin D status. Because circulating 25-OHD level is the best indicator of vitamin D status, the associations of vitamin D with prognosis in patients with cancer are best ascertained using circulating 25-OHD concentrations. However, few studies have examined these associations.

An overview of the relationship between 25-OHD concentrations and prognosis in patients with cancer is particularly essential because of the very high number of cancer survivors in the United States (>13 million; ref. 13) and the high prevalence of vitamin D deficiency among these patients (14).

Authors' Affiliation: Division of Public Health Sciences, Department of Surgery, and Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri

Corresponding Author: Adetunji T. Toriola, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 600 South Taylor Avenue, Campus Box 8100, St. Louis, MO 63110. Phone: 314-286-2668; Fax: 314-747-1020; E-mail: a.toriola@wustl.edu

doi: 10.1158/1055-9965.EPI-14-0053

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

The objectives of this review are to (i) summarize results from studies that have evaluated the associations of circulating 25-OHD concentrations with prognosis among patients with cancer, and (ii) identify gaps and future research needs in this area.

Materials and Methods

We identified studies published between January 2007 and September 2013 using the following databases: PubMed, OvidSP, BioMed Central, EMBASE, and Scopus. Search terms included the following: "vitamin D," "25-hydroxyvitamin D," "calcidiol," "cancer," "survival," "mortality," "prognosis," as well as different types of cancer ("breast," "lung," "colorectal," "prostate," etc.). Search queries in the databases yielded 1,397 articles (Fig. 1). Abstracts were examined for relevance to the topic of study, and full texts were retrieved for applicable abstracts. Reference lists of relevant articles were also examined to identify other studies of interest.

We included studies if they met the following criteria: reported on (i) measurement of circulating 25-OHD, (ii) overall survival, disease-specific survival among patients with cancer or other forms of survival such as distant disease-free survival, disease-free interval, recurrence-free survival, event-free survival, (iii) any other prognosis among patients with cancer, and (iv) published in English. The outcomes were defined as (i) overall survival: time from diagnosis to death as a result of any cause; (ii) cancer-specific survival: time from diagnosis to death from specific cancer; (iii) disease-free survival: time from surgery to the date of the first locoregional recurrence, distant metastasis, detection of a secondary primary tumor, or death from any cause; (iv) disease-free interval: time elapsing between cancer diagnosis and local recurrence and/or lymph node metastasis and/or distant metastasis; (v) distant disease-free survival: time between diagnosis and metastasis at distant sites; (vi) risk of relapse: risk of having local invasive tumor recurrence and/or locoregional lymph node metastasis and/or distant metastasis; (vii) time to progression: time from study entry to disease progression, regardless of the patient's treatment status. Disease progression required 25% increase in measurable tumor or an increase in tumor size in patients whose lesions did not meet criteria for measurable disease; and (vii) time to treatment: the time from diagnosis to disease progression requiring treatment.

Twenty-nine studies met the inclusion criteria. Of these, three articles did not present data on association; hence, data from 26 studies were used in the review. From those 26 articles, we extracted information on study design, age, number of participants and events, types of cancer, effect measures, and confounding factors. Studies were available on the following cancers: breast ($N = 7$), colorectal ($N = 6$), lung ($N = 4$), hematologic ($N = 4$), prostate ($N = 2$), skin ($N = 2$), head-and-neck ($N = 2$), gastric ($N = 1$), and pancreatic ($N = 1$). One study (15) evaluated outcomes across multiple cancer sites (breast, colon, lung, and lymphoma).

Because of the heterogeneity of the studies and the limited data for each cancer type, we performed a systematic review of the effects of circulating 25-OHD levels on prognosis, rather than a meta-analysis.

Results

Breast cancer

Overall survival. Between January 2009 and September 2013, six studies investigated the associations of circulating 25-OHD levels with overall survival in patients with breast cancer (refs. 15–20; Table 1). Elevated circulating 25-OHD concentrations were associated with statistically significantly better survival in two studies (15, 19), borderline statistically significant better survival in two (16, 18), and no associations in last two (17, 20). In one of the studies, lower circulating 25-OHD concentrations were associated with reduced survival among women who did not have chemotherapy [HR = 1.15; 95%

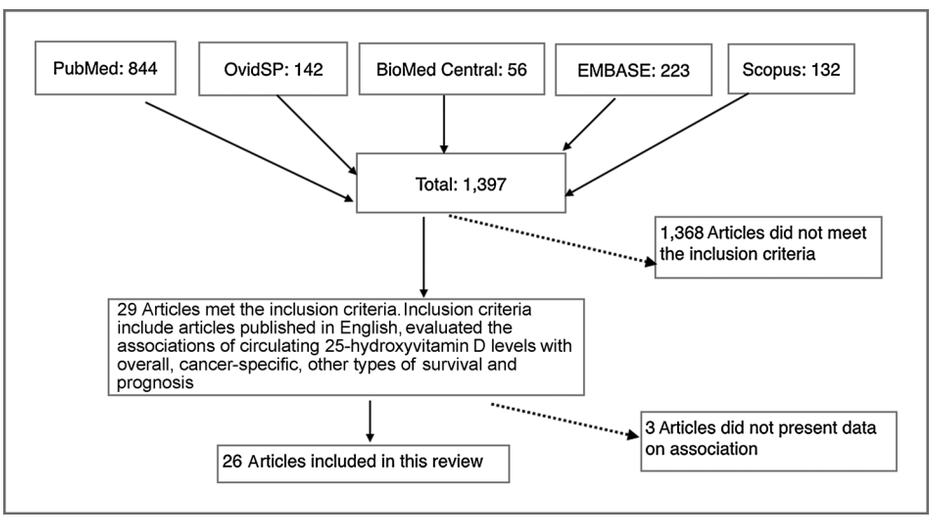

Figure 1. Flow diagram of the literature search.

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 1. Association of circulating 25-OHD levels with prognosis among patients with breast cancer

Reference, country	Design	Number/ events[a]	Age (y)	Type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Overall survival								
Villasenor et al. (17), United States	Cohort of cancer patients	585/110	18–64	*In situ*, stages I–IIIA disease	Per 25 nmol/L increase	0.85 (0.68–1.09)	0.20	Age, tumor stage, BMI, race, study site, tamoxifen use, season of blood draw, treatment, smoking, physical activity
Hatse et al. (19), Belgium	Cohort of cancer patients	1,800/134	22–94	Early and invasive	Per 25 nmol/L increase	0.79 (0.65–0.95)	0.010	BMI, age, tumor size, lymph node involvement, grade, estrogen receptor (ER) status
					>74.9 vs. ≤74.9	0.53 (0.33–0.86)	0.010	
Jacobs et al. (20), United States	Nested case-control	250 matched pairs	18–70	Stages I–IIIA	<49.9	1.13 (0.72–1.79)	0.59	BMI, ethnicity, intervention group, calcium intake, grade
					≥ 49.9	1.0 (Ref.)		
Tretli et al. (15), Norway	Cohort of cancer patients	251/98	36–75	Unspecified	<46	1.0 (Ref.)		Sex, age at diagnosis, season of blood sampling
					46–61	0.55 (0.32–0.95)		
					62–81	0.41 (0.23–0.74)		
					>81	0.37 (0.21–0.67)	<0.01	
Vrieling et al. (18), Germany	Cohort of cancer patients	1,265/174	50–74	*In situ*, stages I–IV	Per 10 nmol/L decrease	1.08 (1.00–1.17)	0.07	Tumor size, nodal status, metastases, tumor grade, ER/PR status, diabetes, detection mode
					<35	1.55 (1.00–2.39)		
					35–55	0.72 (0.45–1.17)		
					>55	1.0 (Ref.)		
Goodwin et al. (16), Canada	Cohort of cancer patients	512/106	≤75	Early stage	<50	1.60 (0.96–2.64)	0.05	Age, tumor stage, nodal stage, estrogen receptor status, grade
					≥50–72	0.98 (0.57–1.69)		
					>72	1.00 (Ref.)		
Breast cancer–specific survival								
Villasenor et al. (17), United States	Cohort of cancer patients	585/48	18–64	*In situ*, stages I–IIIA disease	Per 25 nmol/L increase	1.08 (0.75–1.54)	0.68	Age, tumor stage, BMI, race-ethnicity/study site, tamoxifen use, season of blood draw, treatment used
					<49.9	1.0 (Ref.)		
					49.9–74.9	1.12 (0.54–2.33)		
					>74.9	1.21 (0.52–2.80)		
Hatse et al. (19), Belgium	Cohort of cancer patients	1,800/64	22–94	Early, invasive	Per 25nmol/L increase	0.79 (0.62–1.00)	0.049	BMI, age, tumor size, grade, ER status
			All women		>74.9 vs. ≤74.9	0.49 (0.27–0.89)	0.019	
			Premenopause		>74.9 vs. ≤74.9	0.93 (0.43–2.02)	0.853	
			Postmenopause		>74.9 vs. ≤74.9	0.15 (0.03–0.63)	0.009	
Tretli et al. (15), Norway	Cohort of cancer patients	251/82	36–75	Unspecified	<50	1.0 (Ref.)	0.01	Age, sex, season of blood sampling
					51–67	0.47 (0.26–0.85)		
					68–86	0.53 (0.29–0.95)		
					>86	0.42 (0.21–0.82)		

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 1. Association of circulating 25-OHD levels with prognosis among patients with breast cancer (Cont'd)

Reference, country	Design	Number/ events[a]	Age (y)	Type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Other outcomes								
Recurrence/relapse								
Jacobs et al. (20), United States	Nested case-control	512 matched pairs	18–70	Stages I–IIIA	<24.96 ≥24.96, <49.9 ≥49.9, <74.9 ≥74.9	1.14 (0.57–2.31) 1.00 (0.68–1.48) 1.05 (0.76–1.47) 1.0 (Ref.)	0.85	BMI, ethnicity, intervention group, calcium intake, tumor grade
Hatse et al. (19), Belgium	Cohort of cancer patients	1,800/116[c]	22–94	Early and invasive	>75 vs. ≤75, 1st year >75 vs. ≤75, 3rd year >75 vs. ≤75, 6th year	1.20 (0.63–2.28) 0.50 (0.29–0.85) 0.25 (0.09–0.70)	0.5852 0.0103 0.0082	Age, BMI, tumor size, pN, grade, ER-by-time
Distant disease-free survival/interval								
Hatse et al. (19), Belgium	Cohort of cancer patients	1,800/94	Premenopausal	Early and invasive	>74.9 vs. ≤74.9	Not reported, no association		
Vrieling et al. (18), Germany	Cohort of cancer patients	1,074/135[b]	50–74 Postmenopausal	*In situ*, stages I–IIIA disease	Per 10 nmol/L decrease <35 35–55 >55	1.14 (1.05–1.24) 2.09 (1.29–3.41) 1.16 (0.70–1.94) 1.0 (Ref.)	0.006	Tumor size, nodal status, metastases, tumor grade, ER/PR status, diabetes, detection mode
Goodwin et al. (16), Canada	Cohort of cancer patients	512/116[c]	≤75	Early stage	<50 ≥50–72 >72	1.71 (1.02–2.86) 1.25 (0.73–2.14) 1.0 (Ref.)	0.09	Age, tumor stage, nodal stage, ER, grade
Disease-free survival/interval								
Hatse et al. (19), Belgium	Cohort of cancer patients	1,800/116[c]	Premenopausal Postmenopausal	Early and invasive	Per 25 nmol/L increase	Not reported, no association 0.74 (0.57–0.96)	 0.0225	 Age, tumor size, pN grade, ER-by-time, # positive lymph nodes, tumor grade
Kim et al. (21), Korea	Cohort of cancer patients	310/31[b]	48.9 ± 10.3 (mean)	Luminal	<49.9 49.9–72.4 ≥ 74.9	3.97 (1.77–8.91) 0.82 (0.28–2.37) 1.0 (Ref.)	0.001 0.711	Age, LN positivity, ER status, T stage

[a]Deaths, unless otherwise stated.
[b]Metastases.
[c]Relapse.
[d]Relative risk/odds ratio.

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

confidence interval (CI), 1.03–1.27 per 25 nmol/L decrease], but not among those who had chemotherapy (HR, 0.91; 95% CI, 0.75–1.08; *P*-interaction = 0.06; ref. 18).

Breast cancer–specific survival. Three studies have reported on the associations of circulating 25-OHD with breast cancer survival (15, 17, 19). Circulating 25-OHD was associated with breast cancer survival in two of the other three studies (15, 19), but the effect was limited to postmenopausal (HR, 0.15; 95% CI, 0.03–0.63), and not premenopausal women (HR, 0.93; 95% CI, 0.43–2.02) in one study (19).

Other outcomes. Other breast cancer outcomes include distant disease-free survival (16, 18, 19), disease-free survival (19, 21), and relapse (19, 20). Circulating 25-OHD concentrations were associated with longer distant disease-free survival (16, 18, 19). Likewise, 25-OHD was inversely associated with relapse after 3 years (HR, 0.50; 95% CI, 0.29–0.85) and 6 years (HR, 0.25; 95% CI, 0.09–0.70; ref. 19) but not during the first year of treatment (19) or with recurrence (20).

Colorectal cancer

Overall survival. From 2008 till date, five studies have examined the associations of circulating 25-OHD levels with overall survival in patients with colorectal cancer and one study among patients with colon cancer alone (refs. 15, 22–26; Table 2). One of these studies used prediagnostic 25-OHD levels (22), whereas another one used predicted 25-OHD levels (25). Four of the five studies in patients with colorectal cancer reported better overall survival among those with higher 25-OHD levels compared with those with lower 25-OHD levels (22–25), whereas the study in patients with colon cancer did not (15). Elevated prediagnostic 25-OHD levels were associated with better survival among patients with rectal cancer but not among patients with colon cancer (22).

Colorectal cancer–specific survival. Five studies reported on the associations of circulating 25-OHD with colorectal cancer–specific survival (one on colon cancer–specific survival; refs. 15, 22–25). Elevated 25-OHD concentrations were associated with better colorectal cancer–specific survival in two studies (22, 25).

Other outcomes. Circulating 25-OHD concentrations were not associated with time to progression, confirmed response, and disease-free survival in patients with colorectal cancer (23, 26).

Lung cancer

Overall survival. Four studies have investigated the associations of 25-OHD with overall survival (refs. 15, 27–29; Table 3). Elevated 25-OHD concentrations were associated with better survival in a Norwegian study (HR, 0.19; 95% CI, 0.12–0.30; ref. 15) and worse survival in a Chinese study (HR, 2.54; 95% CI, 1.01–6.41; ref. 27). Zhou and colleagues reported a beneficial effect of 25-OHD on survival among patients with stages IB and IIB non–small cell lung cancer (NSCLC) but not among those with stage IA tumors (29). Heist and colleagues observed no associations between 25-OHD concentrations and survival in patients with stages III and IV NSCLC as well as among patients with adenocarcinoma and squamous cell carcinoma (28).

Other outcomes. *Recurrence-free survival.* Circulating 25-OHD was not associated with recurrence-free survival in the overall analysis but suggestion of an association among patients with stages IB and IIB in a study conducted in Boston, MA (HR, 0.75; 95% CI, 0.45–1.23; *P*-trend = 0.06; ref. 29).

Other cancers

A few other studies have investigated the associations of circulating 25-OHD levels with prognosis in patients with other cancers, including lymphoma (15, 30), leukemia (31, 32), skin (33, 34), head-and-neck (35, 36), gastric (37), pancreatic (38), and prostate cancers (39, 40) with varying results (Table 4). Elevated 25-OHD levels were associated with better overall survival in patients with gastric cancer and lymphoma. Although elevated 25-OHD was not associated with statistically significant better overall survival among patients with skin cancer, it was associated with better recurrence-free survival (HR, 0.79; 95 %CI, 0.64–0.96; ref. 33). The associations of 25-OHD levels with overall survival in prostate and head-and-neck cancers seem equivocal. Of the two studies each conducted among patients with these cancers, one each reported survival advantage with elevated 25-OHD levels, whereas the other did not. For pancreatic cancer, elevated 25-OHD levels were associated with improved survival among patients with stages III and IV pancreatic cancer but not in the overall analysis.

Discussion

In this review, we identified 26 studies published between January 2007 and September 2013 that evaluated the associations of circulating 25-OHD levels with prognosis among patients with cancer. Our review suggests that elevated circulating 25-OHD levels may be associated with better overall survival in patients with breast and colorectal cancers. However, the associations of circulating 25-OHD levels with prognosis in patients with other cancer types are less clear due to the few studies that have investigated these associations.

Although the association of circulating 25-OHD levels with cancer risk has been explored in many studies, its association with prognosis among patients with cancer is poorly understood. A previous review of eight studies published in 2011 had provided an initial summary of the role of circulating 25-OHD levels in prognosis among patients with cancer (41). The review included two studies each on breast, colorectal, and lung cancers and one study each on melanoma and prostate cancer. In addition to the eight studies in that review, our review included 18 newly published studies, which is an indication of the strong emerging interest on the role of vitamin D in prognosis among patients with cancer. Because of the increasing

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 2. Association of circulating 25-OHD levels with prognosis among patients with colorectal cancer

Reference, country	Design	Number/events[a]	Age (y)	Type	25-OHD, nmol/L	RR/OR[f] (95% CI)	*P*-value/trend	Confounders
Overall survival								
Fedirko et al. (22), Europe	Prospective cohort	1,202/541	35–70	CRC	<36.3[b]	1.0 (Ref.)		Age at diagnosis, sex, cancer stage, grade of tumor differentiation, primary tumor location, smoking status, BMI, physical activity, season of blood collection, diagnosis year
					36.4–48.6	0.82 (0.63–1.07)		
					48.7–60.5	0.91 (0.70–1.18)		
					60.6–76.8	0.78 (0.59–1.03)		
					>76.8	0.67 (0.50–0.88)	<0.01	
		1,202/541		CRC	<25[b]	1.0 (Ref.)		
					25–50	0.74 (0.51–1.08)		
					50–75	0.71 (0.49–1.04)		
					75–100	0.57 (0.37–0.89)		
					≥100	0.53 (0.33–0.87)	0.02	
		759/345		Colon cancer	<36.3[b]	1.0 (Ref.)		
					36.4–48.6	0.83 (0.59–1.17)		
					48.7–60.5	1.01 (0.73–1.41)		
					60.6–76.8	0.90 (0.64–1.28)		
					>76.8	0.69 (0.48–1.01)	0.16	
		443/196		Rectal cancer	<36.3[b]	1.0 (Ref.)		
					36.4–48.6	0.78 (0.50–1.21)		
					48.7–60.5	0.69 (0.43–1.13)		
					60.6–76.8	0.60 (0.36–0.99)		
					>76.8	0.55 (0.35–0.88)	<0.01	
Ng et al. (26), United States	Cohort of cancer patients	515/475	26–85	Stage IV CRC	5.7–32.7	1.0 (Ref.)		Age, season of blood collection, sex, baseline performance status, treatment arm, BMI, metastatic sites
					32.9–49.7	0.78 (0.60–1.02)		
					49.9–67.6	1.13 (0.87–1.47)		
					67.9–188.2	0.94 (0.72–1.23)	0.55	
Tretli et al. (15), Norway	Cohort of cancer patients	52/36	32–75	Colon	<46	1.0 (Ref.)		Sex, age at diagnosis, season of blood sampling
					46–61	0.48 (0.18–1.29)		
					62–81	0.61 (0.23–1.59)		
					>81	0.40 (0.10–1.60)	0.23	
Mezawa et al. (23), Japan	Cohort of cancer patients	257/39	65 (mean)	CRC	7.5–17.5	0.50 (0.16–1.54)		Age, gender, month of blood sampling, cancer stage, residual tumor after surgery, time period of surgery, location of tumor, adjuvant chemotherapy, # lymph nodes with metastasis
					19.96–24.96	0.55 (0.18–1.65)		
					27.5–37.4	1.0 (Ref.)		
					39.9–89.9	0.16 (0.04–0.63)	0.009	

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 2. Association of circulating 25-OHD levels with prognosis among patients with colorectal cancer (Cont'd)

Reference, country	Design	Number/events[a]	Age (y)	Type	25-OHD, nmol/L	RR/OR[f] (95% CI)	*P*-value/trend	Confounders
Ng et al. (25), United States	Prospective cohort	1,017/283	30–75	CRC	Quintile 1[c]	1.0 (ref.)		Age at diagnosis, gender, cancer stage, grade of tumor differentiation, primary tumor location, diagnosis year
					Quintile 2	1.19 (0.85–1.68)		
					Quintile 3	1.05 (0.74–1.50)		
					Quintile 4	0.63 (0.43–0.94)		
					Quintile 5	0.62 (0.42–0.93)	0.002	
Ng et al. (24), United States	Prospective cohort	304/123	30–75	CRC	Quartile 1	1.0 (Ref.)		Age at diagnosis, season of blood draw, sex, cancer stage, grade of tumor differentiation, primary tumor location, diagnosis year, BMI at diagnosis, postdiagnostic physical activity
					Quartile 2	0.81 (0.49–1.35)		
					Quartile 3	0.81 (0.48–1.37)		
					Quartile 4	0.52 (0.29–0.94)	0.02	
Colorectal cancer–specific survival								
Fedirko et al. (22), Europe	Prospective cohort	1,202/444	35–70	CRC	<36.3[b]	1.0 (Ref.)		Age at diagnosis, sex, cancer stage, grade of tumor differentiation, primary tumor location, smoking status, BMI, physical activity, season of blood collection, diagnosis year
					36.4–48.6	0.76 (0.56–1.02)		
					48.7–60.5	0.93 (0.69–1.24)		
					60.6–76.8	0.78 (0.58–1.06)		
					>76.8	0.69 (0.50–0.93)	0.04	
		1,202/444		CRC	<25[b]	1.0 (Ref.)		
					25–50	0.73 (0.48–1.11)		
					50–75	0.72 (0.47–1.11)		
					75–100	0.62 (0.38–1.01)		
					≥100	0.55 (0.32–0.94)	0.04	
		759/279		Colon cancer	<36.3[b]	1.0 (Ref.)		
					36.4–48.6	0.77 (0.52–1.14)		
					48.7–60.5	1.05 (0.72–1.52)		
					60.6–76.8	0.96 (0.65–1.40)		
					>76.8	0.79 (0.53–1.19)	0.61	
		443/165		Rectal cancer	<36.3[b]	1.0 (Ref.)		
					36.4–48.6	0.72 (0.45–1.17)		
					48.7–60.5	0.65 (0.38–1.11)		
					60.6–76.8	0.53 (0.31–0.92)		
					>76.8	0.48 (0.29–0.80)	<0.01	
Tretli et al. (15), Norway	Cohort of cancer patients	52/26	32–75	Colon cancer	<44	1.0 (Ref.)		Sex, age at diagnosis, season of blood sampling
					45–56	0.46 (0.15–1.48)		
					57–77	0.73 (0.25–2.15)		
					>77	0.20 (0.04–1.10)	0.16	

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 2. Association of circulating 25-OHD levels with prognosis among patients with colorectal cancer (Cont'd)

Reference, country	Design	Number/events[a]	Age (y)	Type	25-OHD, nmol/L	RR/OR[f] (95% CI)	*P*-value/trend	Confounders
Mezawa et al. (23), Japan	Cohort of cancer patients	257/30	65 (mean)	CRC	Per unit increase	0.98 (0.89–1.08)	0.67	Age at diagnosis, gender, calendar month of blood sampling, cancer stage, residual tumor after surgery, time period of surgery, location of tumor, adjuvant chemotherapy, # lymph nodes with metastasis
Ng et al. (25), United States	Prospective cohort	1,017/119	30–75	CRC	Quintile 1[c]	1.0 (Ref.)		Age at diagnosis, gender, cancer stage, grade of tumor differentiation, primary tumor location, diagnosis year
					Quintile 2	0.99 (0.58–1.68)		
					Quintile 3	1.04 (0.61–1.78)		
					Quintile 4	0.62 (0.34–1.11)		
					Quintile 5	0.50 (0.26–0.95)	0.02	
Ng et al. (24), United States	Prospective cohort	304/96	30–75	CRC	Quartile 1	1.0 (Ref.)		Age at diagnosis, season of blood draw, sex, cancer stage, grade of tumor differentiation, primary tumor location, diagnosis year, BMI at diagnosis, post diagnostic physical activity
					Quartile 2	0.76 (0.41–1.42)		
					Quartile 3	1.04 (0.58–1.89)		
					Quartile 4	0.61 (0.31–1.19)	0.23	
Other outcomes								
Time to progression								
Ng et al. (26), United States	Cohort of cancer patients	515/440[d]	26–85	Stage IV CRC	5.7–32.7	1.0 (Ref.)		Age, season of blood collection, sex, baseline performance status, treatment arm, BMI, metastatic sites
					32.9–49.7	1.14 (0.87–1.49)		
					49.9–67.6	1.23 (0.93–1.62)		
					67.9–188.2	1.07 (0.81–1.42)	0.66	
Confirmed response								
Ng et al. (26), United States	Cohort of cancer patients	515/239[e]	26–85	Stage IV CRC	5.7–32.7	1.0 (Ref.)		Age, season of blood collection, sex, baseline performance status, treatment arm, BMI, metastatic sites
					32.9–49.7	1.15 (0.70–1.91)		
					49.9–67.6	0.98 (0.59–1.63)		
					67.9–188.2	1.12 (0.67–1.89)	0.67	

Abbreviation: CRC, colorectal cancer.
[a]Deaths, unless otherwise stated.
[b]Prediagnostic 25-OHD levels.
[c]Predicted 25-OHD levels.
[d]Progression.
[e]Confirmed tumor response.
[f]Relative risk/odds ratio.

Table 3. Association of circulating 25-OHD levels with prognosis among patients with lung cancer

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[c] (95% CI)	*P*-value/trend	Confounders
Overall survival								
Liu et al. (27), China	Cohort of cancer patients	568/87	25–83	NSCLC	<25.36	1.0 (Ref.)		Age, gender, smoking status, stage, histology, surgical operation, chemotherapy or radiation treatment
					25.36–37.72	1.47 (0.58–3.73)		
					37.72–56.54	1.59 (0.75–3.39)		
					≥ 56.54	2.54 (1.01–6.41)	0.048	
					Trend	1.31 (1.00–1.72)	0.048	
Tretli et al. (15), Norway	Cohort of cancer patients	210/190	42–82	Not specified	<46	1.0 (Ref.)		Age at diagnosis, sex, season of blood sampling
					46–61	0.40 (0.28–0.59)		
					62–81	0.34 (0.22–0.52)		
					>81	0.19 (0.12–0.30)	<0.01	
Heist et al. (28), United States	Cohort of cancer patients	294/233	33–85	Advanced stage NSCLC	<31.4	1.0 (Ref.)		Sex, stage, performance status
					31.4–50.4	1.09 (0.75–1.57)		
					50.7–68.9	1.03 (0.71–1.50)		
					≥69.1	1.08 (0.75–1.57)	0.76	
		156/125		Adenocarcinoma	<31.4	1.0 (Ref.)		
					31.4–50.4	1.13 (0.67–1.91)		
					50.7–68.9	0.82 (0.49–1.37)		
					≥ 69.1	1.34 (0.81–2.19)	0.51	
		51/37		Squamous	<31.4	1.0 (Ref.)		
					31.4–50.4	1.67 (0.65–4.28)		
					50.7–68.9	3.04 (1.05–8.84)	0.14	
					≥69.1	1.60 (0.55–4.66)		
		128/101		Stage III	<31.4	1.0 (Ref.)		
					31.4–50.4	0.87 (0.50–1.52)		
					50.7–68.9	1.17 (0.70–1.96)		
					≥69.1	0.88 (0.49–1.57)	0.98	
		166/132		Stage IV	<31.4	1.0 (Ref.)		
					31.4–50.4	1.32 (0.79–2.21)		
					50.7–68.9	0.99 (0.58–1.72)	0.56	
					≥69.1	1.29 (0.78–2.15)		

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 3. Association of circulating 25-OHD levels with prognosis among patients with lung cancer (Cont'd)

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[c] (95% CI)	*P*-value/trend	Confounders
Zhou et al. (29), United States	Cohort of cancer patients	447/234	31–89	Early-stage NSCLC	<25.5	1.0 (Ref.)		Age, sex, stage, pack-years of smoking, chemotherapy/ radiotherapy, surgery season
					25.2–39.2	1.07 (0.74–1.53)		
					39.4–53.7	0.80 (0.55–1.18)		
					>53.7	0.74 (0.50–1.10)	0.07	
		232/111		Stage IA	<25.5	1.0 (Ref.)		
					25.2–39.2	1.02 (0.56–1.87)		
					39.4–53.7	1.33 (0.77–2.31)		
					>53.7	1.10 (0.62–1.96)	0.53	
		215/123		Stage IB–IIB	<25.5	1.0 (Ref.)		
					25.2–39.2	1.01 (0.63–1.61)		
					39.4–53.7	0.51 (0.29–0.89)		
					>53.7	0.45 (0.24–0.82)	0.02	
Other outcomes								
Recurrence-free survival								
Zhou et al. (29), United States	Cohort of cancer patients	447/269[b]	31–89	Early-stage NSCLC	<25.5	1.0 (Ref.)		Age, sex, stage, pack-years of smoking, surgery season chemotherapy/radiotherapy
					25.2–39.2	1.21 (0.86–1.71)		
					39.4–53.7	0.90 (0.62–1.29)		
					>53.7	0.92 (0.64–1.33)	0.37	
		232/111		Stage IA	<25.5	1.0 (Ref.)		
					25.2–39.2	1.21 (0.70–2.09)		
					39.4–53.7	1.43 (0.86–2.39)		
					>53.7	1.25 (0.75–2.08)	0.32	
		215/123		Stage IB–IIB	<25.5	1.0 (Ref.)		
					25.2–39.2	1.30 (0.85–2.00)		
					39.4–53.7	0.72 (0.45–1.15)		
					>53.7	0.75 (0.45–1.23)	0.06	

[a]Deaths, unless otherwise stated.
[b]Recurrence.
[c]Relative risk/odds ratio.

Table 4. Association of circulating 25-OHD levels with prognosis among patients with other cancer types

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Gastric cancer								
Overall survival								
Ren et al. (37), China	Retrospective cohort of cancer patients	197/106	60 (mean)	Gastric carcinoma	<50 ≥50	1.0 (ref) 0.59 (0.37–0.91)	0.019	Clinical stage, season of blood draw
Pancreatic cancer								
Overall survival								
Cho et al. (38), United States	Cohort of cancer patients	178/NA	NA	All patients	<50 ≥50	Not statistically significant, NA	NA	NA
				Stages III and IV cancer	<50 ≥50	1.99 (1.16–3.43) 1.0 (ref)	0.013	NA
Skin cancer								
Overall survival								
Newton-Bishop et al. (33), United Kingdom	Cohort of cancer patients	872/141	NA	Melanoma	Per 20 nmol/L increase	0.83 (0.68–1.02)	NA	Age, sex, Townsend score, tumor site, Breslow thickness, BMI
Skin cancer–specific survival								
Samimi et al. (34), France	Cohort of cancer patients	89/19	31–98	Merkel cell carcinoma	<50 >50	5.28 (0.75–36.95) 1.0 (ref)	0.093	Age, tumor size, time to vitamin D assessment, impaired immune function, metastasis at presentation, period of sampling
Recurrence-free survival								
Newton-Bishop et al. (33), United Kingdom	Cohort of cancer patients	872/173[b]	NA	Melanoma	Per 20 nmol/L increase ≤41.3 41.3–61.4 > 61.4	0.79 (0.64–0.96) 1.0 (ref) 0.70 (0.42–1.14) 0.57 (0.33–0.97)	NA	Age, sex, Townsend score, tumor site, Breslow thickness, BMI
Nodal and/or distant metastasis								
Samimi et al. (34), France	Cohort of cancer patients	89/33	31–98	Merkel cell carcinoma	<50 ≥50	2.89 (1.03–8.13) 1.0 (ref)	0.043	Age, tumor size, time to vitamin D assessment, impaired immune function, metastasis at presentation, period of sampling
Head-and-neck cancers								
Overall survival								
Gugatschka et al. (35), Austria	Cancer patients	88 cases/NA	63 (mean)	Squamous cell carcinoma (SCC)	NA	0.89 (0.83–0.97)	0.006	Univariable analysis
Meyer et al. (36), Canada	Cohort of cancer patients	522/223	62.5 (mean)	Overall (Stage I–II)	<48 49–63 64–78 >78	1.0 (ref) 0.75 (0.51–1.10) 0.93 (0.64–1.36) 0.85 (0.57–1.28)	0.65	Season of blood collection, stage, site, age, smoking, alcohol consumption, BMI
Recurrence								
Meyer et al. (36), Canada	Cohort of cancer patients	522/119[b]	62.5 (mean)	Overall (Stage I–II)	<48 49–63 64–78 >78	1.0 (ref) 0.99 (0.58–1.69) 1.20 (0.71–2.05) 1.12 (0.65–1.93)	0.56	Season of blood collection, stage, site

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 4. Association of circulating 25-OHD levels with prognosis among patients with other cancer types (Cont'd)

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Disease-free survival								
Gugatschka et al. (35), Austria	Cohort of cancer patients	88 cases/NA	63 (mean)	SCC	NA	0.85 (0.75–0.96)	0.01	Univariable analysis
Prostate cancer								
Overall survival								
Fang et al. (39), United States	Cohort of cancer patients	1,822/595	NA	Overall	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.10 (0.87–1.39) 1.05 (0.83–1.34) 1.06 (0.83–1.34) 1.0 (ref)	0.46	Age at diagnosis, BMI, physical activity, smoking, Gleason score, TNM stage, $1,25(OH)_2D$
Tretli et al. (40), Norway	Cohort of cancer patients	160/61	52–82	Overall	<50 50–80 >80	1.0 (ref) 0.40 (0.20–0.78) 0.24 (0.11–0.53)	NA	Patient group, age, tumor differentiation grade, patient functional status at time of blood collection
		97/45		Among patients receiving hormone therapy	<50 50–80 >80	1.0 (ref) 0.18 (0.07–0.46) 0.09 (0.03–0.27)		
Prostate cancer–specific survival								
Fang et al. (39), United States	Cohort of cancer patients	1,822/202[c]	NA	Overall	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.31 (0.86–1.99) 1.32 (0.87–2.00) 1.09 (0.70–1.70) 1.0 (ref)	0.14	Age at diagnosis, BMI, physical activity, smoking, Gleason score, TNM stage, $1,25(OH)_2D$
Tretli et al. (40), Norway	Cohort of cancer patients	160/52	52–82	Overall	<50 50–80 >80	1.0 (ref) 0.33 (0.14–0.77) 0.16 (0.05–0.43)	NA	Patient group, age, tumor differentiation grade, patient functional status at time of blood collection
Hematologic cancers								
Overall survival								
Lymphoma								
Tretli et al. (15), Norway	Cohort of cancer patients	145/75	37–79	Overall	<46 46–61 62–81 >81	1.0 (ref) 0.59 (0.32–1.11) 0.46 (0.25–0.86) 0.33 (0.16–0.69)	<0.01	Sex, age at diagnosis, season of blood sampling
Drake et al. (30), United States	Cohort of cancer patients	370/100	19–94	Diffuse large B-cell lymphoma	>62.5 <62.5	1.0 (ref) 1.99 (1.27–3.13)	0.003	International Prognostic Index (IPI), immunochemo-therapy vs. all other therapy
		70/29		T-cell lymphoma	>62.5 <62.5	1.0 (ref) 2.38 (1.04–5.41)	0.04	International Prognostic Index
		71/19		Mantle cell lymphoma	>62.5 <62.5	1.0 (ref) 1.35 (0.53–3.39)	0.53	Mantle Cell International Prognostic Index (MCIPI)
		285/19		Follicular lymphoma (FL)	>62.5 <62.5	1.0 (ref) 1.52 (0.60–3.88)	0.38	FLIPI, FL grade 3, rituximab-based therapy, chemotherapy vs. none
		109/8		Post-FL (marginal zone and lymphoplasmacytic lymphoma)	>62.5 <62.5	1.0 (ref) 2.76 (0.58–13.1)	0.2	Stage, performance status
		78/18		Others	>62.5 <62.5	1.0 (ref) 2.08 (0.79–5.49)	0.14	Stage, performance status

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 4. Association of circulating 25-OHD levels with prognosis among patients with other cancer types (Cont'd)

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Leukemia								
Pardanani et al. (31), United States	Cohort of cancer patients	247/129	14–83	Primary myelofibrosis	<62.4 <24.96	1.2 (0.8–1.6) 1.2 (0.7–2.1)	(NA)	Disease-specific prognostic variables
		74/42	44–89	*De novo* myelodysplastic syndromes	<62.4	1.4 (0.7–2.7)	NA	Disease-specific prognostic variables
Shanafelt et al. (32), United States	Discovery cohort	390/34	63 (median)	Chronic lymphocytic leukemia (CLL)	<62.4	2.39 (1.21–4.70)	0.01	NA
	Confirmation cohort	153/62	67 (median)	CLL	<62.4	1.63 (0.99–2.69)	0.06	NA
	Combined cohorts	543/96		CLL	<62.4	1.47 (0.97–2.23)	0.07	Age, sex, Rai stage, CD38, ZAP-70, IGHV, CD49d, cytogenetic abnormalities (FISH)
Cancer-specific survival								
Tretli et al. (15), Norway	Cohort of cancer patients	145/62	37–79	Overall	<44 44–60 61–77 >77	1.0 (ref) 0.71 (0.36–1.40) 0.45 (0.21–94) 0.39 (0.18–0.83)	0.01	Sex, age at diagnosis, season of blood sampling
Drake et al. (30), United States	Cohort of cancer patients	370/90	19–94	Diffuse large B-cell lymphoma	>62.5 <62.5	1.0 (ref) 2.16 (1.33–3.51)	0.002	IPI, immunochemotherapy vs. all other therapy
		70/28		T-cell lymphoma	>62.5 <62.5	1.0 (ref) 2.26 (0.99–5.17)	0.05	IPI
		71/19		Mantle cell lymphoma	>62.5 <62.5	1.0 (ref) 1.35 (0.53–3.39)	0.53	MCIPI
		285/9		FL	>62.5 <62.5	1.0 (ref) 0.90 (0.23–3.49)	0.88	IPI, FL grade 3, rituximab-based therapy, all other chemotherapy vs. observation
		109/8		Post-FL (marginal zone and lymphoplasmacytic lymphoma)	>62.5 <62.5	1.0 (ref) 2.76 (0.58–13.1)	0.2	Stage, performance status
		78/14		Others	>62.5 <62.5	1.0 (ref) 1.73 (0.58–5.17)	0.33	Stage, performance status
Event-free survival (lymphoma)								
Drake et al. (30), United States	Cohort of cancer patients	370/132	19–94	Diffuse large B-cell lymphoma	>62.5 <62.5	1.0 (ref) 1.41 (0.98–2.04)	0.07	IPI, immunochemotherapy vs. all other therapy
		70/49		T-cell lymphoma	>62.5 <62.5	1.0 (ref) 1.94 (1.04–3.61)	0.04	IPI
		71/45		Mantle cell lymphoma	>62.5 <62.5	1.0 (ref) 1.09 (0.59–2.01)	0.78	MCIPI
		285/104		FL	>62.5 <62.5	1.0 (ref) 1.07 (0.71–1.62)	0.75	FLIPI, FL grade 3, rituximab-based therapy, all other chemotherapy vs. observation
		109/39		Post-FL (marginal zone and lymphoplasmacytic lymphoma)	>62.5 <62.5	1.0 (ref) 0.98 (0.51–1.89)	0.95	Stage, performance status
		78/35		Others	>62.5 <62.5	1.0 (ref) 1.15 (0.57–2.32)	0.71	Stage, performance status

(Continued on the following page)

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Table 4. Association of circulating 25-OHD levels with prognosis among patients with other cancer types (Cont'd)

Reference, country	Design	Number/ events[a]	Age (y)	Cancer type	25-OHD, nmol/L	RR/OR[d] (95% CI)	*P*-value/trend	Confounders
Time to treatment (leukemia)								
Shanafelt et al. (32), United States	Discovery cohort	390/131	63 (median)	CLL	<62.4	1.66 (1.16–2.37)	0.005	NA
	Confirmation cohort	152/70	67 (median)	CLL	<62.4	1.59 (0.99–2.56)	0.05	NA
	Combined cohorts	542/201		CLL	<62.4	1.47 (1.11–1.96)	0.008	Age, sex, Rai stage, CD38, ZAP-70, IGHV, CD49d, cytogenetic abnormalities (FISH)
Leukemia-free survival								
Pardanani et al. (31), United States	Cohort of cancer patients	247/NA	14–83	Primary myelofibrosis	<62.4	1.8 (0.8–4.4)	NA	NA
					<24.96	1.2 (0.2–4.1)		
		74/NA	44–89	*De novo* myelodysplastic syndromes	<62.4	1.3 (0.3–4.0)	NA	NA

[a]Deaths, unless otherwise stated.
[b]Recurrence.
[c]Death from prostate cancer or development of bone metastases.
[d]Relative risk/odds ratio.

number of people living with cancer, the importance of evaluating the associations of vitamin D with outcomes among patients with cancer cannot be overemphasized. Currently, close to 14 million Americans are living with a diagnosis of cancer and the number is expected to increase to 18 million by 2022 (13). At the same time, studies have reported a high prevalence of vitamin D deficiency among patients with cancer. In a recent review of 37 studies, 67% of the patients with cancer had vitamin D insufficiency (25-OHD levels between 25–50 nmol/L; ref. 14). If vitamin D is associated with prognosis among patients with cancer, the potential public health and translational importance could be enormous. Nevertheless, this research area is still in its infancy and more work needs to be done to tease out the effects of vitamin D on prognosis in patients with cancer. Below, we highlight a few areas in this emerging field that deserve more attention if this potential is to be realized.

The role of tumor characteristics and lifestyle factors

Only a few studies evaluated the associations of vitamin D with prognosis stratified by tumor characteristics and lifestyle factors; hence, there is paucity of information on factors that modify the associations of 25-OHD with prognosis in patients with cancer. Race, body mass index (BMI), tumor subsite, molecular subtype, as well as stage-stratified analyses are essential as they are important determinants of survival and circulating 25-OHD levels. For instance, non-Caucasian patients with breast cancer have a 2-fold increased risk of vitamin D deficiency compared with Caucasian patients with breast cancer, and obese patients with breast cancer have a 3-fold increased risk of vitamin D deficiency compared with normal-weight patients with breast cancer (42). Circulating 25-OHD levels are lower in patients with localized or regional disease than women with *in situ* disease (43) and in women with triple-negative breast cancer than women with other breast cancer subtypes (44). The EPIC study demonstrated survival advantage among patients with rectal cancer with elevated 25-OHD levels, but not among patients with colon cancer, which is in line with the null effect reported in a study limited to patients with colon cancer (15). Drake and colleagues demonstrated better survival associated with higher 25-OHD levels among patients with diffuse large B-cell, and T-cell lymphoma but not among other lymphoma subtypes (30). Hence, an in-depth investigation of how tumor characteristics and lifestyle factors modify the associations of vitamin D with prognosis is needed. Only two of the six breast cancer studies reported analyses stratified by stage at diagnosis and hormone receptor status (18, 21), one with BMI (18), and none with race. Of particular importance and interest is to determine whether part of the racial and obesity-related differences in cancer survival can be explained by differences in the 25-OHD levels. It has also been suggested that circulating 25-OHD levels may be a biologic marker for health status among patients with cancer, especially physical activity (45, 46). Patients with cancer

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

with better health status may be more physically active and have a greater exposure to sun, which is an important determinant of circulating 25-OHD levels. Thus, physical activity may confound the association of 25-OHD levels with survival in patients with cancer (45).

Impact of time of blood draw

Patients with cancer change their lifestyle and eating habits after a diagnosis of cancer, hence, postdiagnostic 25-OHD levels may not be representative of usual levels before cancer diagnosis.

Although nothing is known about individual longitudinal changes in 25-OHD levels after a diagnosis of cancer, the prevalence of vitamin D insufficiency (<50 nmol/L) in patients with cancer can be as high as 67%, compared with 35% within the general population (14, 47, 48). In a study, 74% of patients with breast cancer had vitamin D insufficiency (49), suggesting that prevalence of vitamin D insufficiency is higher among patients with cancer compared with the general population. Furthermore, patients with cancer have been reported to have a 2.5-fold increased odd of having vitamin D insufficiency compared with non-cancer patients within the same geographic area (50).

Likewise, chemotherapy might influence 25-OHD levels (51, 52). Patients with colorectal cancer receiving chemotherapy were three-times more likely to have vitamin D deficiency than those not receiving chemotherapy (52). Similarly, patients with early-stage breast cancer treated with adjuvant chemotherapy had a 32% reduction in 25-OHD levels at day 147 of treatment compared with prechemotherapy levels (51). Although most studies measured 25-OHD levels in pretreatment blood samples, some did not, and in some studies, circulating 25-OHD levels in blood samples collected more than 2 years after diagnosis were related to prognosis. To highlight the importance of timing of blood collection, Vrieling and colleagues reported a statistically significant association between circulating 25-OHD levels and breast cancer survival in analysis conducted using samples taken before initiation of chemotherapy but not in samples taken after initiation of therapy (18). Thus, studies evaluating the associations of circulating 25-OHD with cancer prognosis should consider using pretreatment blood samples, rather than posttreatment samples. In addition, a sizeable number of studies did not take into consideration, or correct for, season of blood draw in their analyses despite the well-documented seasonal differences associated with 25-OHD levels.

Vitamin D sufficiency

There is a wide variability in 25-OHD cutoff points related to prognosis in the studies. Some studies derived their cutoff points based on the distribution within their study population, whereas others used median splits and other categories based on sufficient and insufficient 25-OHD levels. Because of the emerging role of vitamin D in many health outcomes, the definition of vitamin D deficiency has extended beyond its relationship with skeletal health alone. Vitamin D deficiency has been traditionally defined as circulating 25-OHD levels <25 nmol/L because clinical evidence of skeletal diseases such as rickets become manifest below this level (53). Because of emerging evidence of the role of vitamin D in other health outcomes, the concept of vitamin D sufficiency based on 25-OHD levels required to maximize intestinal calcium absorption, prevent secondary hyperparathyroidism, as well as maintain optimal health in at-risk groups has gained a lot of traction over the last decade (4, 54, 55). Circulating 25-OHD levels needed for maximal suppression of parathyroid hormone has been estimated to be between 70 and 80 nmol/L; hence, an expert consensus has adopted 25-OHD levels of 75 nmol/L to indicate vitamin D sufficiency, whereas levels <50 nmol/L indicate insufficiency and intermediate levels indicate relative insufficiency (4, 55–57). Many studies have reported protective effect of 25-OHD on cancer risk at levels indicative of sufficiency (≥75 nmol/L). While some of the studies in our review investigated the associations of 25-OHD with prognosis using sufficient versus insufficient levels, many others did not. Since there is a biologic rationale, future studies on 25-OHD and prognosis among patients with cancer should consider evaluating the associations of vitamin D with prognosis based on sufficient 25-OHD levels. In addition, future studies should consider reporting how a unit increase in circulating 25-OHD (preferably 25 nmol/L) might affect prognosis.

This review suggests that vitamin D may be associated with prognosis in patients with breast and colorectal cancer. Importantly, because low 25-OHD levels among patients with cancer can be corrected, this might pave way for studies evaluating the utility of correcting vitamin D deficiency in the management of patients with cancer. This is especially important given the recent review showing that although circulating 25-OHD levels are associated with improved outcomes in observational studies, results from intervention studies have not confirmed these associations (46). Although vitamin D replacement therapy successfully corrected deficient and suboptimal 25-OHD levels among patients with cancer (58), the impact of this correction on prognosis is unknown. Hence, more observational studies, as well as randomized clinical trials, are needed to further evaluate the associations of vitamin D with prognosis among patients with cancer before vitamin D supplementation among patients with cancer can be considered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

A.T. Toriola is supported by the Washington University School of Medicine, Barnes-Jewish Hospital Foundation, and Siteman Cancer Center.

Received January 15, 2014; revised March 18, 2014; accepted March 24, 2014; published OnlineFirst April 1, 2014.

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

References

1. Lee JE, Li H, Chan AT, Hollis BW, Lee IM, Stampfer MJ, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. Cancer Prev Res 2011;4:735–43.
2. Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. J Clin Oncol 2011;29:3775–82.
3. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 2010;46: 2196–205.
4. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
5. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80:1689S–96S.
6. IARC Working group on Vitamin D. Vitamin D and cancer. Lyon, France: IARC Press; 2008.
7. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer 2007;7:684–700.
8. Kim YI. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? Int J Gastroenterol Hepatol 2006;55:1387–9.
9. Ulrich CM, Potter JD. Folate and cancer–timing is everything. JAMA 2007;297:2408–9.
10. Song J, Medline A, Mason JB, Gallinger S, Kim YI. Effects of dietary folate on intestinal tumorigenesis in the apcMin mouse. Cancer Res 2000;60:5434–40.
11. Grant WB. The likely role of vitamin D from solar ultraviolet-B irradiance in increasing cancer survival. Anticancer Res 2006;26:2605–14.
12. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002;94: 1867–75.
13. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62:220–41.
14. Teleni L, Baker J, Koczwara B, Kimlin MG, Walpole E, Tsai K, et al. Clinical outcomes of vitamin D deficiency and supplementation in cancer patients. Nutr Rev 2013;71:611–21.
15. Tretli S, Schwartz GG, Torjesen PA, Robsahm TE. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. Cancer Causes Control 2012;23:363–70.
16. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. J Clin Oncol 2009;27:3757–63.
17. Villasenor A, Ballard-Barbash R, Ambs A, Bernstein L, Baumgartner K, Baumgartner R, et al. Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. Cancer Causes Control 2013; 24:759–67.
18. Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast Cancer Res 2011;13:R74.
19. Hatse S, Lambrechts D, Verstuyf A, Smeets A, Brouwers B, Vandorpe T, et al. Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. Carcinogenesis 2012;33:1319–26.
20. Jacobs ET, Thomson CA, Flatt SW, Al-Delaimy WK, Hibler EA, Jones LA, et al. Vitamin D and breast cancer recurrence in the Women's Healthy Eating and Living (WHEL) Study. Am J Clin Nutr 2011;93: 108–17.
21. Kim HJ, Lee YM, Ko BS, Lee JW, Yu JH, Son BH, et al. Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer. Ann Surg Oncol 2011;18:1830–6.
22. Fedirko V, Riboli E, Tjonneland A, Ferrari P, Olsen A, Bueno-de-Mesquita HB, et al. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European ppulations. Cancer Epidemiol Biomarkers Prev 2012;21:582–93.
23. Mezawa H, Sugiura T, Watanabe M, Norizoe C, Takahashi D, Shimojima A, et al. Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study. BMC cancer 2010;10:347.
24. Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. J Clin Oncol 2008;26:2984–91.
25. Ng K, Wolpin BM, Meyerhardt JA, Wu K, Chan AT, Hollis BW, et al. Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. Br J Cancer 2009;101:916–23.
26. Ng K, Sargent DJ, Goldberg RM, Meyerhardt JA, Green EM, Pitot HC, et al. Vitamin D status in patients with stage IV colorectal cancer: findings from Intergroup trial N9741. J Clin Oncol 2011; 29:1599–606.
27. Liu Y, Chen W, Hu ZB, Xu L, Shu YQ, Pan SY, et al. Plasma Vitamin D Levels And Vitamin D Receptor Polymorphisms Are Associated with Survival of Non-small Cell Lung Cancer. Chin J Cancer Res 2011; 23:33–7.
28. Heist RS, Zhou W, Wang Z, Liu G, Neuberg D, Su L, et al. Circulating 25-hydroxyvitamin D, VDR polymorphisms, and survival in advanced non-small-cell lung cancer. J Clin Oncol 2008;26:5596–602.
29. Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. J Clin Oncol 2007; 25:479–85.
30. Drake MT, Maurer MJ, Link BK, Habermann TM, Ansell SM, Micallef IN, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. J Clin Oncol 2010;28:4191–8.
31. Pardanani A, Drake MT, Finke C, Lasho TL, Rozell SA, Jimma T, et al. Vitamin D insufficiency in myeloproliferative neoplasms and myelodysplastic syndromes: clinical correlates and prognostic studies. Am J Hematol 2011;86:1013–6.
32. Shanafelt TD, Drake MT, Maurer MJ, Allmer C, Rabe KG, Slager SL, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. Blood 2011;117:1492–8.
33. Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, et al. Serum 25-hydroxyvitamin D3 levels are associated with breslow thickness at presentation and survival from melanoma. J Clin Oncol 2009;27:5439–44.
34. Samimi M, Touze A, Laude H, Le Bidre E, Arnold F, Carpentier A, et al. Vitamin D deficiency is associated with greater tumor size and poorer outcome in Merkel cell carcinoma patients. J Eur Acad Dermatol Venereol 2014;28:298–308.
35. Gugatschka M, Kiesler K, Obermayer-Pietsch B, Groselj-Strele A, Griesbacher A, Friedrich G. Vitamin D status is associated with disease-free survival and overall survival time in patients with squamous cell carcinoma of the upper aerodigestive tract. Eur Arch Otorhinolaryngol 2011;268:1201–4.
36. Meyer F, Liu G, Douville P, Samson E, Xu W, Adjei A, et al. Dietary vitamin D intake and serum 25-hydroxyvitamin D level in relation to disease outcomes in head and neck cancer patients. Int J Cancer 2011;128:1741–6.
37. Ren C, Qiu MZ, Wang DS, Luo HY, Zhang DS, Wang ZQ, et al. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. J Transl Med 2012;10:16.
38. Cho M, Peddi PF, Ding K, Chen L, Thomas D, Wang J, et al. Vitamin D deficiency and prognostics among patients with pancreatic adenocarcinoma. J Transl Med 2013;11:206.
39. Fang F, Kasperzyk JL, Shui I, Hendrickson W, Hollis BW, Fall K, et al. Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. PLoS ONE 2011;6:e18625.
40. Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. Br J Cancer 2009;100:450–4.
41. Buttigliero C, Monagheddu C, Petroni P, Saini A, Dogliotti L, Ciccone G, et al. Prognostic role of vitamin d status and efficacy of vitamin D supplementation in cancer patients: a systematic review. Oncologist 2011;16:1215–27.

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

42. Friedman CF, DeMichele A, Su HI, Feng R, Kapoor S, Desai K, et al. Vitamin d deficiency in postmenopausal breast cancer survivors. J Womens Health 2012;21:456–62.
43. Neuhouser ML, Sorensen B, Hollis BW, Ambs A, Ulrich CM, McTiernan A, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. Am J Clin Nutr 2008;88:133–9.
44. Peppone LJ, Rickles AS, Janelsins MC, Insalaco MR, Skinner KA. The association between breast cancer prognostic indicators and serum 25-OH vitamin D levels. Ann Surg Oncol 2012;19:2590–9.
45. Ulrich CM, Holmes RS. Shedding light on colorectal cancer prognosis: vitamin d and beyond. J Clin Oncol 2008;26:2937–9.
46. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76–89.
47. Centers for Disease and Control. Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S Population. Atlanta (GA): National Center for Environmental Health; 2012.
48. Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, et al. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. Breast Cancer Res Treat 2010;119:111–8.
49. Crew KD, Shane E, Cremers S, McMahon DJ, Irani D, Hershman DL. High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol 2009;27:2151–6.
50. Churilla TM, Lesko SL, Brereton HD, Klem M, Donnelly PE, Peters CA. Serum vitamin D levels among patients in a clinical oncology practice compared to primary care patients in the same community: a case-control study. BMJ Open 2011;1:e000397.
51. Santini D, Galluzzo S, Vincenzi B, Zoccoli A, Ferraro E, Lippi C, et al. Longitudinal evaluation of vitamin D plasma levels during anthracycline- and docetaxel-based adjuvant chemotherapy in early-stage breast cancer patients. Ann Oncol 2010;21:185–6.
52. Fakih MG, Trump DL, Johnson CS, Tian L, Muindi J, Sunga AY. Chemotherapy is linked to severe vitamin D deficiency in patients with colorectal cancer. Int J Colorectal Dis 2009;24:219–24.
53. Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol 2006;54:301–17.
54. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351:805–6.
55. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28.
56. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713–6.
57. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997;7:439–43.
58. Vashi PG, Trukova K, Lammersfeld CA, Braun DP, Gupta D. Impact of oral vitamin D supplementation on serum 25-hydroxyvitamin D levels in oncology. Nutr J 2010;9:60.

Published OnlineFirst April 1, 2014; DOI: 10.1158/1055-9965.EPI-14-0053

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Circulating 25-hydroxyvitamin D Levels and Prognosis among Cancer Patients: A Systematic Review

Adetunji T. Toriola, Nhi Nguyen, Kristen Scheitler-Ring, et al.

Cancer Epidemiol Biomarkers Prev 2014;23:917-933. Published OnlineFirst April 1, 2014.