Prevalence of serum vitamin D deficiency and insufficiency in cancer: Review of the epidemiological literature

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Abstract. Vitamin D deficiency has been found to be associated with a variety of cancers, including prostate, multiple myeloma, colorectal and breast cancer. Several studies have shown vitamin D levels to have an inverse relation with cancer mortality, while others have considered it a potential risk factor. Vitamin D is believed to influence cancer prevalence, risk and survival; hence the need to assess vitamin D levels in cancer. Although numerous studies have been conducted to demonstrate vitamin D deficiency as a risk factor for cancer, relatively few have studied its prevalence. Moreover, studies estimating prevalence differ from each other, with respect to study population, sample size, study design, definition of vitamin D deficiency used and method of vitamin D assessment (with most studies limited to one particular type of cancer with relatively small sample sizes). Therefore, we qualitatively reviewed the epidemiological evidence in the oncology literature on the prevalence of vitamin D deficiency and insufficiency as measured by serum vitamin D concentrations.

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Introduction

Vitamin D is the prehormone important for maintaining normal calcium homeostasis and mineralization of the skeleton. Humans acquire vitamin D from exposure to sunlight, from their diet and from dietary supplements (1). Vitamin D produced in the skin upon sun exposure or ingested from the diet is converted in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D used for evaluating the vitamin D status of patients. 25(OH)D is hydroxylated in the kidneys to form the biologically active metabolite 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] (1,2).

Although the biologically active form of vitamin D is 1,25(OH)$_2$D, it is not considered a good biomarker due to its short half-life and tight homeostatic control (3). Serum 25(OH)D is an excellent biomarker of vitamin D status, representing both cutaneous synthesis and dietary intake (4). Adequate levels of vitamin D depend on age and therefore definitions of vitamin D deficiency vary. The appropriate thresholds for vitamin D deficiency are debated (4,5). The most widely accepted optimal level of serum 25(OH)D is 35-55 ng/ml. One study showed that for all health-related end points, the most advantageous serum levels for 25(OH)D appear to be at least 30 ng/ml, and for cancer prevention desirable levels are between 36 and 48 ng/ml (6). The average older man and woman need intakes of at least 20-25 mcg (800-1,000 IU) per day of vitamin D to reach a serum 25(OH)D level of 30 ng/ml.

Brain, prostate, breast and colon tissues, among others, as well as immune cells, have a vitamin D receptor (VDR) and respond to 1,25(OH)$_2$D, the active form of vitamin D. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase that converts 25(OH)D to 1,25(OH)$_2$D (7,8). The active form of vitamin D has been shown to exert potent cell regulatory effects in cells other than those involved in calcium homeostasis. The effects are thought to be mediated through the VDR (9). Binding of VDR by 1,25(OH)$_2$D leads to multiple cellular effects, including induction of differentiation and apoptosis (10,11) and inhibition of proliferation (12), angiogenesis (13) and metastatic potential (14,15). Thus, vitamin D is believed to play an important role in the etiology and treatment of cancer.

Vitamin D deficiency has been found to be associated with a variety of cancers, including prostate (16,17), multiple myeloma, colorectal and breast cancer (18). Certain studies

have shown vitamin D levels to have an inverse relation with cancer mortality (19-25), while others have considered it a potential risk factor. Higher vitamin D concentrations are associated with a 3-fold decreased risk for pancreatic cancer (highest vs. lowest quintile, >26.2 vs. <12.8 ng/ml) (26). Grant demonstrated that much of the geographic variation in cancer mortality rates in the US can be attributed to variations in solar UV-B radiation exposure. Clearly, improving vitamin D status appears vital to overall health, particularly in non-summer months (27). The evidence that higher 25(OH)D levels through increased sunlight exposure or dietary supplement intake inhibit colorectal carcinogenesis is substantial (28,29). The biologic evidence for an anti-cancer role of 25(OH)D is also strong for prostate cancer, but the epidemiologic data have not been supportive (30). The above data indicate that vitamin D influences cancer prevalence, risk and survival and hence the need to assess vitamin D levels in cancer.

Although numerous studies have been conducted to demonstrate vitamin D deficiency as a risk factor for cancer, relatively few have studied its prevalence. Most of the studies estimating prevalence have been limited to one particular type of cancer with relatively small sample sizes. Therefore, we qualitatively reviewed the epidemiological evidence in the literature on the prevalence of vitamin D deficiency and insufficiency as measured by serum 25(OH)D concentrations.

2. Search strategy and selection criteria

We performed a systematic search of the literature using the MEDLINE database (January 2000 through May 2010) to identify articles on the prevalence of serum vitamin D deficiency and insufficiency in cancer. We searched using the terms 'cancer/carcinoma' in combination with 'vitamin D deficiency', 'vitamin D insufficiency' and 'serum vitamin D/25(OH)D levels/concentration'. We also searched the bibliographies of the selected studies to identify relevant articles that we might have missed during the primary MEDLINE search. To be included in the review, a study must have been published in English, must have reported on data collected in humans with cancer, must have had measured serum vitamin D or serum 25(OH)D at single or multiple time points and must have utilized any of the following study designs (case-control, cohort, cross-sectional, prospective, retrospective, case series, longitudinal, clinical trial). There were no restrictions according to age, ethnicity, type or stage of cancer. As we were interested in empirical reports that had investigated the prevalence of serum vitamin D deficiency and insufficiency in cancer, we did not include letters and meeting abstracts. All studies reviewed in this report are summarized in tables under separate headings and arranged chronologically by the year of publication.

3. Quality assessment

Although we did not formally rate the quality of reports we reviewed, we recorded and presented information on variables that may reflect the quality of reporting. The variables included years of data collection, study design, sample size, cancer type and stage, definition of vitamin D deficiency used, vitamin D assessment method, prevalence reported and supplementation recommended.

4. Studies on deficiency and insufficiency of serum vitamin D in breast cancer

Table I describes studies investigating the deficiency and insufficiency of serum vitamin D in patients with breast cancer. The studies are arranged chronologically by the year of publication.

Nogues *et al* reported a prevalence of 85-92% of vitamin D deficiency in breast cancer patients. In their study, treatment with 16,000 IU of vitamin D every 2 weeks increased vitamin D plasma levels significantly in ~76.5% of subjects with baseline vitamin D deficiency (plasma levels <30 ng/ml) over 3 months of follow-up. Notably, in the few subjects that had baseline vitamin D levels ≥30 ng/ml, despite being prescribed vitamin D supplements (800 IU), their vitamin D levels did not increase significantly (31). Neuhouser *et al* assessed serum 25-25(OH)D status and its relationship to breast density in 426 breast cancer survivors. Most participants (76.8%) had vitamin D insufficiency or frank deficiency. No association of serum 25(OH)D with either breast density or breast dense area was observed. It was concluded that, despite the strong association of mammographic density with breast cancer risk, the mechanism is not likely to be mediated by vitamin D (32). Khan *et al* reported the safety and efficacy of vitamin D supplementation using 50,000 IU weekly on post-menopausal women. In their study, the prevalence of vitamin D deficiency was 63%. They also studied the effect of vitamin D-ss (standard supplementation) and vitamin D-HD (high dose) supplementation on serum 25(OH)D levels. Their results suggested that 50,000 IU of vitamin D3, when administered weekly to postmenopausal women starting adjuvant letrozole, resulted in clinically significant improvement in disability from joint symptoms (33).

Crew *et al* reported a prevalence of 74% of vitamin D deficiency in breast cancer patients. They also observed that 400 IU of cholecalciferol daily for 1 year increased serum 25(OH)D levels only modestly, by <3 ng/ml, in only 15% of premenopausal women. Although the DRI for vitamin D in pre-menopausal women is only 200 IU daily, their study suggested that a dose of 400 IU daily was inadequate in breast cancer patients, even to maintain skeletal health, and was probably too low for meaningful anticancer effects (34). Rainville *et al* observed the vitamin D status in different breast cancer phenotypes: luminal A, luminal B, HER2+/ER- and triple-negative. When assessing all of the breast cancer patients (91 total), it was found that 54 patients (62%) had baseline vitamin D levels in the deficiency range <32 ng/ml. Thirteen of the fifteen triple-negative breast cancer patients (87%) were found to be vitamin D deficient, prior to initiation of adjuvant therapy. These data may suggest that low vitamin D levels are more prevalent in triple-negative phenotype (35). Waltman *et al* determined whether serum 25(OH)D concentrations were below normal (<30 ng/ml) in 29 breast cancer survivors receiving aromatase inhibitor therapy and whether musculoskeletal symptoms were related to these low vitamin D levels. The mean (SD) serum 25(OH)D level was 25.62 (4.93) ng/ml; 86% (n=25) had levels <0 ng/ml. The prevalence of vitamin D insufficiency in this sample was high despite the fact that their mean daily intake of vitamin D supplements was 665 IU and the mean time in the sun in the past week was reported as 39 min (36).

Table I. Studies investigating the deficiency and insufficiency of serum vitamin D in patients with breast cancer.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency	Recommended supplementation with vitamin D
Nogues X, 2010, Spain (31)	Jan. 2006-Dec. 2008	Prospective non-randomized clinical trial, 232	Breast	Deficiency, <30 Severe deficiency, <10	Competitive immuno-luminometric direct assay with direct-coated magnetic microparticles (DiaSorin Iberia SA, Madrid, Spain)	Overall prevalence: Deficiency, 88.1%; Severe deficiency, 21.2% January-March (n=50): Deficiency, 92%; Severe deficiency, 46% April-June (n=54): Deficiency, 90.6%; Severe deficiency, 20.8% July-September (n=46): Deficiency, 5.7%; Severe deficiency, 7.1% October-December (n=82): Deficiency, 85.2%; Severe deficiency, 13.6%	16,000 IU every 2 weeks
Neuhouser ML, 2010, USA (32)	New Mexico, July 96-Mar. 99, Washington, Sept. 97-Sept. 98, Los Angeles, May 95-May 98	Health, Eating, Activity and Lifestyle (HEAL) study – a population based, multicenter, multiethnic prospective cohort study, 426	Breast (in situ, stage I or stage II-IIIA)	Insufficient, <16 Borderline sufficient, 16-32 Adequate, ≥32	The Medical University of South Carolina using a radioimmunoabsorbant assay (DiaSorin, Inc., Stillwater, MN, USA)	Serum vitamin D (ng/ml) [mean (SD)] 24.6 (9.77) Insufficient pts, 103/426 (24.2%) Borderline pts, 224/426 (52.58%) Adequate pts, 99/426 (23.2%)	NA
Khan QI, 2010, USA (33)	NA	Prospective clinical trial, 60	Breast	Deficiency, ≤20 Insufficiency, 21-31 Optimum, 40	Quest Diagnostics	Deficiency, 18/60 (30%) Insufficiency, 20/60 (33%) Optimum, 22%	50,000 IU weekly for pts with serum levels <40 ng/ml
Crew KD, 2009, USA (34)	Mar. 2002-June 2006	Prospective, 103	Breast	Severe deficiency, <12 Deficiency, <20 Insufficiency, 20-29 Sufficiency, ≥30	Radioimmunoassay (RIA) (DiaSorin, Inc.)	Deficiency, 74% (median 17 ng/ml), White women, 66% Black, 80%, Hispanic, 84% Severe deficiency, 12% Sufficiency, 6%	Women in the general population and breast cancer to consume vitamin D up to 3,000 IU daily to increase serum 25-OHD to sufficient levels
Rainville C, 2009, USA (35)	NA	Case series, 91 (luminal A=65, luminal B=6, HER2⁺/ER⁻, 5 and triple⁻, 15)	Breast	Deficiency, <32	Immunodiagnostic System (IDS) kit by EIA method was used on a DSX system analyzer by DYNEX	In total breast cancer patients, 54/91 (62%) Triple-negative breast cancer, 13/15 (87%)	2,000 IU daily, orally, in combination with moderate sunlight is usually enough to raise serum 25(OH)D levels to 52 ng/ml

Table I. Continued.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency (ng/ml)	Recommended supplementation with vitamin D
Waltman NL, 2009, USA (36)	NA	Pilot exploratory study, 29	Breast, *In situ* (n=1), Stage I (n=15), Stage II (n=13)	Deficiency, <10 Severe insufficiency, 10-19 Moderate insufficiency, 20-29 Optimal, >30	25(OH)D I-radioimmunoassay (DiaSorin, Inc.)	Overall prevalence: <30, 25/29 (86%) <10, 0 (0%) 10-19, 2 (6.9%) 20-29, 23 (79.3%) >30, 4 (13.8%) Serum 25(OH)D levels: Mean 25.62 Standard deviation 9.23 Range 17-41	≥2,000 IU daily to maintain optimal bone health
Neuhouser ML, 2008, USA (37)	1995-1999	Cross-sectional, 790	Breast, Localized 424 Regional 182 *In situ* 184	Frank deficiency, <10 Insufficiency, 10 to <32 Sufficiency, ≥32	Radioimmunoabsorbant assay (DiaSorin, Inc.)	Deficiency/insufficiency prevalence in all pts, 597/790 (75.6%) Frank deficiency, 49 women (6.2%) Insufficiency, 548 women (69.4%)	NA
Wang-Gillam A, 2008, USA (38)	1st June 2002-30th Sept. 2006	Retrospective, 209	Breast	Deficiency, <20	NA	<10, 15/209 (7.2%) 10-19, 42/209 (20.1%) 20-30, 71/209 (34%) >30, 81/209 (38.8%)	50,000 IU of vitamin D twice weekly for 8-10 weeks
De Lyra EC, 2006, Brazil (39)	June 2001-Mar. 2005	Prospective study, 88 with breast cancer and 35 without	Breast, (clinical stages I to IV)	NA	¹²⁵I radioimmunoassay (RIA) kit (DiaSorin, Inc.)	Serum levels of 25(OH)D3 in breast cancer pts classified by clinical stage (CS): CS I, II (n=44), 36±16 CS III, IV (n=15), 41±20	NA
Palmieri C, 2006, UK (40)	NA	Prospective observational, 279 Caucasian women	Breast, (stage I or II, 204; stage III or IV, 75)	NA	Radioimmunoassay (ImmunoDiagnostic Systems, IDS, Boldon, UK)	Early stage (I and II): Range 6-73.6 Mean 22.8 95% CI 21.08-24.2 Stage III or metastatic stage IV: Range 6.4-28.4 Mean 18.4 95% CI 16.36-20.72	NA

Neuhouser *et al* described the vitamin D status in a breast cancer survivor cohort of 790 women. Five hundred and ninety-seven (75.6%) of the women had low serum 25(OH) D, suggesting vitamin D insufficiency of 69.4% (levels from 10 to <32 ng/ml) and frank deficiency of 6.2% (levels <10 ng/ml). Women with localized (n=424) or regional (n=182) breast cancer had lower serum 25(OH)D than did women with *in situ* disease (n=184) (P=0.05 and P=0.03, respectively) (37). Wang-Gillam *et al* examined the prevalence of vitamin D deficiency in 321 breast cancer patients treated with bisphosphonates. Two hundred and nine (65.1%) had their 25(OH) D levels checked at least once. Of these patients, 57 (27.3%) had a serum 25(OH)D level <20 ng/ml. Only 113 (42.3%) of 267 patients who were prescribed a bisphosphonate for osteoporosis also took a daily vitamin D supplement, and among metastatic bone disease patients, the rate for vitamin D supplementation was even lower at 13.0%. The study hypothesized that low rates of vitamin D supplementation could be one reason for vitamin D deficiency (38). De Lyra *et al* investigated the serum levels of 25(OH)D3 and its active form 1,25(OH)$_2$D3 in 88 Brazilian breast cancer patients and 35 women without cancer. Although no differences in 25(OH) D3 serum concentration were found, 1,25(OH)$_2$D3 (40±21 pg/ml) levels in breast cancer patients were lower than in women without cancer (53±23 pg/ml). The lack of a difference in the serum levels of 25(OH)D3 between women with and without breast cancer supports the probability that a low circulating concentration of 1,25(OH)$_2$D3 in breast cancer patients is not attributed to 25(OH)D3 insufficiency (39). Palmieri *et al* prospectively measured circulating levels of 25(OH)D in 279 Caucasian women with invasive breast cancer, 204 women with early-stage disease and 75 women with locally advanced or metastatic disease. The results depicted that patients with early-stage breast cancer had significantly higher circulating levels of 25(OH)D (mean serum levels 22.8 ng/ml) than those with advanced disease (mean serum levels 18.4 ng/ml) (P<0.005) (40).

5. Studies on deficiency and insufficiency of serum vitamin D in colorectal cancer

Table II describes studies investigating the deficiency and insufficiency of serum vitamin D in patients with colorectal cancer (CRC). The studies are arranged chronologically by the year of publication.

Charalampopoulos *et al* determined the serum levels of vitamin D metabolites and parathyroid (PTH) in patients with colorectal cancer and found: i) no significant difference in the serum levels of 25(OH)D3 in each Dukes' clinical stage in cancer patients, ii) serum 1,25(OH)$_2$D3 levels decreased with advanced cancer stages, and iii) serum levels of PTH showed a corresponding increase with advanced cancer stages. Low serum levels of 1,25(OH)$_2$D3 on one hand, and increased levels of PTH in patients with colorectal cancer on the other, may be strongly related to the carcinogenetic process (41). Fakih *et al* carried out a study in the US comprising 315 patients with CRC, where 25-OH vitamin D status was dichotomized into two categories; 'very low' (<15 ng/ml) and 'low to normal' (>15 ng/ml). Twenty-nine out of 135 (21%) patients in stage 1 to 3 of CRC had serum levels of vitamin D in the 'very low'

category along with 58 out of 180 (32%) patients in stage 4. It was recommended that patients with CRC, particularly those receiving chemotherapy, should be considered for aggressive vitamin D replacement strategies (42). Niv *et al* demonstrated an inverse correlation between serum levels of the active metabolite of vitamin D and colorectal carcinoma stage. The study compared serum 1,25(OH)$_2$D3, 25(OH)D3 and PTH levels of colorectal carcinoma patients to those of healthy controls and found that serum vitamin D metabolite levels did not correlate with gender, age, tumor localization or histologic grade (43).

6. Studies on deficiency and insufficiency of serum vitamin D in other and multiple cancer sites

Table III describes studies investigating the deficiency and insufficiency of serum vitamin D in patients with other as well as multiple cancer sites. The studies are arranged chronologically by the year of publication.

Hofmann *et al* evaluated within-person variability in 25(OH)D concentrations across serum samples collected at three time points over a 5-year period among 29 participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. They observed relatively low within-subject variability and fairly high correlations in 25(OH)D measured from samples collected at study baseline, after 1 year and after 5 years. These findings suggest that serum 25(OH)D concentration at a single time point may be a useful biomarker of long-term vitamin D status in population-based studies of various diseases (44). Laney *et al*, in a recent pilot study, found the levels of vitamin D and the rates of vitamin D deficiency to be similar between patients with thyroid nodules, thyroid cancer in remission and active thyroid cancer. Vitamin D deficiency (<30 ng/ml) was not significantly different between groups and was not affected by season of measurement, age or cancer stage. This study did not find any association between vitamin D deficiency and the histologic type of thyroid cancer, the stage of thyroid cancer or the status of the disease (45). Thill *et al* evaluated the expression of the prostaglandin (PG)-metabolizing enzymes COX-2 and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) compared to the vitamin D receptor (VDR) in benign and malignant ovarian tissues. Additionally, they determined the 25(OH)$_2$D3 serum levels. They detected significantly higher expression of the PG-metabolizing enzymes 15-PGDH and COX-2 in malignant tissue, and PGE$_2$ serum levels were 2-fold higher in tumor patients. They found mean serum vitamin D levels to be 29.15±2.74 ng/ml in healthy women and 25.23±1.57 ng/ml in women with ovarian cancer (46).

McCombie *et al* recruited 25 patients with a history of non-melanoma skin cancer, who were not taking vitamin D or calcium supplements, from outpatient dermatology clinics at Royal Prince Alfred Hospital, Sydney. Using the target value of 20 ng/ml, 12 participants (48%) were vitamin D deficient at the end of winter, compared to one (4%) at the end of summer. Despite mean reported daily sun exposure falling within recommended guidelines, half of the participants were vitamin D deficient at the end of winter, with almost all demonstrating reductions in winter 25(OH)D levels (47). Nurnberg *et al* examined the association between serum

Table II. Studies investigating the deficiency and insufficiency of serum vitamin D in patients with colorectal cancer.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency (ng/ml)	Recommended supplementation with vitamin D
Charalampopoulos A, 2010, Greece (41)	NA	Prospective study, 140 cancer pts and 48 healthy individuals	Colorectal (clinical stages Duke's A=12, B=52, C=62 and D=14)	NA	Radioimmunoassay	Mean serum levels: In cancer pts, 70 In controls, 72 Range 38-98	NA
Fakih MG, 2009, USA (42)	1st April 2006-31st Jan. 2007	Retrospective, 315 (stages 1 to 3, 135 pts, stage 4, 180 pts)	Colorectal (stages 1 to 4)	Very low, ≤15 Low to normal, >15	Immunochemiluminometric assay (ICMA)	Pts with <15: Stages 1 to 3, 29/135 (21.4%) Stage 4, 58/180 (32.2%) Males, 42/173 (24.2%) Females, 45/142 (31.6%) Rectal, 34/94 (36.1%) Colon, 53/221 (23.9%)	Aggressive vitamin D with dosages exceeding 400 IU/day to be considered in deficient patients
Niv Y, 1999, Israel (43)	NA	Case control, 84 cancer pts and 30 controls	Colorectal (stages 1 to 4)	NA	The 25(OH)D3 fraction was submitted to a competitive protein binding assay using diluted rachitic rat serum as the binding protein	Serum levels (mean ± SD) of vitamin D: Stage 1 (n=10), 27.0±9.9 Stage 2 (n=29), 28.4±9.5 Stage 3 (n=25), 27.8±9.4 Stage 4 (n=20), 24.5±5.1 Controls (n=30), 21.7±5.7 Males, 27.1±8.6 in cancer pts and 21.1±5.2 in controls Females, 27.3±9.1 in cancer pts and 23.4±7.1 in controls	NA

25(OH)D levels and clinical and histopathological data among 205 patients with malignant melanoma. Serum 25(OH)D levels were significantly reduced in stage IV melanoma patients as compared to stage I melanoma patients (P=0.006). They also found a trend towards a greater tumor thickness with low (<10 ng/ml) serum 25(OH)D levels (median 2.55 mm) as compared to those with 25(OH)D serum levels >20 ng/ml (median 1.5 mm). Lastly, the patients with low 25(OH)D serum levels (<10 ng/ml) had earlier distant metastatic disease (median 24.37 months) as compared to those with 25(OH)D serum levels >20 ng/ml (median 29.47 months) (48). Trump et al in a case control study found the frequency of vitamin D deficiency (<20 ng/ml) and insufficiency (20-31 ng/ml) to be 40 and 32%, respectively in men with recurrent prostate cancer. Among men with localized prostate cancer, 18% were deficient, 50% were insufficient and 32% were normal. Among controls, 31% were deficient, 40% were insufficient and 29% were normal. This study clearly showed a high frequency of abnormally low 25-OH vitamin D levels among patients with prostate cancer, regardless of disease status or treatment (49).

Badros et al measured the prevalence of vitamin D deficiency in 100 multiple myeloma (MM) patients and showed that 40% had vitamin D deficiency, defined by serum 25(OH)D levels <14.4 ng/ml. Thirty-five percent had vitamin D insufficiency, defined by levels of 14.4-30 ng/ml. Only 25% had sufficient levels, defined as >30 ng/ml. They found no significant correlation between vitamin D status and MM activity (remission, relapsed or newly diagnosed), presence or absence of lytic bone disease and/or fractures or history of osteonecrosis of the jaw (50). Everett et al conducted a study in patients at the Lynchburg Hematology-Oncology Clinic, where the number of patients tested for the first time from May to September were 86, 89, 72, 59 and 81, respectively. Of those tested, most had vitamin D levels <30 ng/ml (75.4, 84.1, 66.6, 69.3 and 63%, respectively). The study concluded that oncology clinicians must be aware of the potential negative effects of low vitamin D levels in their patient populations and should consider testing for and treating this deficiency or insufficiency in their practices (51). Reinhold et al measured the serum 25(OH)D concentration among subjects in a German polyclinic. In >50% of these 174 subjects, the 25(OH)D concentration was <20 ng/ml. In most subject groups, a seasonal decrease of 25(OH)D concentration was observed during the winter period. An age-related decrease in such a concentration was also observed in subjects with prostatic hyperplasia examined in the late summer/early autumn period and in female cancer subjects, at the exclusion of patients with breast cancer. In the latter patients, however, a positive correlation prevailed between age and 25(OH)D concentration (52).

Hollender et al carried out a study in patients treated for gastric non-Hodgkin's lymphoma and found that of 33 patients out of 40 who met for follow-up examination after treatment, 17 patients had a partial gastrectomy (PG), 9 a total gastrectomy (TG) and 7 patients were not operated on. The patients in the TG group had significant weight loss. Moreover, the patients in the TG group had a lower serum vitamin D than the other groups. They further concluded that when surgery is necessary, a PG should be performed when possible and that patients should receive dietary advice before leaving the hospital after surgery and possibly life-long iron, calcium, vitamin D,

folate and vitamin B12 supplementation (53). Lammert et al measured serum 25(OH)D concentrations in 55 patients with neurofibromatosis 1 (NF1) and 58 healthy controls. The mean serum 25(OH)D concentration was 14.0 ng/ml among the patients with NF1 compared to 31.4 ng/ml among the healthy controls (P=0.0001). The strong correlation observed between NF1 patients and low serum vitamin D concentrations was unexpected. It is possible that patients with NF1 with multiple dermal neurofibromas are more likely to cover their skin and thus receive less sunlight than patients with NF1 who have fewer dermal tumors (54). Plant and Tisman demonstrated that out of 60 patients of different cancer types, when 25(OH)D insufficiency was defined as a serum level of <30 ng/ml, 43 (72%) patients were found to be insufficient. Even at the lower definition of insufficiency, <20 ng/ml, 24 of 60 patients (40%) were insufficient. This study showed that the deficiency of vitamin D (72%) was prevalent among newly diagnosed patients with cancer and could play a role in cancer development and host response to tumor and therapy (55).

Reichrath and Querings tested the hypothesis whether low serum levels of 25(OH)D may be a risk factor for the development of malignant melanoma. This study found that the mean (23.563 ng/ml) and median (24.591 ng/ml) 25(OH)D serum levels of these melanoma patients were in the normal range (20-50 ng/ml), indicating no relationship between serum levels of 25(OH)D and development of malignant melanoma (56). Tangpricha et al determined the prevalence of vitamin D deficiency in an outpatient cancer care clinic at Boston University Medical Center. A control group of healthy adults without cancer was recruited the previous year during the same months. Of the 56 patients with cancer, 27 (48%) had vitamin D deficiency (≤ 20 ng/ml), in comparison to only 6 (12%) of the 50 healthy control subjects (57).

7. Discussion

Vitamin D inadequacy constitutes a largely unrecognized epidemic in many populations worldwide (58-60). It has been reported in healthy children (61), adolescents (62) and adults (63,64). Lower vitamin D levels are associated with advancing age (65,66), female gender (67-69), history of diabetes (70), hypertension, greater body mass index (71) and a lower estimated glomerular filtration rate (72). Vitamin D levels vary by region and are greater in summer than in winter months (73,74). Higher skin melanin levels increase the risk of vitamin D deficiency. Of late, there has been an increasing interest in the role of vitamin D in cancer etiology and outcomes and, as a result, several studies have reported the prevalence of vitamin D deficiency and insufficiency in patients with different types of cancer. However, the existing studies on this topic differ from each other with respect to study population, sample size, study design, definition of vitamin D deficiency used and method of vitamin D assessment. Therefore, we conducted a qualitative review of the existing literature with the goal of understanding the current status and providing insights on the directions for future research.

Twenty-seven studies were reviewed and most (n=12) were conducted prospectively to assess the 25(OH)D serum levels in different types of cancer patients. The other studies included retrospective (n=3), cross-sectional (n=2), case series

Table III. Studies investigating the deficiency and insufficiency of serum vitamin D in patients with other and multiple cancer sites.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency (ng/ml)	Recommended supplementation with vitamin D
Hofman JN, 2010, USA (44)	NA	29 participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Prostate, lung, colorectal and ovarian cancer screening pts	NA	Heartland Assays, Inc. (Ames, IA, USA) by competitive chemiluminescence-immunoassay using the DiaSorin Liaison 25-OH Vitamin D TOTAL Assay, Italy	Serum levels at baseline (n=28) Mean (SD) 24.0 (14.6), Median 24.08, Range 13.48-39.84 at 1 year (n=29) Mean (SD) 23.92 (15.9), Median 23.8, Range 11.44-37.68 at 5 years (n=26) Mean (SD) 22.64 (16.2), Median 22.04, Range 9.64-39.28	NA
Laney N, 2010, USA (45)	15th Dec. 2001-6th Feb. 2009	Retrospective pilot study, 111; active thyroid cancer, 24; remission, 45; non-cancer controls with thyroid nodules, 42	Thyroid	Deficiency, <30	Tandem mass spec for pts not on supplemental vitamin D >800 IU per day. If they were receiving vitamin D >800 IU per day, levels were assayed utilizing either Diaosrin or Nichols assays	Active thyroid cancer, 42% Thyroid cancer in remission, 44% Thyroid nodules, 52% Active thyroid cancer: <19, 0/24 (0%) 10-30, 11/24 (46%) >30, 13/24 (54%) In remission: <10, 2/45 (4%) 10-30, 18/45 (40%) >30, 25/45 (56%) Thyroid nodules: <10, 1/42 (2%) 10-30, 22/42 (52%) >30, 19/42 (45%)	NA
Thill M, 2010, Germany (46)	Oct.-Feb.	Prospective non-consecutive case series, Tumor pts, 20 Healthy pts, 20	Primary ovarian carcinoma	NA	Elecsys chemiluminescent immunoassay (Roche Diagnostics Germany)	Mean vitamin D serum levels: Healthy women, 29.15±2.74 Ovarian cancer, 25.32±1.57	NA
McCombie AM, 2009, Australia (47)	Feb. 2006 and Feb. 2007 and Aug. 2006	Prospective, 25	Non-melanoma skin	Frank deficiency, <10 Marginal deficiency, 10-20 Suboptimal, <32	Radioimmunoassay (DiaSorin, Saluggia, Italy)	Using target value of 20 ng/ml: Vitamin D deficiency at the end of winter, 12/25 (48%) and at the end of summer, 1/25 (4%) Significant reduction in mean 25(OH)D levels in winter (summer, 27.6±1.36; winter, 23.6±2.48; P<0.05)	NA

Table III. Continued.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency (ng/ml)	Recommended supplementation with vitamin D
Nurnberg B, 2009, Germany (48)	Dec. 1997-Mar. 2007	Retrospective study, 205 cancer pts, 141 healthy controls	Malignant melanoma	Deficiency, <20	Liaison 25-OH Vitamin D-Assay (DiaSorin, Dietzenbach, Germany)	<20 in melanoma, 160/205 (78.1%) in controls, 89/141 (63.1%); <10 in melanoma, 41/205 (20%) in controls, 39/141 (27.7%); >20 in melanoma, 45/205 (22%) in controls, 52/141 (36.9%); Median melanoma, 14.3 controls, 15.6; Mean melanoma, 16.9; controls, 18.7	A single dose of 50,000 IU vitamin D once a week for 8 weeks or 50,000 IU of vitamin D once a month
Trump DL, 2009, USA (49)	1st Jan. 2005-28th Feb. 2007	Case control, 120 recurrent cancer pts, 50 localized cancer pts and 100 controls	Prostate	Deficiency, <20 Insufficiency, 20-31 Normal, 32-100	Recurrent cancer pts using a commercial immunochemiluminometric assay, and localized cancer pts and controls using a radioimmunoassay	Prevalence in recurrent prostate pts: Deficiency, 48/120 (40%) Insufficiency, 38/120 (32%) Normal, 34/120 (28%) In localized prostate cancer: Deficiency, 9/50 (18%) Insufficiency, 25/50 (50%) Normal, 16/50 (32%) In controls: Deficiency, 31/100 (31%) Insufficiency, 40/100 (40%) Normal, 29/100 (29%)	NA
Badros A, 2008, USA (50)	Sept.-Oct. 2006	Prospective consecutive case series, 100	Multiple myeloma	Deficiency, ≤14.4 Insufficiency, 14.4-30 Sufficiency, >30	NA	Deficiency, 40/100 (40%) (male, 20; female, 20) Insufficiency, 35/100 (35%) (male, 14; female, 21) Sufficiency, 25/100 (25%) (male, 8; female, 17)	For levels ≤14.4 ng/ml, 50,000 IU twice weekly for 6 weeks; For levels 14.4-30 ng/ml, 50,000 IU weekly for 6 weeks, then 1,000 IU/day
Everett PC, 2008, USA (51)	May-Sept. 2006	NA, 387 (May, 86; June, 89; July, 72; Aug., 59; Sept., 81)	NA	Deficiency, <10 Insufficiency, 10.1-31.9	NA	Deficiency in pts: <30 ng/ml May, 75.4%; June, 84.1%; July, 66.6%; Aug., 69.3%; Sept., 63%	50,000 IU daily for 1 week, then 50,000 IU 1-3 times/week until 50-75 ng/ml, then 1,666 IU daily

Table III. Continued.

First author, year, place (ref.)	Data collection	Study design, sample size	Cancer type, stage	Definition of vitamin D deficiency (ng/ml)	Method of vitamin D measurement	Prevalence of vitamin D deficiency (ng/ml)	Recommended supplementation with vitamin D
Reinhold U, 2008, Germany (52)	NA	Prospective study, 174 subjects (97 cancer pts)	Prostatic carcinoma (n=20), prostatic hyperplasia (n=75), melanoma (n=41), breast (n=26), ovarian (n=7), cervix (n=3)	Deficiency, <20	Radioimmunoassay (DiaSorin, Inc.)	Prevalence of vitamin D levels <20: >50% pts out of total 174 Prostate: <70 years mean levels, 24.2±1.8 >70 years, 7/8 with levels <20 during winter (mean 20.3±3.1) and 3/6 with levels <20 during late summer (mean 14.7±2.5) Melanoma: mean levels during winter/ early spring (n=15), 13.0±1.6; during late summers (n=7), 22.0±3.2 Ovarian and cervix <20, 7/10 Breast <20: <56 years, 12/13, ≥56 years, 4/13	NA
Hollender A, 2006, Norway (53)	1990-1999 (follow-up: May-June 2001)	Prospective cross-sectional study, 33	Gastric non-Hodgkin's lymphoma	Reference value for 25(OH)D, 12-44	High-performance liquid chromatography at Hormone Laboratory, Aker University Hospital	Patients with vitamin D <12: Total gastrectomy, 5/9 (55.55%) Partial gastrectomy: Billroth II, 1/10 (10%) Billroth I, 0/4; Local resection, 0/3 Radiation therapy, 0/7	NA
Lammert M, 2006, Germany (54)	NA	Convenient sample, Neurofibromatosis (NF1), 55 Healthy controls, 58	Dermal neurofibromas	Deficiency, <20	Automated chemiluminescence protein binding assay (Nichols Institute Diagnostics, San Clemente, CA, USA)	Deficiency in patients with NF1, 72% In controls, 21% Deficiency in patients with dermal neurofibromas: 10-99 fibromas, 9/16 (56%) 100-999 fibromas, 20/24 (83%) ≥1,000 fibromas, 6/7 (86%)	NA
Plant AS, 2006, USA (55)	NA	Prospective, 60	Breast (n=10), colon (n=15), lymphoma (n=3), prostrate (n=24), lung (n=2), other (n=16)	Low definition, <20 High definition, <30	Nichols Advantage assay kit (Nichols Institute Diagnostic)	Levels <20, 24/60 (40%) Levels <30, 43/60 (72%)	1,000-4,000 IU daily, orally, to maintain serum levels between 32 and 52 ng/ml
Reichrath J, 2004, Germany (56)	NA	Cross-sectional study, 14	Melanoma	Normal range, 20-50	Nichols Advantage assay, Nichols Institute Diagnostika GmbH, Bad Nauheim, Germany	Serum levels: Mean 23.563; median 24.591 Levels <20, 6/14 (42.8%) Levels 20-50, 8/14 (57.1%)	NA
Tangpricha V, 2004, USA (57)	July, Aug. and Sept.	Case control, 56 cancer pts and 50 healthy controls	All patients in the outpatient cancer clinic	Deficiency, ≤20	Nichols Advantage chemiluminescent assay	Deficiency in cancer pts, 27/56 (48%) Deficiency in controls, 6/50 (12%) Mean values 21.3±10 for cancer vs. 33.9±10 for healthy controls	50,000 IU once a week for 8 weeks, then 400 IU daily as a maintenance dose

(n=1), convenience sample (n=1) and case-control study (n=2) designs. Furthermore, two studies used data from other existing studies with a larger sample size, such as The Health, Eating, Activity, and Lifestyle (HEAL) study and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). Ten studies were conducted in breast cancer patients exclusively, three on colorectal, two on melanoma and one each on gastric lymphoma, multiple myeloma, neurofibroma, prostate, ovarian, thyroid and non-melanoma skin cancers, while the remaining five studies were based on a heterogenous group of cancer patients.

While comparing the cut-off levels for definition of vitamin D deficiency, we found that the majority of the studies (n=11) used a threshold of <20 ng/ml. The other studies used different cut-offs ranging from 10 to 32 ng/ml. Most of the studies (n=10) measured the serum 25(OH)D levels using the radioimmunoassay, while some of the other studies used Nichols Advantage assay kit (n=3), high-performance liquid chromatography (n=1), protein binding assay (n=2), competitive immunoluminometric direct assay (n=2) and chemiluminescent immunoassay (n=2). Many of these studies showed a prevalence of vitamin D deficiency >70% (31,34-37,48,51,54). A few studies (n=9) reported a prevalence rate between 40 and 70%, while the other studies (n=4) reported rates lower than 40%. Six studies reported only the mean serum vitamin D levels.

Some studies provided an estimate of vitamin D deficiency across stage of the disease, as well as season of vitamin D assessment. An inverse correlation between serum levels of vitamin D and carcinoma stage was demonstrated in three studies (40,42,43). According to these studies, the serum levels of 25(OH)D were significantly higher in patients with early-stage cancer than in those with locally advanced or metastatic disease. An exception to this observation was one study on ovarian cancer patients (39) in which stage III and IV carcinoma patients had higher 25(OH)D serum levels than in stage I and II patients. A few studies also showed lower serum 25(OH)D levels in blood samples drawn during winter (31,47,52) depicting variations in the prevalence rate according to sun exposure. Some studies also reported results by gender. Badros *et al* reported an equal distribution of males and females with deficient serum 25(OH)D levels among patients with multiple myeloma (50). Similarly, in colorectal cancer patients, Fakih *et al* reported almost equal mean 25(OH)D levels among males and females (42). Moreover, Niv *et al* reported a higher prevalence rate of deficiency in females (31.6%) than in males (24.2%) among colorectal cancer patients (43). In addition, a study by Crew *et al* also reported that vitamin D deficiency was slightly less common in white women (66%) compared to black (80%) and Hispanic (84%) women (34).

Some studies also reported on supplementation recommendations to address vitamin D deficiency. Most studies suggested an aggressive vitamin D replacement strategy, including 50,000 IU weekly (n=3) or 50,000 IU twice a week (n=1) or 50,000 IU 1-3 times a week (n=1), while the others suggested a daily dose of vitamin D, including 2,000 IU (n=2) or 3,000 IU (n=1) orally. Thus, the recommended dosage by all studies ranged from 8,000 to 50,000 IU, one to three times a week for deficient patients. A few studies also suggested a maintenance dose regime ranging from 400 to 2,000 IU daily after the serum levels were raised to normal.

In conclusion, this review confirms a high prevalence of vitamin D deficiency in multiple cancer sites. Healthcare providers play important roles in disease prevention, health promotion and education. Since vitamin D deficiency is a widespread public health issue linked to cancer and other health risks, healthcare providers should not ignore this easily correctable condition. Therefore, evaluation of vitamin D levels and vitamin D supplementation for deficient individuals should be taken into consideration, while providing anticancer treatment. Optimizing vitamin D levels provides 'win-win' benefits of correcting vitamin D deficiency, promoting bone health and potentially reducing cancer risks. Given the variation found in the studies in this review regarding the levels of 25(OH)D used to define deficiency, the method used to evaluate 25(OH)D, and even recommendations for supplementation for deficient individuals, additional research needs to be carried out to determine acceptable standards in these areas.

Since the prevalence of vitamin D deficiency appears to be high in multiple cancer sites, future research evaluating the impact of correcting and maintaining adequate vitamin D levels on survival outcomes and secondary prevention of cancer is essential.

Acknowledgements

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