Low 25-hydroxyvitamin D levels in people with a solid tumor cancer diagnosis: the tip of the iceberg?

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Abstract

Purpose Low serum 25-hydroxyvitamin D [25(OH)D] levels have been linked to both cancer incidence and poor prognosis. The frequency of 25(OH)D tests and clinical factors associated with low levels in cancer patients are unknown.

Patients and methods Electronic medical records from 2006 to 2007 of 39,252 adult solid tumor patients were reviewed. Data included demographics, cancer sites (primary and metastatic), and first serum 25(OH)D level during the study period. Laboratory data, comorbidities, selected medications, and anticancer treatment within the prior 2 months were recorded. Data were compared between (1) those tested and not tested and (2) 25(OH)D levels ≤10 ng/ml (deficient), 11–30 ng/ml (insufficient), and ≥31 ng/ml (sufficient). Stepwise logistic regression identified independent predictors of low serum 25(OH)D levels.

Results The cohort was 86 % Caucasian and 48 % female with a mean age of 63±14 years (mean ± SD). The most prevalent cancer was breast (19 %). In total, 2,098 (5 %) had a 25(OH)D test. Of those tested, 133 (6 %) had levels ≤10 ng/ml and 1,311 (62 %) 11–30 ng/ml. Tests were more frequent in females and in those with breast, skin, and thyroid cancers ($P<0.001$). Low 25(OH)D levels were associated (in univariable analyses) with male gender, non-Caucasian race, gastrointestinal tumor primary sites, metastatic disease, benign liver disease, low serum albumin, and elevated liver enzymes. Significant factors in multivariable models for 25(OH)D levels ≤10 and ≤30 ng/ml included non-Caucasian race, primary cancer site, and test calendar month. Vitamin D supplements and recent antineoplastic medication were associated with sufficient levels.

Conclusions Low (deficient or insufficient) 25(OH)D serum levels were highly prevalent in people with solid tumors. Vitamin D tests were infrequent and paradoxically less often done in high-risk groups. Tests were more frequent in females and in those with breast, skin, and thyroid cancers. Further research should examine role of routine 25(OH)D tests, the clinical consequences of low levels, and therapeutic supplementation in people with cancer.

Keywords Bone · Cancer · Nutrition · Solid tumors · Vitamin D

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Introduction

Epidemiologic studies have associated lower 25-hydroxyvitamin D [25(OH)D] levels with higher prevalence of several diseases (including cancer, cardiac, and

immunological disorders) and also overall mortality rates [1–4]. Vitamin D has been implicated in cancer biology, prevalence, and prognosis [5]. Epidemiological studies have revealed inverse relationships between ultraviolet B radiation exposure, vitamin D dietary intake, 25(OH)D levels, and cancer mortality [5, 6]. Life expectancy in breast, colon, head, and neck cancer; lymphoma; and melanoma has been inversely related to serum 25(OH)D level [7–12]. Vitamin D receptors and conversion enzymes are present in many normal and cancerous (breast, colon, immune system, and pancreas) human cells. Vitamin D is a paracrine and autocrine hormone that regulates cell growth and differentiation [1]. Calcitriol (1,25-hydroxyvitamin D, 1,25(OH)D) has many anti-proliferative actions in tumor cell lines including cell cycle arrest, apoptosis induction, angiogenesis inhibition, increased cellular adhesion, and potentiation of chemotherapy cell death [13, 14].

Vitamin D3 is predominantly produced by ultraviolet B (UVB) radiation absorption in the skin. In the presence of adequate exposure to sunlight, dietary sources of vitamins D2 and D3 (fatty fish, vegetables, fortified foods) make a minor contribution to physiologic levels. Vitamins D2 and D3 are activated by hydroxylation, first by the liver (25(OH)D) then by the kidneys (1,25(OH)D). The recommended 25(OH)D serum level for both optimal bone health and disease prevention is controversial. Serum 25(OH)D levels >30 ng/ml have been recommended to prevent both bone and systemic diseases, including cancer [15–17]. Levels ≤10 ng/ml are more likely (but not universally) associated with clinical bone disease (osteomalacia). Levels between 10 and 30 ng/ml are often termed "insufficient" and associated with osteoporosis and hip fractures [1].

Deficiency is highly prevalent in the US population as well as medical inpatients (57 %) [18, 19]. In addition to lack of sun exposure, risk factors for deficiency include pigmented skin, malnutrition, older age, obesity, drugs (anticonvulsants, corticosteroids), and conditions that interfere with absorption and metabolism (e.g., gastrointestinal (GI), liver, or kidney diseases) [1]. Despite vitamin D supplementation, people may still be deficient [19, 20].

People with cancer may have extra risk factors for deficiency. Insufficient sunlight exposure may occur from photosensitizing drugs or frequent hospitalizations. Nutritional deficiency may arise from anorexia, nausea, and malabsorption. Data on 25(OH)D levels in people diagnosed with and/or being treated for cancer are limited. Studies have tended to focus on a single diagnostic group and stage (e.g., breast or colon cancer) or a small sample of patients attending an oncology or radiotherapy clinic. Varied definitions of deficiency [25(OH)D levels <20 to <40 ng/ml] have been used. Deficiency estimates in these cohorts ranged from 27 to 82 % [7, 21–26]. This wide range may relate to the population studied, sampling season, geographic region, or the definition of deficiency used in the studies. The clinical consequences of vitamin D insufficiency in cancer patients are unknown. The frequency of 25(OH)D measurement in routine cancer care is undocumented. No study has compared levels in people across the whole spectrum of primary cancer sites. The goals of this study were to investigate the incidence and clinical predictors of 25(OH)D tests and the factors which predicted low levels in people diagnosed with solid tumors in Cleveland, OH, USA.

Methods

This cohort study involved clinical data from an electronic medical record at the Cleveland Clinic (My Practice/EPIC, Copyright 1979–2011, EPIC Systems Corporation, Verona, WI, USA). The protocol was approved by the Cleveland Clinic Institutional Review Board. All people with a solid tumor cancer diagnosis (determined by International Classification of Disease Version 9 codes) as the primary reason for a clinical encounter in 2006 and 2007 were included. Non-melanoma skin cancers were included. Hematologic malignancies (including multiple myeloma) were excluded. The number of cancer patients with 25(OH)D laboratory tests was determined. From September 2006 through 2007, all 25(OH)D tests by Cleveland Clinic Laboratories used a radio-immunoassay (Diasorin, Stillwater, MN, USA) which detects 100 % of serum 25(OH)D2 and 25(OH)D3. Before September 2006, tests were performed by an external laboratory using unknown methodology.

The cohort was divided into three groups by 25(OH)D levels: ≤10 ng/ml (deficient), 11–30 ng/ml (insufficient), and ≥31 ng/ml (sufficient). These levels were chosen because <10 ng/ml is the level most frequently associated with clinical osteomalacia and <30 ng/ml is the normal reference range for the test in our institution. These definitions also allow comparison with recent US demographic data from the Third National Health and Nutrition Examination Survey study [18]. Clinical data collected from the medical record included demographic information, diagnosis (cancer primary and metastatic sites), calendar month of 25(OH)D test, and selected comorbidities (chronic liver disease, chronic renal disease, inflammatory bowel disease, osteoporosis, pathologic fracture, parathyroid disease). Biochemical data (serum albumin, calcium, creatinine, liver enzymes) <2 months prior to or on the 25(OH)D test day were recorded. Prescription medications [antineoplastic (hormonal or chemotherapy), vitamin D supplements, corticosteroids, and anticonvulsants] within 2 months before the vitamin D test were recorded. Chemotherapy and radiation therapy treatment was determined by Current Procedural Terminology billing codes (© 2010 American Medical Association).

Statistics

Demographic data and cancer primary site were compared between those who had a 25(OH)D level measured and those who did not. Clinical factors (demographic, disease, laboratory, medications) were then compared between the following groups:

- 25(OH)D tested vs not tested
- 25(OH)D ≤10, 11–30, and ≥31 ng/ml

Results were rounded to one decimal place. 25(OH)D serum level data were normally distributed so parametric statistical techniques were used. Chi-square tests compared categorical variables and T tests continuous variables. The frequency of insufficient and deficient results detected by each test methodology (unknown vs Diasorin radioimmunoassay) was compared by chi-square test. $P<0.10$ allowed variables to enter the model; $P<0.05$ allowed them to remain. Interactions between model variables were also tested. A Spearman correlation was performed to examine the association between number of tests performed and time (month and year) of the study period.

Results

A total of 39,252 solid tumor cancer patients were identified. Mean age was 63 years (SD±14); 48 % were female. Two thousand ninety-eight (5 %) had a 25(OH)D test during the study period. Demographic data for the entire population and those tested are in Table 1. Testing varied by gender (more common in females, $P<0.0001$) and by primary tumor type ($P<0.0001$) on chi-square analysis. Specifically testing in patients with breast cancer was more common than those without breast cancer [617 of 7,353 (8 %) vs 1,481 of 31,899 (5 %), chi-square $P<0.001$]. Test incidence increased linearly over the study period (Spearman correlation $r=0.887$, $P<0.001$; see Fig. 1).

In those tested ($n=2,098$), the mean 25(OH)D level was 27 ng/ml (±15). One thousand three hundred eleven (62 %) of those tested had levels between 11 and 30 ng/ml and 133 (6 %) ≤10 ng/ml. Vitamin D levels were more frequently abnormal (<30 ng/ml) with the older unknown testing methodology (prior to September 2006) than the radioimmunoassay test [1,110 of 1,531 (59 %) vs 348 of 567 (73 %), chi-square $P<0.001$]. Of the combined total 1,444 with low levels, 406 (28 %) were prescribed vitamin D supplements compared with 281 of the 654 (43 %) with 25(OH)D ≥31 ng/ml (chi-square $P<0.001$). Clinical factors associated with 25(OH)D levels are in Tables 2 and 3. Univariable associations (chi-square) with deficient and insufficient levels included demographic characteristics

Table 1 Demographic data

|	25(OH) vitamin D			
	Population $N=39,253$ N (%)	Not tested $N=37,154$ (95 %) N (%)	Tested $N=2,098$ (5 %) N (%)	P
Mean age (SD)	63.4 (±14)	63.3 (14)	65.1 (13)	<0.0001
Female	19,029 (48)	17,636 (48)	1,392 (66)	<0.0001
Race				
Caucasian	33,563 (86)	31,733 (85)	1,830 (87)	<0.0001
African-American	3,114 (8)	2,933 (8)	180 (9)	
Other/unknown	2,577 (6)	2,488 (7)	88 (4)	
Cancer diagnosis				
Breast	7,353 (19)	6,736 (18)	617 (29)	<0.0001
Colon/rectum	2,366 (6)	2,282 (6)	84 (4)	
Gynae	1,668 (4)	1,603 (4)	65 (3)	
Kidney/bladder	4,749 (12)	4,604 (12)	145 (7)	
Liver/pancreas/ upper GI	2,233 (6)	2,055 (6)	178 (9)	
Lung	2,190 (6)	2,117 (6)	73 (4)	
Prostate	6,922 (17)	6,697 (18)	225 (11)	
Skin	5,938 (15)	5,539 (15)	399 (19)	
Thyroid	970 (3)	798 (2)	172 (8)	
Other	4,863 (12)	4,723 (13)	140 (7)	
Metastatic				
No	37,485 (95)	35,511 (96)	1,974 (94)	<0.001
Yes	1,767 (5)	1,643 (4)	124 (6)	

Upper GI upper gastrointestinal, including esophagus, stomach, and small intestine

(gender and race) and test month (see Fig. 2). Calendar month was associated on univariable analysis with insufficient levels (chi-square $P<0.001$) but not deficient levels (chi-square $P=0.21$).

Disease factors associated with 25(OH)D levels ≤10 and 11–30 ng/ml in univariable analysis (chi-square) were cancer primary site, metastatic disease, and benign or malignant liver disease. Certain comorbidities (pathologic fractures and osteoporosis) were associated with higher levels. On further analysis, females were more likely to have osteoporosis [526 of 1,393 (38 %) of females vs 198 of 705 (28 %) of males, chi-square $P<0.001$] and be prescribed vitamin D supplements [537 of 1,393 (39 %) of females vs 150 of 705 (21 %) of males, chi-square $P<0.001$].

Laboratory indicators compatible with impaired nutrition or liver dysfunction (low albumin or high bilirubin, aspartate aminotransferase, and alanine aminotransferase) were associated with lower 25(OH)D levels ≤10 and 11–30 ng/ml on univariable analysis. Prescribed vitamin D supplements and antineoplastic medications were both associated with sufficient levels (≥31 ng/ml). Concurrent anticonvulsant

Fig. 1 Number of 25(OH)D tests per month over time of the study. Spearman correlation number of tests with time $r=0.887$, $P<0.001$
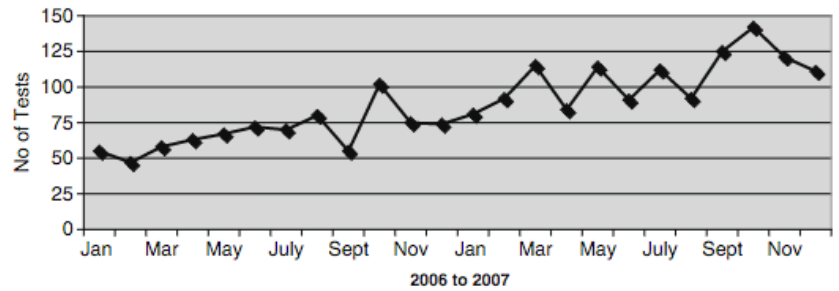
medications were associated with an increased risk of levels ≤10 ng/ml.

The multivariable stepwise logistic regression models for levels ≤10 and ≤30 ng/ml are in Tables 4 and 5. A logistic regression analysis of predictors of vitamin D levels as a continuous variable was also performed. The predictors in this model were the same as the categorical models shown in the tables. Other factors (age and gender) were included in the final model, but they dropped out due to lack of significance. Associated factors for both included race, cancer primary site, and test calendar month. Comorbidities (combined) and pre-scribed vitamin D medication were protective. Interactions between variables in the models were tested, but none retained significance.

Discussion

This study is the first to describe the frequency of 25(OH)D tests in a large cohort of patients with the whole spectrum of solid tumor cancer diagnoses. While tests were infrequent overall, most of those tested were deficient (<10 ng/ml) or insufficient (11–30 ng/ml). Prevalence of testing varied by gender and cancer type. Paradoxically tests were more frequent in groups at lower risk of insufficiency, in particular women and those with specific cancer types. Testing was most frequent in people diagnosed with cancers of the thyroid (18 %), breast (8 %), liver/pancreas/upper GI system (8 %), and skin 7 %. Retesting data were not available. It is noteworthy that only 4 % of colon cancer patients in our cohort were

Table 2 Demographic and clinical associations with 25(OH)D levels

Factor	Total	≤10 ng/ml N (%)	11–30 ng/ml N (%)	≥31 ng/ml N (%)	P
N		133	1,311	654	
Mean age (SD)		61.7 (12)	65.4 (13)	65.2 (12)	0.007
Sex					
Female	1,393	76 (57)	859 (66)	458 (70)	0.010
Male	705	57 (43)	452 (35)	196 (30)	
Race					
Caucasian	1,830	86 (65)	1,135 (87)	609 (93)	<0.0001
African-American	180	34 (26)	117 (9)	29 (4)	
Other/unknown	88	13 (10)	59 (5)	16 (3)	
Cancer diagnosis					
Breast	617	33 (25)	390 (30)	194 (30)	<0.0001
Colon/rectum	84	10 (8)	53 (4)	21 (3)	
Gynecologic	65	3 (2)	44 (3)	18 (3)	
Kidney/bladder	145	12 (9)	102 (8)	31 (5)	
Liver/pancreas/upper GI	178	38 (29)	109 (8)	31 (5)	
Lung	73	2 (2)	51 (4)	20 (3)	
Prostate	225	11 (8)	144 (11)	70 (11)	
Skin	399	9 (7)	232 (18)	158 (24)	
Thyroid	172	8 (6)	99 (8)	65 (10)	
Other	140	7 (5)	87 (7)	46 (7)	
Metastatic disease	124	8 (6)	89 (7)	27 (4)	0.053
Malignant liver disease	157	32 (24)	98 (8)	27 (4)	<0.001

T test (age) and chi-square (all categorical variables)

Upper GI upper gastrointestinal, including esophagus, stomach, and small intestine

Table 3 Clinical associations with 25(OH)D levels

Factor	Total	≤10 ng/ml N (%)	11–30 ng/ml N (%)	≥31 ng/ml N (%)	P
Comorbidities					
Multiple	930	85 (40)	519 (42)	326 (50)	0.003
Benign liver disease	161	43 (20)	83 (7)	35 (5)	<0.001
Inflammatory bowel disease	35	1 (0.5)	23 (2)	11 (2)	0.24
Fracture history	46	2 (1)	23 (2)	21 (3)	0.068
Osteoporosis	724	46 (22)	406 (33)	272 (42)	<0.001
Parathyroid disease	53	6 (3)	28 (2)	19 (3)	0.68
Renal disease	44	3 (1)	29 (2)	12 (2)	0.56
Laboratory investigations					
Albumin <3.5 g/dl	143	51 (33)	74 (9)	18 (5)	<0.001
ALT >45 (F), >50 (M) U/l	100	23 (15)	61 (7)	16 (4)	<0.001
AST>40 U/l	185	44 (29)	111 (14)	30 (8)	<0.001
Bilirubin>1.5 mg/dl	76	31 (18)	36 (4)	9 (2)	<0.001
Calcium <8.5, >10.5[a] mg/dl	119	19 (12)	69 (9)	31 (8)	0.33
Creatinine >1.4 mg/dl	167	24 (14)	103 (11)	40 (9)	0.16
Creatinine≥2.0 mg/dl	85	12 (7)	53 (6)	20 (4)	0.40
GGT>35 (F), >50 (M) U/l	58	5 (46)	33 (31)	20 (27)	0.47
LD>220 U/l	70	15 (42)	39 (21)	16 (17)	0.012
Drug therapy					
Anticonvulsant	254	37 (18)	137 (11)	80 (12)	0.044
Antineoplastic	361	23 (11)	202 (16)	136 (21)	0.002
Chemotherapy[b]	125	12 (6)	71 (6)	42 (6)	0.84
Corticosteroids	454	46 (22)	276 (22)	132 (20)	0.53
Radiotherapy[b]	16	2 (1)	8 (1)	6 (1)	0.78
Vitamin D medication	687	35 (17)	371 (30)	281 (43)	<0.001

Chi-square tests

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase, *LD* lactate dehydrogenase

[a] Corrected by serum albumin levels (Corr Ca=total calcium+ 0.8 [4−serum albumin])
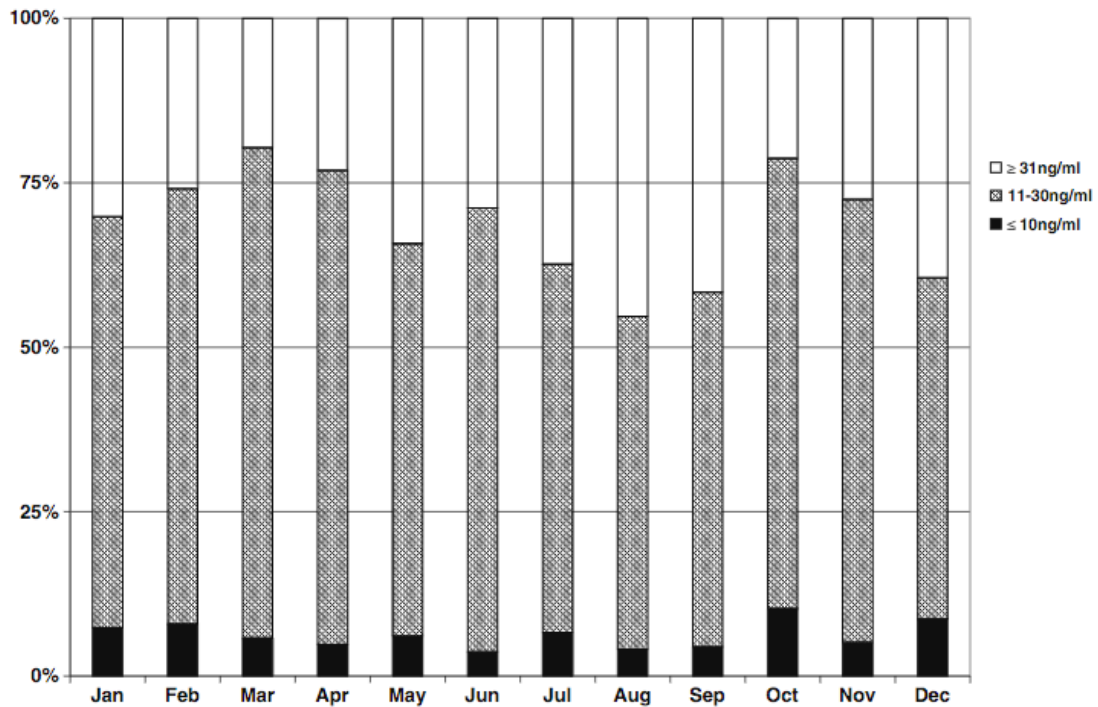
[b] Procedural billing codes

Fig. 2 25(OH)D levels by calendar month

Table 4 Multivariable predictors—25(OH)D ≤10 ng/ml

Effect	Level	OR (95 % CI)	P
Race	Caucasian	1.00 (REF)	<0.001
	African-American	4.17 (2.61, 6.66)	
	Other	2.59 (1.32, 5.08)	
Cancer type	Breast	1.00 (REF)	<0.001
	Colon/rectum	2.21 (1.01, 4.83)	
	Gynecological	0.84 (0.24, 2.92)	
	Kidney/bladder	1.39 (0.68, 2.83)	
	Liver/pancreas/ upper GI	4.69 (2.69, 8.17)	
	Lung	0.43 (0.10, 1.87)	
	Prostate	0.73 (0.35, 1.50)	
	Skin	0.49 (0.23, 1.05)	
	Thyroid	0.89 (0.39, 2.00)	
	Other	0.90 (0.38, 2.12)	
Test month	1 (January)	1.00 (REF)	0.14
	2	1.21 (0.48, 3.10)	
	3	0.83 (0.32, 2.16)	
	4	0.67 (0.24, 1.93)	
	5	0.86 (0.34, 2.17)	
	6	0.63 (0.21, 1.85)	
	7	0.93 (0.37, 2.31)	
	8	0.51 (0.18, 1.44)	
	9	0.65 (0.24, 1.77)	
	10	1.63 (0.73, 3.67)	
	11	0.62 (0.24, 1.61)	
	12 (December)	1.54 (0.64, 3.70)	
Comorbidities		0.69 (0.46, 1.05)	0.084
Vitamin D supplement		0.40 (0.25, 0.66)	<0.001
Anti-convulsant		1.92 (1.17, 3.15)	0.010

Upper GI upper gastrointestinal, including esophagus, stomach, and small intestine

Table 5 Multivariable predictors—25(OH)D ≤30 ng/ml

Effect	Level	OR (95 % CI)	P
Race	Caucasian	1.00 (REF)	<0.001
	African-American	2.33 (1.52, 3.56)	
	Other	1.85 (1.04, 3.28)	
Cancer type	Breast	1.00 (REF)	<0.001
	Colon/rectum	1.09 (0.62, 1.90)	
	Gynae	1.08 (0.59, 1.99)	
	Kidney/bladder	1.24 (0.78, 1.97)	
	Liver/pancreas/ upper GI	1.78 (1.12, 2.84)	
	Lung	0.90 (0.51, 1.61)	
	Prostate	0.79 (0.55, 1.13)	
	Skin	0.61 (0.45, 0.83)	
	Thyroid	0.55 (0.37, 0.82)	
	Other	0.61 (0.38, 0.98)	
Metastatic		1.71 (1.02, 2.85)	0.041
Test month	1 (January)	1.00 (REF)	<0.001
	2	1.23 (0.71, 2.13)	
	3	1.84 (1.07, 3.17)	
	4	1.52 (0.88, 2.63)	
	5	0.83 (0.51, 1.37)	
	6	1.12 (0.67, 1.89)	
	7	0.69 (0.42, 1.13)	
	8	0.48 (0.29, 0.79)	
	9	0.60 (0.37, 0.98)	
	10	1.62 (0.98, 2.65)	
	11	1.11 (0.67, 1.83)	
	12 (December)	0.67 (0.41, 1.10)	
Comorbidities		0.68 (0.55, 0.83)	<0.001
Anti-neoplastic drugs		0.63 (0.48, 0.85)	0.002
Vitamin D supplement		0.54 (0.44, 0.66)	<0.001

Upper GI upper gastrointestinal, including esophagus, stomach, and small intestine

tested despite consistent epidemiologic data linking vitamin D status with colon cancer incidence and survival [27–29]. Least often tested were those with cancers of the lung, prostate, or gynecological system (all 3 %). Non-Caucasians were less often tested, although dark skin pigmentation is a recognized insufficiency risk factor [18, 23, 30]. Tests increased linearly in frequency over the study period and may be even more common now. This may reflect heightened interest in vitamin D in the general media and medical literature [31].

Levels of 25(OH)D in our cohort resembled recent US population data (77 % with 25(OH)D 11–30 ng/ml, 6 % 25(OH)D ≤10 ng/ml) and other single diagnosis cancer studies [7, 18, 21, 23]. Our data likely significantly under-represent actual prevalence of insufficiency in the cancer population as known high-risk groups were tested less often. Risk factors for low vitamin D levels previously observed, and confirmed by our data, include non-Caucasian race and

calendar month [21, 23]. This reflects the direct relationship between serum 25(OH)D and exposure and absorption of UVB radiation. Melanin in pigmented skin absorbs UVB efficiently, so less is available to stimulate vitamin D production [1]. Vitamin D deficiency (25(OH)D<10 ng/ml) was most prevalent in cancers of the upper gastrointestinal tract and pancreas and did not vary with calendar month. Levels in this range may be more related to nutritional inadequacy or malabsorption than lack of sunlight. We chose to use sampling month rather than season due to varying definitions of the start and end of seasons internationally. Use of months provides more exact data. For example, there was a high prevalence of insufficient results in October, which may not be evident when pooled with other months. More advanced cancer (metastatic disease) was associated with vitamin D insufficiency (25(OH)D<30 ng/ml) in multivariable analysis. This

association has been demonstrated previously in breast cancer and radiotherapy patient cohorts [23, 26]. Low vitamin D levels are often linked with other predictors of poor cancer outcomes including obesity and lack of exercise, which may partly explain this association [30]. Alternatively, it may be that anorexia–cachexia associated with metastatic disease contributes to inadequate dietary intake of vitamin D.

Clinical risk factors for low 25(OH)D levels previously identified in general medical inpatients have included anticonvulsant drugs, kidney disease, low serum albumin and calcium, and high serum alkaline phosphatase [19]. Our data confirmed the crucial role of liver function in 25(OH)D production with both benign and malignant liver disease and serum liver function tests being associated with lower vitamin levels in univariable analyses. Kidney function (measured by serum creatinine) and benign renal disease were not associated. This is not surprising as the product of renal conversion (1,25(OH)D) was not tested. 1,25(OH)D measurement is not recommended as it is tightly regulated by the kidney and parathyroid [1]. Many other tissues produce it in a paracrine manner; thus, serum levels may not reflect biologically active tissue levels.

Female gender, certain comorbidities (in particular osteoporosis), and prescribed antineoplastic or vitamin D supplements were associated with higher 25(OH)D levels. Females in our cohort had higher rates of osteoporosis and were more often prescribed supplements, possibly explaining their higher 25(OHD) levels. Patients prescribed vitamin D supplements were more likely to have sufficient 25(OH)D levels, yet 59 % of them still had levels ≤30 ng/ml. High insufficiency rates in people taking multivitamins or vitamin D supplements have been documented previously [19–21]. Individual response to vitamin D supplements varies widely, possibly from individual genetic factors, race, dietary calcium, or adiposity [32, 33]. Vitamin D doses in over the counter multivitamins vary but typically are 200–400 IU [17]. These doses are still inadequate to ensure serum levels >30 ng/ml for healthy people with limited sunlight exposure (1,000 IU daily) [17, 34, 35]. Certain cancer patients (especially those with malabsorption, weight loss, or liver involvement) may need still higher doses for optimal levels or to reverse low levels. High-dose supplementation (8,000 IU per day) in cancer patients increased 25(OH)D levels an average of 17 ng/ml after 3 months [36].

There is little information about the clinical significance of low 25(OH)D levels in cancer. Potential consequences of vitamin D insufficiency include muscle weakness, falls, fractures, and shorter survival [1]. Clinically evident vitamin D deficiency is associated with muscle weakness, fatigue, bone pain, and possibly depression, all common clinical problems in people with advanced cancer [37–39]. Vitamin D supplementation has been reported to reduce joint pain in patients
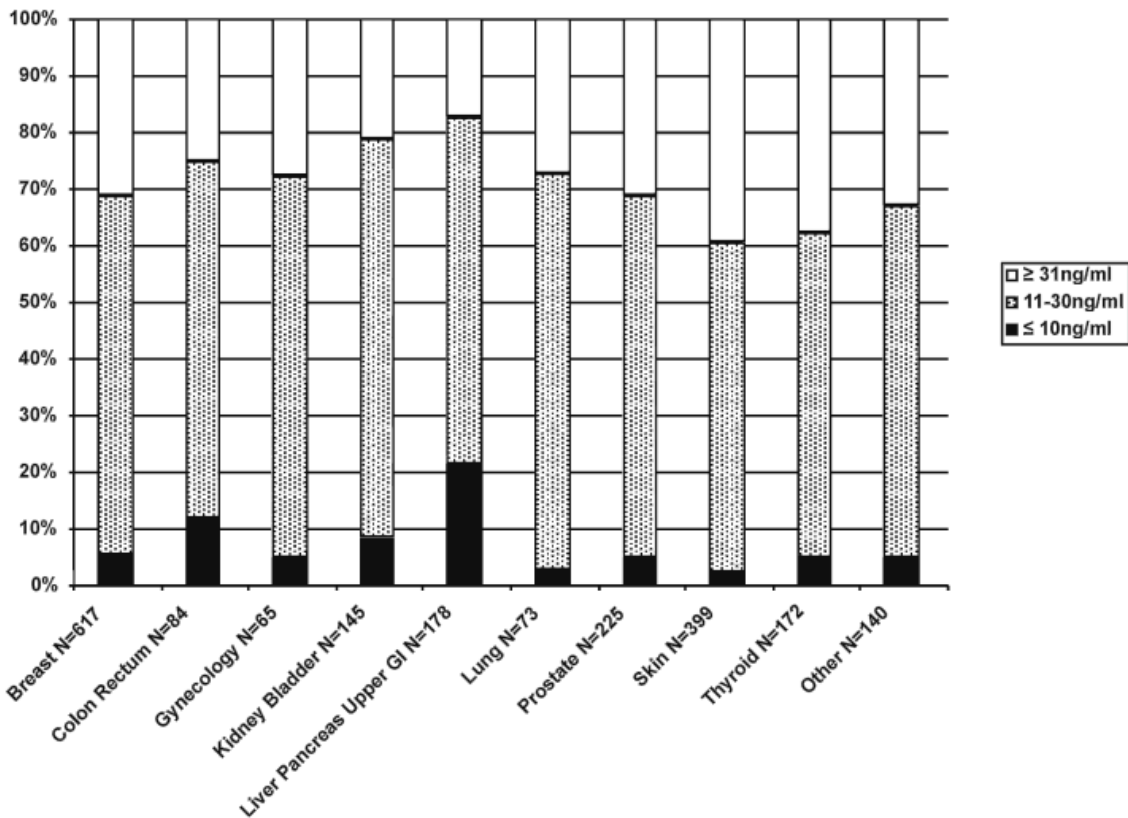

Fig. 3 25(OH)D levels and primary cancer site. *Upper GI* upper gastrointestinal, including esophagus, stomach, and small intestine

taking aromatase inhibitors [40]. There are no data about outcomes of either universal or selective 25(OH)D screening or supplementation after a cancer diagnosis.

Several confounders (e.g., body weight, diet, and exercise) influence serum 25(OH)D levels and may contribute to the epidemiologic links with cancer outcomes [30, 32]. It is, however, biologically plausible that vitamin D has a role in cancer prognosis. In vivo studies demonstrated multiple anti-proliferative effects of vitamin D; receptor polymorphisms have also variably been associated with cancer prognosis [41]. Prognosis in several cancers (breast, colon, lung, lymphoma, melanoma, prostate) has been associated with the calendar season of cancer diagnosis, extent of UVB exposure or serum 25(OH)D level [7, 8, 42–46]. Poor health outcomes (including cancer survival) in African Americans may be linked to low 25(OH)D levels [47].

This retrospective electronic medical record study had several limitations. The first was a probable test selection bias. Test indications in our study population could not be identified. Tests may have been initiated by patients or physicians, either for screening or due to a known vitamin D-associated condition (e.g., osteoporosis). We do not have longitudinal data about re-testing of those found to be deficient or insufficient. We could not assess non-prescribed multivitamin or vitamin D usage, nor the dose, compliance, or timing of prescribed vitamin D. The use of medical records (even electronic) had inherent difficulties. Coding accuracy and consistency of coding likely affected the observations. Data on height, weight, and symptoms, although sought, were so rarely documented as to be inadequate for analysis.

Significant variation in 25(OH)D laboratory results may occur [48]. Reference ranges are often not comparable between different test methods [48]. We were not able to determine the methodology used prior to September 2006. This test methodology was associated with a higher frequency of abnormal results than the newer methodology, highlighting the variability in results provided by different laboratory tests. Vitamin D2 (found in most supplements) is not consistently detected by some methods [48]. This may result in erroneous diagnosis of insufficiency in those prescribed supplements. The Cleveland Clinic normal reference range currently is 31–80 ng/ml; thus, we used ≤30 ng/ml to define low levels in our study. Standardized 25(OH)D reference materials are under development to promote uniformity between laboratories, but are not yet routinely used [49].

This study is the largest description to date of vitamin D testing in people with solid tumor cancer diagnoses. Testing was infrequent but there was a high prevalence of low 25(OH)D levels in those tested (Fig. 3). It suggests the need for prospective studies with universal testing to establish accurate prevalence rates of insufficiency and deficiency, identify risk factors, and assess consequences of low 25(OH)D in people with cancer. While many diseases, including cancer, have been linked to low dietary vitamin D and serum levels, data are lacking about outcomes of routine tests and supplements. There is some evidence that high 250HD levels may be harmful and reduce survival, e.g., in pancreatic and prostate cancers [50, 51]. Randomized trials of vitamin D supplementation on clinical outcomes (including symptoms and survival) are needed. Cancer-specific recommendations could then be made for testing and supplementation. Recommendation for supplementation would likely be individualized and based upon serum 25(OH)D level [31].

Conclusions

Low 25(OH)D levels were highly prevalent in people with solid tumors. Vitamin D tests were infrequent. Risk factors for low levels included non-Caucasian race, test calendar month, primary cancer site, and metastatic disease. Those known to be at high risk for insufficiency were less often tested and so possibly significantly under-diagnosed. Prescribed vitamin supplements did not ensure adequate 25(OH)D levels. Prospective studies are needed to elicit both the prevalence and consequences of low vitamin D in cancer cohorts. More evidence is needed before routine screening, and supplementation recommendations can be made for people with cancer.

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