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Vitamin D deficiency and its relationship to cancer stage in patients who underwent thyroidectomy for papillary thyroid carcinoma.

Anita Sulibhavi[a], Matthew L. Rohlfing[a,*], Scharukh M. Jalisi[b], David B. McAneny[c], Gerard M. Doherty[d], Michael F. Holick[e], J. Pieter Noordzij[a]

[a] Department of Otolaryngology—Head & Neck Surgery, Boston Medical Center, Boston, MA, United States of America
[b] Department of Otolaryngology – Head & Neck Surgery, Beth Israel Deaconess Medical Center, Boston, MA
[c] Department of Surgery, Boston Medical Center, Boston, MA, United States of America
[d] Department of Surgery, Brigham and Women's Medical Center, Boston, MA, United States of America
[e] Division of Endocrinology, Department of Medicine, Boston Medical Center, Boston, MA, United States of America

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ABSTRACT

Purpose: As imaging technology improves and more thyroid nodules and malignancies are identified, it is important to recognize factors associated with malignancy and poor prognosis. Vitamin D has proven useful as a prognostic tool for other cancers and may be similarly useful in thyroid cancer. This study explores the relationship of Vitamin D to papillary thyroid carcinoma stage while accounting for socioeconomic covariates.

Materials and methods: The medical records of all patients who underwent thyroidectomy at one institution between 2000 and 2015 were reviewed. Subjects with non-papillary thyroid cancer pathology, prior malignancy, and without Vitamin D levels were excluded. The remaining 334 patient records were examined for cancer stage, Vitamin D levels, Vitamin D deficiency listed in history, and demographic and comorbid factors.

Results: Vitamin D laboratory values showed no significant relationship to cancer stage ($p = 0.871$), but patients with Vitamin D deficiency documented in the medical record were more likely to have advanced disease (28.6% versus 14.7%; $p = 0.028$). The patients with documented Vitamin D deficiency also had lower 25-hydroxyvitamin D nadirs (21.5 ng/mL versus 26.5 ng/mL, $p = 0.008$) and were more likely to be on Vitamin D supplementation (92.6% versus 41.8%, $p < 0.001$).

Conclusions: The results suggest that Vitamin D deficiency may have value as a negative prognostic indicator in papillary thyroid cancer and that pre-operative laboratory evaluation may be less useful. This is important because Vitamin D deficiency is modifiable. While different racial subgroups had different rates of Vitamin D deficiency, neither race nor socioeconomic status showed correlation with cancer stage.

1. Introduction

Thyroid cancer is the most common endocrine malignancy and the ninth most common malignancy overall in the United States [1]. Established prognostic factors in thyroid cancer include age, sex, tumor histopathology, tumor size, presence of lymphovascular invasion and extra-capsular spread, nodal spread, and distant metastases [2]. Improvements in imaging techniques, specifically in ultrasound, have led to an increase in early detection of both benign and malignant thyroid masses [3]. With more of these masses being identified, it is important to recognize high risk prognostic features in order to expedite workup and treatment in cases that are more likely to be malignant and aggressive. Vitamin D levels have become useful as a prognostic indicator for other malignancies, including breast, colon, and prostate [4–6]. For these reasons, there has been recent interest in studying Vitamin D and its role as a prognostic factor in thyroid malignancies [7].

Vitamin D is actually a group of fat soluble compounds ingested from the diet or synthesized in response to sun exposure that regulate intestinal absorption of calcium, magnesium, and phosphates. These compounds also regulate signaling pathways that influence the cellular life cycle, angiogenesis, and cellular invasion [8]. Low levels of Vitamin D have been associated with Hashimoto's Thyroiditis and Graves' Disease, likely due to immune modulation effects [9]. Animal studies have

* Corresponding author.
E-mail addresses: asulibha@bu.edu (A. Sulibhavi), Matthew.rohlfing@bmc.org (M.L. Rohlfing), sjalisi@bidmc.harvard.edu (S.M. Jalisi), David.McAneny@bmc.org (D.B. McAneny), gmdoherty@partners.org (G.M. Doherty), Michael.Holick@bmc.org (M.F. Holick), Pieter.Noordzij@bmc.org (J.P. Noordzij).

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shown that Vitamin D can have anti-proliferative and anti-inflammatory effects in the settings of Type 1 diabetes and ulcerative colitis [10,11]. Despite these important health contributions, Vitamin D deficiency is common in the United States, especially in certain racial groups, including African Americans [12]. Given that many Americans are Vitamin D deficient, recognizing and correcting the deficiency could be an important prognostic and therapeutic factor in the setting of thyroid malignancy.

This study seeks to determine if Vitamin D levels and Vitamin D deficiency have prognostic value in the setting of papillary thyroid carcinoma, the most common thyroid malignancy. Additional analyses seek to determine if subgroups defined by race or socioeconomic status show different patterns of Vitamin D deficiency. This study also aims to clarify the role of Vitamin D as a prognostic factor while controlling for social factors, because low socioeconomic status is known to be associated with Vitamin D deficiency and poorer head and neck cancer outcomes [12,13]. These authors hypothesize that independent of socioeconomics and race, Vitamin D deficiency may be associated with higher cancer stage and therefore could represent a potential target for intervention in patients with papillary thyroid carcinoma.

2. Materials and methods

2.1. Subjects and data collection

A total of 676 patients who underwent thyroidectomy from January 1, 2000 to December 21, 2015 at Boston Medical Center, an urban, safety-net hospital, were originally identified. The study was approved by the Institutional Review Board at this institution. Patients were excluded if they had history of non-thyroidal malignancy, did not have pre-operative 25-hydroxyvitamin D [25(OH)D] levels available, or had a final pathology report inconsistent with papillary thyroid malignancy. After exclusions, 334 subjects remained. The TNM stage was recorded from the electronic medical record, as it was determined by the clinicians treating the patient at the time, based on radiological and pathological data. Thyroid cancer stage was then categorized into early stage (Stage I and II) and late stage (Stage III and IV). Staging criteria was determined by the AJCC recommendations at the time of the patient's treatment, thus including some patients categorized by the 6th edition criteria and some categorized by 7th edition criteria.

Each patient's lowest serum 25(OH)D level from the year prior to thyroidectomy was recorded, along with the serum 25(OH)D level measured most recently prior to surgery. Values < 20 ng/mL are considered deficient at this institution, while 21–29 ng/mL is insufficient, and values > 30 ng/mL are considered sufficient. There is still ongoing debate regarding the optimal vitamin D cut-off values, and they vary by institution [14]. Patients were also stratified by whether “Vitamin D Deficiency” was listed as a problem in the electronic medical record. This would have been dependent on individual provider practice and judgment and was not recorded automatically based on laboratory values. Use of Vitamin D supplementation at the time of serum level measurement was also recorded. Other clinical and demographic data collected included age, sex, length of hospital stay after surgery, and home postal address. Postal addresses were used to determine the median income of the patient's home zip code as a proxy for socioeconomic status, using the United States census data [15].

2.2. Statistical analysis

Statistical analyses were conducted using SPSS Version 24 (IBM, Armonk, NY). Descriptive statistics are shown in Table 1, with demographics and risk factors stratified by the outcome variable (early versus late stage disease). Categorical variables were compared with Chi-square tests, and continuous variables were compared with two-tailed *t*-tests. From these analyses, risk factors and demographics with *p*-values of 0.2 or lower were consider potential confounders and selected to be included in multivariate analysis [16].

Table 1
Demographic variables and risk factors by thyroid malignancy stage.

Characteristic	Overall (N = 334)	Stage I and II (N = 291)	Stage III and IV (N = 43)	p-Value
Gender				
Female	274 (82.0%)	243 (83.5%)	31 (72.1%)	0.087
Male	60 (18.0%)	48 (16.5%)	12 (27.9%)	
Age at diagnosis				
Mean ± SD	46.3 ± 13.8	44.6 ± 13.5	58.0 ± 9.7	< 0.001
BMI				
Mean ± SD	29.5 ± 6.9	29.1 ± 6.8	31.9 ± 7.7	0.013
Race				
Black/African American	61 (18.3%)	52 (17.9%)	9 (20.9%)	0.741
White	170 (50.9%)	151 (51.9%)	19 (44.2%)	
Hispanic/Latino	18 (5.4%)	17 (5.8%)	1 (2.3%)	
Asian	21 (6.3%)	17 (5.8%)	4 (9.3%)	
Declined/Not available	41 (12.3%)	35 (12.0%)	6 (14.0%)	
Other	23 (6.9%)	19 (6.5%)	4 (9.3%)	
Ethnicity				
Not Hispanic/Latino	280 (83.8%)	244 (83.8%)	36 (83.7%)	1.000
Hispanic/Latino	54 (16.2%)	47 (16.2%)	7 (16.3%)	
Vitamin D Deficiency (documented)				
No	274 (83.5%)	244 (85.3%)	30 (71.4%)	0.028
Yes	54 (16.5%)	42 (14.7%)	12 (28.6%)	
Vitamin D supplementation (pre-op)				
No	167 (50.0%)	148 (50.9%)	19 (44.2%)	0.514
Yes	167 (50.0%)	143 (49.1%)	24 (55.8%)	
Vitamin D lowest value				
Mean ± SD	25.7 ± 12.6	25.7 ± 12.7	25.4 ± 12.1	0.871
Vitamin D lowest value, season				
Winter	95 (28.4%)	80 (27.5%)	15 (34.9%)	0.398
Spring	80 (24.0%)	74 (25.4%)	6 (14.0%)	
Summer	82 (24.6%)	70 (24.1%)	12 (27.9%)	
Fall	77 (23.1%)	67 (23.0%)	10 (23.3%)	

Binary logistic regression was used to assess the relationship between the independent variables and the primary outcome variable. Covariates selected from the univariate analyses were added to the unadjusted model one at a time. Variables that caused the odds ratio (OR) of the primary outcome to change by > 10% were considered confounders and kept in the model. Those that did not cause a change of this magnitude were not added to the base model [15]. The final model is described in Table 1. Findings were considered statistically significant at $p < 0.05$.

3. Results

When cancer stage was analyzed using laboratory values for 25(OH)D rather than clinical history per problem list, no significant difference in 25(OH)D levels was observed between early and advanced stages ($p = 0.871$). However, patients with Vitamin D deficiency documented in their history did have significantly higher rates of advanced stage malignancy when compared to patients without this documentation (28.6% versus 14.7%; $p = 0.028$). The association between Vitamin D deficiency and cancer stage remained significant in multivariate analysis ($p = 0.011$) while controlling for gender, age, and body mass index (BMI), which were identified as potential confounders in the univariate analysis (Table 2). Further analysis sought to delineate why patients with documented Vitamin D deficiency were more likely to have to have advanced stage disease while laboratory values alone were not predictive. Patients with documented Vitamin D deficiency had significantly lower 25(OH)D nadirs (21.5 ng/mL versus 26.5 ng/mL, $p = 0.008$), and they were over twice as likely to be given Vitamin D

Table 2
Binary regression model to predict advanced thyroid malignancy stage from possible predictors identified in bivariate analysis. Vitamin D deficiency is defined as being included as a diagnosis in the electronic medical record.

Variable	Odds ratio	95% CI Low	95% CI High	*p* value
Male gender	1.94	0.87	4.33	0.108
Age (years)	1.08	1.05	1.11	< **0.001**
BMI	1.06	1.01	1.11	**0.012**
Vitamin D deficiency	2.80	1.27	6.20	**0.011**
Constant	0.00	–	–	–

P values less than 0.05 were considered significant and are bolded.

supplementation, with 92.6% on supplementation versus 41.8% on supplementation ($p < 0.001$, Fig. 1).

Race and ethnicity did not meet the criteria for inclusion in the multivariate regression model and were not significantly associated with cancer stage ($p = 0.741$ and $p = 1.000$). Still, analysis was performed to define patterns of Vitamin D deficiency among racial subgroups (Fig. 2). This comparison showed higher levels of documented Vitamin D deficiency in Black and African American patients (30%) compared to Asian, White, Hispanic/Latino, and all others (24%, 10%, 11%, 18%, respectively; $p = 0.011$). Since race was not independently associated with the main outcome thyroid cancer stage, this is not expected to affect the conclusions but does support prior published findings [12].

Median income of home zip code was similarly not associated with cancer stage and thus was not included in the multivariate regression model ($p = 0.636$). Patients with documented Vitamin D deficiency showed a trend towards lower home zip code median income, but this did not reach statistical significance ($p = 0.223$, Fig. 3).

Given that Vitamin D levels can be related to sunlight exposure, the season in which the Vitamin D levels were tested was considered as a potential confounding variable. Season of measurement was not significantly associated with cancer stage and thus was not included in the multivariate regression model ($p = 0.398$). The means of the Vitamin D nadirs for each season were compared, demonstrating an expected seasonal trend that was not statistically significant ($p = 0.209$, Fig. 4).

4. Discussion

In this cohort, the Vitamin D laboratory values were not predictive of thyroid cancer stage, but documented Vitamin D deficiency did show an association with thyroid cancer stage. Additional analysis showed that patients with documented vitamin D deficiency were over twice as likely to be on supplementation at the time of surgery compared to patients with no such documentation (92.6% versus 41.8%, $p < 0.001$, Fig. 3). This suggests that supplementation may have altered the laboratory values, falsely representing the supplemented patients as having normal vitamin D levels. Also, those patients with documented vitamin D deficiency and vitamin D supplementation may have had more severe deficiency, leading their providers to recommend supplementation. Overall, the medical records documentation of vitamin D deficiency was associated with more advanced stage malignancy. The discrepancy between this finding and the equivocal findings from the laboratory values suggest that documentation may have been more accurate than laboratory values in representing the true Vitamin D status.

One previous study by Kim et al. reported a similar finding of Vitamin D deficiency being associated with poor clinicopathological features for patients in South Korea. Specifically in females, they showed that preoperative 25(OH)D levels had prognostic value and that patients with lower levels had more aggressive disease with poorer outcomes [3]. This study was strengthened by large sample size but did not consider race or socioeconomic status and may not be applicable to patients in the United States. The results presented in the current study reinforce the prognostic value of Vitamin D in papillary thyroid cancer, and the differing findings related to laboratory 25(OH)D levels may represent different patterns of supplementation and measurement. Other studies have published results suggesting that Vitamin D status does not have prognostic value. Ahn et al. used preoperative 25(OH)D levels and saw no correlation with clinical, pathological, or recurrence data in a cohort of 820 patients with papillary thyroid cancer who underwent thyroidectomy [17].

Papillary thyroid cancer is often an indolent disease recognized incidentally by imaging studies or routine physical exam. But in its advanced stages, it can become much more aggressive. The 5-year survival rates are near 100% for Stage 1 and 2 papillary thyroid carcinoma but drop to 51% for Stage 4 disease [16]. For this reason, recognition of negative prognostic factors related to stage can be

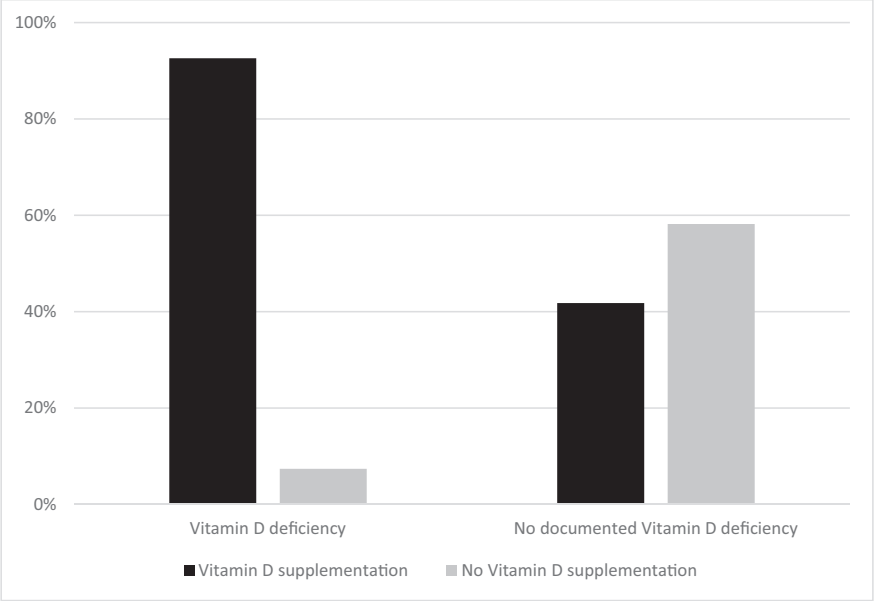

Fig. 1. Proportion of patients on Vitamin D supplementation at time of surgery stratified by documentation of Vitamin D deficiency.

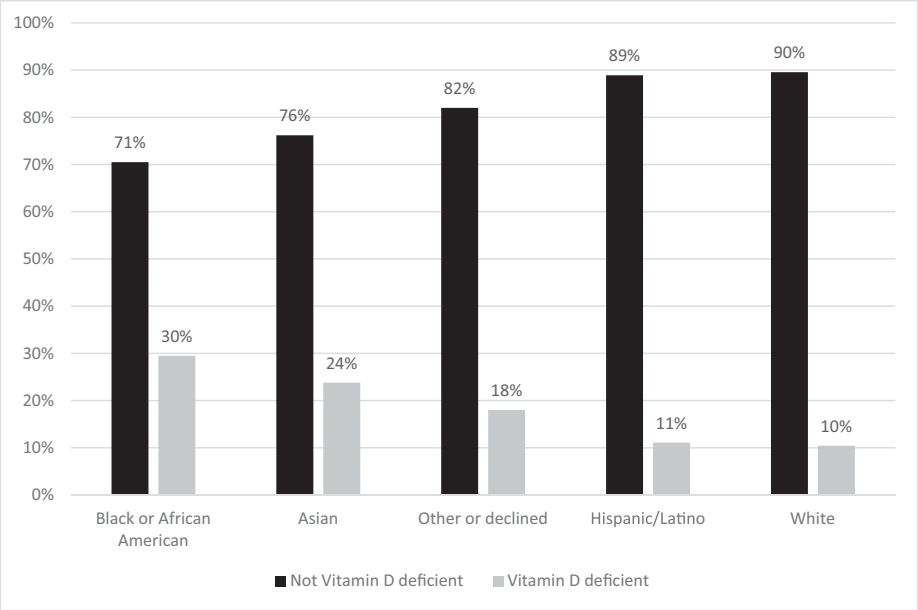

Fig. 2. Proportions of Vitamin D deficiency across racial subgroups ($p = 0.004$).

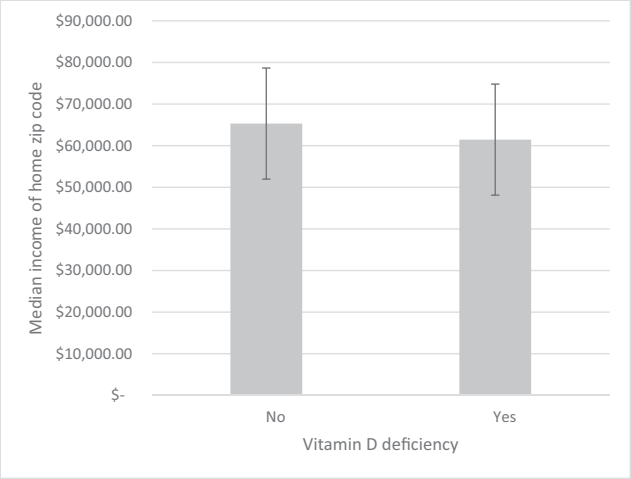

Fig. 3. Comparison of median income by home zip code between patients with and without history of vitamin D deficiency ($p = 0.233$).

important in determining treatment plans.

Since prior studies have recognized relationships between race, ethnicity and socioeconomic status and Vitamin D deficiency [12], these were considered as confounders in the current study. While there were significant differences in documented Vitamin D deficiency in different racial groups (Fig. 2), race itself was not associated with the main outcome variable, the papillary thyroid carcinoma stage. Clinicians should be able to identify Black or African American and Asian populations as being at elevated risk for Vitamin D deficiency, but since race showed no associated with cancer stage, it was not included in the multivariate analysis. The median home income of the patient's home zip code is an imperfect but useful proxy for socioeconomic status [15]. There was a nonspecific trend towards lower median home income in the Vitamin D deficient group, but the median income of the home zip code was not associated with the cancer stage (Fig. 4).

Vitamin D is an important potential prognostic factor because it is easily modifiable, and many of the previously identified risk factors such as age, sex, and tumor size are not modifiable. Vitamin D can be given therapeutically to patients with thyroid malignancies. Several preclinical studies have demonstrated growth arrest of thyroid cancer after administration of certain 1,25-dihydroxyvitamin D [1,25(OH)D] analogs by inhibiting tumor proliferation, further demonstrating the impact that vitamin D status may have on thyroid cancer progression [18]. Another recent study sought to evaluate whether the vitamin D receptor could be used as a cancer therapy target for poorly differentiated thyroid cancers. They found promising results, albeit depending on presence of specific genotypes of the Vitamin D receptor [19]. There have been other case reports of Vitamin D3 (cholecalciferol) being used as a therapeutic measure to halt progression of advanced cases of thyroid cancer [20].

This study has several limitations. This was conducted as a retrospective review of the medical records and thus has inherent recording bias. This medical center serves mostly patients from New England. As this region has a long winter, Vitamin D deficiency may be more prevalent in this population and may vary more drastically across seasons [21]. Although no significant differences were found between the average Vitamin D levels by season in this study, there may be long-term impacts of climate not accurately represented by one-time measurements. The study only addresses patients with papillary thyroid cancer. Age was considered and controlled for as a confounding variable, but the exact influence of age is difficult to determine given that the staging system differs by age. Also, patients staged by both AJCC 6th and 7th edition criteria are combined in this study because the staging system at the time of their treatment was used, and the study spans both time periods.

Strengths of this study include analysis of the impact of socioeconomic status and race on the relationship between vitamin D status and thyroid cancer staging. Additionally, this patient demographic is diverse in culture, age, and financial status, allowing for robust analysis of these factors. Future work should consider the effect of Vitamin D deficiency and Vitamin D supplementation on the natural history of papillary thyroid carcinoma and on the long term prognosis of patients treated for the disease.

5. Conclusions

This study demonstrates that Vitamin D status and Vitamin D deficiency may have prognostic value in cases of papillary thyroid carcinoma. While the laboratory values did not correlate with cancer stage, documented Vitamin D deficiency did show that correlation. The cohort with documented Vitamin D deficiency did have lower 25(OH)D nadirs

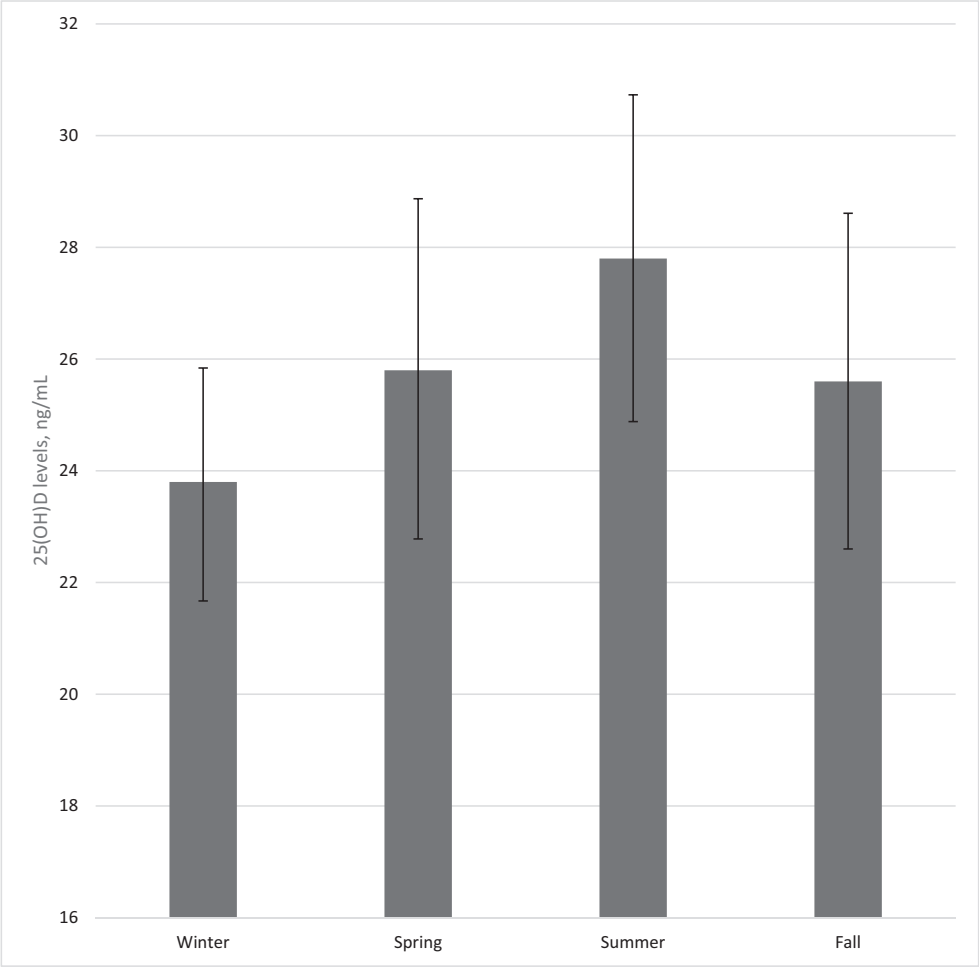

Fig. 4. Lowest measured pre-operative Vitamin D levels (in ng/mL of 25(OH)D) stratified by season in which they were collected. Seasons were defined as Winter (December to February), Spring (March to May), Summer (June to August), and Fall (September to November). Error bars represent 95% confidence intervals of the means.

and was more likely to be on Vitamin D supplementation, potentially explaining why the laboratory values were less predictive of cancer stage. These findings are significant because Vitamin D deficiency is easily modifiable and could prove to be a useful therapeutic target for improving outcomes for this disease. More study is needed to identify the contributions of pre-operative and post-operative Vitamin D supplementation and their effects on long term outcomes.

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Conflict of interest disclosures

No conflicts of interest exist for the authors in this study.

Presentation

Poster Presentation at the 3rd World Congress on Thyroid Cancer at Boston Convention Center, July 27th–30th 2017, Boston, Massachusetts.

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