Association Between Reduced Plasma 25-Hydroxy Vitamin D and Increased Risk of Cancer in Patients With Inflammatory Bowel Diseases

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BACKGROUND & AIMS: **Vitamin D deficiency is common among patients with inflammatory bowel diseases (IBD) (Crohn's disease or ulcerative colitis). The effects of low plasma 25-hydroxy vitamin D (25[OH]D) on outcomes other than bone health are understudied in patients with IBD. We examined the association between plasma level of 25(OH)D and risk of cancers in patients with IBD.**

METHODS: **From a multi-institutional cohort of patients with IBD, we identified those with at least 1 measurement of plasma 25(OH)D. The primary outcome was development of any cancer. We examined the association between plasma 25(OH)D and risk of specific subtypes of cancer, adjusting for potential confounders in a multivariate regression model.**

RESULTS: **We analyzed data from 2809 patients with IBD and a median plasma level of 25(OH)D of 26 ng/mL. Nearly one-third had deficient levels of vitamin D (<20 ng/mL). During a median follow-up period of 11 years, 196 patients (7%) developed cancer, excluding nonmelanoma skin cancer (41 cases of colorectal cancer). Patients with vitamin D deficiency had an increased risk of cancer (adjusted odds ratio, 1.82; 95% confidence interval, 1.25–2.65) compared with those with sufficient levels. Each 1-ng/mL increase in plasma 25(OH)D was associated with an 8% reduction in risk of colorectal cancer (odds ratio, 0.92; 95% confidence interval, 0.88–0.96). A weaker inverse association was also identified for lung cancer.**

CONCLUSIONS: **In a large multi-institutional IBD cohort, a low plasma level of 25(OH)D was associated with an increased risk of cancer, especially colorectal cancer.**

Keywords: Crohn's Disease; Ulcerative Colitis; Vitamin D; Malignancy; Colorectal Cancer.

See editorial on page 828.

The effects of vitamin D on bone metabolism are well recognized.[1,2] However, there is increasing recognition of the pleotropic effect of vitamin D on a spectrum of diseases, including autoimmunity, cardiovascular health, and cancer.[3–5] Epidemiologic studies suggest an increased risk of and mortality from cancer in residents of higher latitudes with lower ultraviolet light exposure, an association that may be mediated in part through vitamin D.[1,3,6] Furthermore, prospective cohorts have demonstrated an inverse association between plasma 25-hydroxy vitamin D (25[OH]D), the most stable measure of vitamin D status, and cancers of the colon, breast, and prostate.[7–12] The strongest evidence of an anticarcinogenic effect of vitamin D comes from a randomized controlled trial of over a thousand women in which supplementation with calcium and vitamin D reduced the risk of cancer by nearly 60%.[13]

Deficiency of vitamin D is common in patients with inflammatory bowel diseases (IBD; Crohn's disease [CD], ulcerative colitis [UC]) and may even precede the diagnosis of IBD.[14–16] However, there has been only limited

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; IQR, interquartile range; OR, odds ratio; 25(OH)D, 25-hydroxy vitamin D; UC, ulcerative colitis.

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study of the longitudinal consequences of low vitamin D in patients with IBD, particularly outside its effect on bone metabolism. Cross-sectional studies suggested an association between vitamin D status and disease activity,[17,18] a finding that was confirmed in a study from our group demonstrating an inverse association with IBD-related hospitalizations and surgery.[19] Furthermore, we also demonstrated that normalization of plasma 25(OH)D is associated with a reduction in this risk of IBD-related surgery.[19] No prior studies have examined the effect of vitamin D status on the risk of cancers in patients with IBD.

Using a well-characterized multi-institutional IBD cohort, we examined the association between plasma 25(OH)D and the risk of cancer. We then examined the association with specific types of cancers to see if the anticarcinogenic effect of vitamin D is specific to certain cancer subtypes in the IBD population.

Methods

Study Cohort

The development of our study cohort has been described in detail in previous publications.[19,20] In brief, we first identified all potential IBD patients by the presence of one or more *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (*ICD-9-CM*) codes for CD (555.x) or UC (556.x) in our electronic medical record (EMR). The EMR, initiated in 1986, covers 2 major teaching hospitals and affiliated community hospitals in the Greater Boston area and serves a population of over 4 million patients. From this cohort, we developed a classification algorithm incorporating codified data (*ICD-9-CM* codes for disease complications), use of IBD-related medications identified through the electronic prescriptions, as well as free-text concepts (such as the term *Crohn's disease*) identified using natural language processing. Our classification algorithm had a positive predictive value of 97% that was confirmed by a medical record review of an independent sample. Our final IBD cohort consisted of 5506 patients with CD and 5522 with UC.

Measurement of Plasma 25-hydroxy Vitamin D

The present study included all patients who had at least one available plasma 25(OH)D measured as part of the routine clinical care. Prior studies have demonstrated good intraclass correlation and stability of measures of plasma vitamin D with intraclass correlation coefficients of 0.72 and 0.52 at 3 and 10 years, respectively, comparable with the intraclass correlation coefficients for plasma cholesterol, an accepted marker of long-term cardiovascular risk.[21] Patients who had their vitamin D status assessed only after the diagnosis of cancer were excluded. Plasma 25(OH)D was measured using radioimmunoassay prior to 2008 and high performance liquid chromatography since. The lowest plasma 25(OH)D value was used to classify patients as deficient ($<$20 ng/mL), insufficient (20.0–29.9 ng/mL), and sufficient ($\geq$30 ng/mL) according to the current guidelines. IBD patients who had at least one measured 25(OH)D were similar in age but more likely to be female, require immunomodulator or biologic therapy, and undergo an IBD-related surgery or hospitalization compared with the rest of the patients in our IBD cohort.

Variables and Outcomes

We extracted information on patient age, sex, race (white, black, or other) as well as age at the first diagnosis code of IBD. We ascertained the use of IBD-related medications, including 5-aminosalicylates, systemic corticosteroids, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate) and anti–tumor necrosis factor biologics (infliximab, adalimumab, certolizumab pegol), and dates of IBD-related hospitalization and surgery.

Our primary outcome was the diagnosis code in the EMR of any malignancy excluding nonmelanoma skin cancers. This was further subdivided into solid organ tumors (*ICD-9-CM* 140–172.9, 174–195.8), hematologic malignancies including leukemia and lymphoma (*ICD-9-CM* 200–208.9), and metastatic cancers (*ICD-9-CM* 196–199.1). We then stratified by the type of cancer for the most common malignancies, including breast cancer (174.x), colorectal cancer (153.x–154.x), lung cancer (162.x), prostate cancer (185.x), melanoma (172.x), and pancreatic cancer (157.x). A chart review of random sets of 50 patients with each cancer type revealed a positive predictive value of 80% to 90%.

Table 1. Characteristics of the Study Cohort

Characteristic	N = 2809 (%)
Median age (IQR) (*y*)	46 (32–60)
Female	1712 (61)
UC	1244 (44)
Median age at first IBD diagnosis code (IQR) (*y*)	38 (27–52)
Ever biologic use	629 (22)
Immunomodulator use	1129 (40)
IBD-related hospitalizations	1135 (40)
Bowel resection	453 (16)
Race	
White	2444 (87)
Black	213 (8)
Other	152 (5)
Median duration of follow-up (IQR)	11 (5–18)
Median plasma 25(OH)D level (IQR)	26 (17–35)
Vitamin D status	
Deficient	885 (32)
Insufficient	807 (29)
Normal	1117 (40)
Any cancer	196 (7)
Metastatic cancer	72 (3)

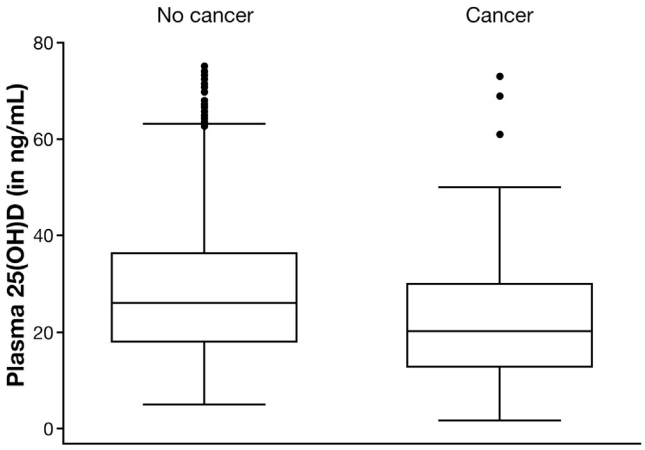

Figure 1. Plasma 25(OH)D levels in patients, stratified by subsequent diagnosis of cancer.

Statistical Analysis

All data analysis was performed using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized using medians and interquartile ranges (IQR); categorical variables were expressed as proportions. The *t* test was used to compare continuous variables, and the chi-square test (with Fisher's exact modification when appropriate) was used to compare categorical variables. Univariate logistic regression was used to examine the association between vitamin D status and the diagnosis of cancer. Vitamin D levels were modeled both as a continuous variable in increments of 1 ng/mL as well as an ordinal variable stratified as described above. Planned subgroup analyses were performed by the type of cancer. We also examined if the association with the vitamin D status differed by sex, IBD type, or immunosuppressant use. To examine if the difference in cancer diagnoses was due to greater intensity of health care utilization in those with low vitamin D levels (and consequently, richer follow-up in our medical system), we adjusted for a variable termed *fact density*. Each outpatient visit, inpatient stay, laboratory test, radiology examination, and inpatient or outpatient procedure constitutes a *fact*. Dividing this by the duration of follow-up in our system yields a *fact density* that is a measure of intensity of health care utilization per unit of time of follow-up within our health care system. A 2-sided P value $<.05$ in the multivariate model indicated independent statistical significance. The study was approved by the institutional review board of Partners Healthcare.

Results

Study Cohort

Our cohort included 2809 IBD patients with a median age of 46 years (IQR, 32–60 years) (Table 1). Over half the cohort was women (61%) and a majority was white (87%). The median age at the first diagnosis code for IBD was 38 years. Nearly half the patients required immunomodulators, whereas one-quarter was exposed to anti–tumor necrosis factor biologic therapy. The median plasma 25(OH)D level in our cohort was 26 ng/mL (IQR, 17–35 ng/mL). Nearly one-third of the cohort was deficient in vitamin D (<20 ng/mL), and a similar proportion had insufficient (20.0–29.9 ng/mL) levels. During a median follow-up of 11 years, 196 patients (7%) developed cancer, excluding nonmelanoma skin cancer. Seventy-two patients (3%) developed metastatic cancer. The median interval between the measurement of 25(OH)D and the first diagnosis code for cancer was 627 days (IQR, 268–1380 days).

Plasma Vitamin D and Risk of Cancer

The mean plasma 25(OH)D in patients who subsequently developed cancer was 5 ng/mL lower than in those who did not develop cancer (22.8 ng/mL vs 27.5 ng/mL, P <.0001) (Figure 1). Among the 881 patients who had deficient levels of vitamin D, 88 (10%) developed any cancer compared with 4% of patients with normal levels of plasma 25(OH)D (P <.001), yielding an odds ratio (OR) of 2.38 (95% confidence interval [CI], 1.67–3.39) (Table 2). This difference remained independently significant on multivariate analysis adjusting for age, sex, race, season of measurement, duration of follow-up, use of immunosuppression, and type of IBD (adjusted OR, 1.82; 95% CI, 1.25–2.65). Patients with insufficient levels of plasma 25(OH)D had an intermediate cancer risk.

Each 1-ng/mL increase in plasma 25(OH)D was associated with a similar reduction in risk of nonmetastatic (OR, 0.97; 95% CI, 0.95–1.00) and metastatic cancer (OR, 0.98; 95% CI, 0.96–1.00; P <.05 for both)

Table 2. Plasma 25(OH)D and Risk of All Malignancy in Patients With IBD

Vitamin D stratum	No cancer, n (%)	Cancer, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
≥30 ng/mL	1065 (95)	52 (5)	1.0	1.0
20.0–29.9 ng/mL	741 (92)	66 (8)	1.82 (1.25–2.66)	1.69 (1.15–2.51)
<20 ng/mL	793 (90)	92 (10)	2.38 (1.67–3.38)	1.82 (1.25–2.65)

[a]Adjusted for age, sex, race, season of measurement, duration of follow-up, immunosuppression use, and IBD type.

Table 3. Plasma 25(OH)D and Risk of Malignancy in Patients With IBD Stratified by Subgroups

Subgroup	Adjusted OR[a,b]	95% CI	*P* value
By metastatic status			
Nonmetastatic	0.97	0.95–1.00	.02
Metastatic cancer	0.98	0.96–1.00	.01
Sex			
Male	0.97	0.95–0.99	.01
Female	0.98	0.97–1.00	.03
IBD type			
CD	0.98	0.96–1.00	.02
UC	0.98	0.96–1.00	.02

[a]For each 1-ng/mL increase in plasma 25(OH)D.
[b]Adjusted for age, sex, race, season of measurement, duration of follow-up, immunosuppression use, and IBD type.

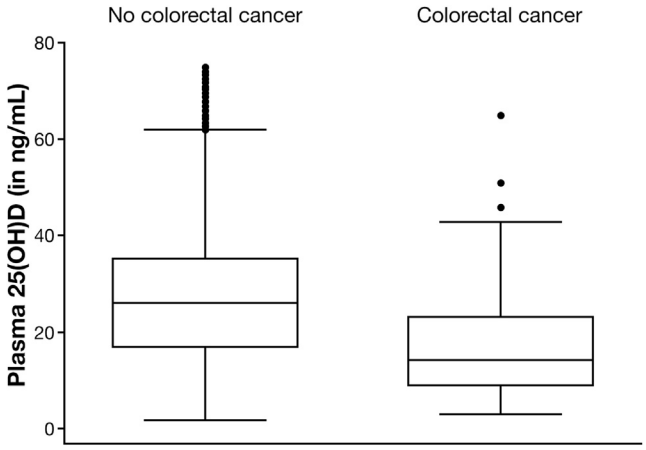

Figure 2. Plasma 25(OH)D levels in patients, stratified by subsequent diagnosis of colorectal cancer.

(Table 3). The magnitude of reduction in risk was similar across IBD types and sex. Adjusting for the intensity of health care utilization did not result in significant changes to our final estimates (OR, 1.83; 95% CI, 1.24–2.69).

Vitamin D and Incidence of Specific Cancers

We then examined if the association with plasma 25(OH)D was confined to specific cancers. The strongest inverse association was identified for colorectal cancer with a 6% reduction in risk for each 1-ng/mL increase in plasma 25(OH)D (OR, 0.94; 95% CI, 0.91–0.97) (Table 4, Figure 2). A statistically significant inverse association was also identified for lung cancer (OR, 0.95; 95% CI, 0.90–0.99). None of the other common cancers demonstrated a significant association.

Discussion

Vitamin D has pleiotropic effects on the immune system[4,16,22–24] and has been associated with reduced risk of autoimmunity, cardiovascular disease, and cancer.[4,5,23–25] However, no prior studies have examined the association between vitamin D and cancer in chronic immune-mediated diseases where mechanisms of cancer may be distinct and other competing factors may influence both the vitamin D status and risk of cancer. In a multi-institutional IBD cohort, we demonstrate an inverse association between plasma 25(OH)D and the risk of malignancy, with statistically significant inverse associations with colorectal cancer and lung cancer.

Vitamin D deficiency is common in patients with IBD, with most studies reporting up to a third of patients being deficient and an equal proportion with insufficient levels.[14,16–18] Such deficiency does not appear to be solely a consequence of the disease,[17,18] as similar levels of deficiency have been reported in those with newly diagnosed IBD,[14] and it may even precede the diagnosis of IBD.[15] There has been limited examination of the longitudinal implications of vitamin D deficiency in an IBD population. Low plasma 25(OH)D is associated with increased risk of IBD-related hospitalizations and surgery; normalization of plasma 25(OH)D is associated with a reduction in this risk.[19] The main findings from our study suggest that, in addition to its association with disease activity, low vitamin D levels in patients with IBD may also contribute to an increased risk of malignancy, particularly that of colorectal cancer. This provides further evidence supporting the incorporation of the routine assessment of vitamin D status in the care of IBD patients and appropriate treatment to prevent long-term complications.

Few studies have examined the association between vitamin D status and the overall risk of cancer. A large cohort study of 9949 men and women followed for a median of 8 years found no association between vitamin D and overall cancer or site-specific cancer incidence.[26] However, in another prospective study from Germany, vitamin D deficiency was associated with an increased risk for overall mortality and cardiovascular and cancer mortality.[27] A randomized controlled trial of 1179

Table 4. Plasma 25(OH)D and Risk of Individual Cancers in Patients With IBD

Type of cancer	No. of cases	Adjusted OR (95% CI)[a,b]	*P* value
Colon cancer[c]	41	0.94 (0.91–0.97)	.01
Breast cancer	31	0.99 (0.96–1.02)	.47
Prostate cancer	19	1.00 (0.97–1.05)	.82
Hematologic	45	0.98 (0.95–1.00)	.10
Lung cancer	19	0.95 (0.90–0.99)	.02
Pancreatic cancer	13	0.97 (0.92–1.02)	.26
Melanoma	19	1.01 (0.98–1.05)	.50

[a]For each 1-ng/mL increase in plasma 25(OH)D.
[b]Adjusted for age, sex, race, season of measurement, duration of follow-up, immunosuppression use, and IBD type.
[c]Additionally adjusted for presence of primary sclerosing cholangitis.

postmenopausal women randomized to calcium and vitamin D (1000 mg/1100 units) supplementation demonstrated a 60% reduction in cancer risk with vitamin D supplementation and an even stronger effect excluding cancers diagnosed within the first year.[13] Although the Women's Health Initiative trials of calcium and vitamin D supplementation did not identify a similar benefit, this could potentially be explained by the lower dose of vitamin D (400 IU daily) used in the trials.[28] A statistically significant reduction in colorectal cancer (CRC) risk was identified in the Women's Health Initiative trial in patients who were noted to have a significant increase in their plasma 25(OH)D.[29] Considerable biological plausibility suggests an anticancer effect of vitamin D. The local production of 1,25-dihydroxy D (1,25 $[OH]_2D_3$) inhibits cancer cells through pathways involving cyclin-dependent kinase inhibitor synthesis, Wnt/β-catenin, mitogen activated protein–kinase, and nuclear factor-κB[3]. In addition, $1,25(OH)_2D_3$ promotes proapoptotic mechanisms and the induction of autophagy leading to the death of cancer cells.[3,30–33]

There is particularly strong evidence supporting a role of vitamin D in the development of sporadic colon cancer.[7,11] In large epidemiologic studies, low plasma 25(OH)D was associated with an increased risk of CRC in men and women.[7,9,11] Expression of the vitamin D receptor is down-regulated in colitis-associated dysplasia and may be involved in progression to CRC.[34] The Wnt/β-catenin pathways also play a role in the pathogenesis of CRC; $1,25(OH)_2D_3$ inhibits signaling through this pathway.[35,36] Finally, vitamin D could enhance differentiation of colon cancer cells through induction of adhesion molecules, such as E-cadherin.[3] However, there are significant differences in the molecular pathology of colitis-associated cancer compared with sporadic CRC. Mutation in the tumor suppressor gene p53 occurs earlier and more frequently in colitis-associated cancer than sporadic CRC.[37] In contrast, mutation at the APC gene occurs early in sporadic colon cancer. Furthermore, epigenetic differences may exist between sporadic and colitis-associated cancer. Our findings suggest that the role of vitamin D in the development of CRC may be through pathways that are common to both sporadic and colitis-associated cancers.

There is less biologic data to explain the association between the vitamin D and lung cancer.[33] First, this result could potentially be confounded by smoking status, which is the strongest risk factor for lung cancer. However, smoking has not been shown to be consistently associated with vitamin D status and is, thus, unlikely to be differentially distributed to explain the association. In a study by Afzal et al[38] from the Copenhagen heart study, lower plasma 25(OH)D was associated with an increased risk of all tobacco-related cancers, including lung cancer (OR, 1.19; 95% CI, 1.09–1.31). In a Norwegian cohort, early mortality within 18 months of the diagnosis was higher in patients diagnosed with lung cancer during the winter/spring months when compared with those diagnosed during summer.[39]

There are a few implications to our findings. To our knowledge, ours is the first study to demonstrate an association between plasma 25(OH)D and the risk of malignancy, particularly CRC in an IBD cohort. Prior observational studies have demonstrated that the normalization of vitamin D status can be associated with a reduction in risk of surgeries and hospitalizations, particularly in patients with CD.[19] Furthermore, a randomized controlled trial by Jorgensen et al[40] demonstrate a trend toward reduced rates of relapse in patients supplemented with vitamin D compared with placebo. Our findings suggest that the reduction in colorectal cancer risk may also be achievable through supplementation with vitamin D, though a prospective clinical trial to examine this hypothesis would likely be prohibitively large and require a considerable length of follow-up.

There are several limitations to our study. First, because our cohort is based primarily at 2 referral centers, the population may be skewed toward greater severity of underlying IBD. Second, we did not have information on body mass index or smoking status, both of which have been associated with overall risk of malignancy and colorectal cancer. However, an effect of body mass index and smoking on IBD-related cancers has not been noted previously. Third, we did not have information on medications such as aspirin and nonsteroidal anti-inflammatory drugs, both of which have been inversely associated with the development of CRC. However, long-term use of such medications is uncommon in patients with IBD because of their potential to trigger disease relapses. Fourth, we were not able to perform fine adjustments for the disease duration and activity, which may have relevance with regard to colorectal cancer risk. However, it is also unclear if disease activity is a confounder or could plausibly be within the causal pathway given the association between low vitamin D and disease severity and the impact of normalization of vitamin D on the prevention of relapse and reducing IBD-related surgeries and hospitalization. Fifth, for inclusion in our study, patients had to have their vitamin D level measured within our health care system. For a cancer diagnosis to be captured, the patient should have had at least one *ICD-9* code for the relevant cancer within our system (at diagnosis or subsequently on referral for surgical or oncologic management). Finally, the measurement of vitamin D was a part of routine clinical care and not systematically performed across all patients; fewer than half of our IBD cohort had a measured plasma 25(OH)D. Nevertheless, to our knowledge, this remains the largest cohort containing information on the vitamin D status of patients with IBD. The diagnosis of cancer was made based on codes within our EMR and not using systematic links to regional or national cancer registries. However, one would expect such misclassification to bias the results toward the null, making ours a conservative estimate.

In conclusion, using a large multi-institutional IBD cohort, we demonstrated that low plasma 25(OH)D is

associated with an increased risk of metastatic and nonmetastatic cancers. In particular, the association was strongest for colorectal cancer. An assessment of vitamin D status should routinely be part of comprehensive care of patients with IBD.

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Conflicts of interest
The authors disclose no conflicts.

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