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Chemotherapy is linked to severe vitamin D deficiency in patients with colorectal cancer

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Abstract

Background—Preclinical and clinical evidence support an association between vitamin D deficiency and an increased risk of colorectal cancer. Normal vitamin D status has been linked to favorable health outcomes ranging from decreased risk of osteoporosis to improved cancer mortality. We performed a retrospective study to assess the impact of metastatic disease and chemotherapy treatment on vitamin D status in patients with colorectal cancer residing in Western New York.

Materials and methods—Patients, 315, with colorectal cancer treated in a single institute were assayed for 25-OH vitamin D. The association of age, gender, primary disease site and stage, body mass index, and chemotherapy with vitamin D status was investigated.

Results—Vitamin D deficiency was common among participants with a median 25-OH vitamin D level of 21.3 ng/ml (optimal range 32–100 ng/ml). Primary site of disease and chemotherapy status were associated with very low 25-OH vitamin D levels (≤15 ng/ml) on multivariate analysis. Patients receiving chemotherapy and patients with a rectal primary were fourfold and 2.6-fold more likely to have severe vitamin D deficiency on multivariate analysis than nonchemotherapy patients and colon cancer primary patients, respectively.

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Conclusions—Chemotherapy is associated with a significant increase in the risk of severe vitamin D deficiency. Patients with colorectal cancer, especially those receiving chemotherapy, should be considered for aggressive vitamin D replacement strategies.

Keywords

Colorectal cancer; vitamin D; 25-hydroxy vitamin D; Chemotherapy

Introduction

Several epidemiological studies have supported an association between vitamin D deficiency and an increased risk of colorectal cancer. Garland et al. demonstrated an indirect association between vitamin D status and risk of colorectal cancer through the study of colorectal cancer incidence and sunlight exposure in the US [1]. A strong inverse relationship was noted between sunlight exposure and colorectal cancer mortality in metropolitan states [1]. These investigators hypothesized that increased sunlight exposure protects against colorectal cancer through the increased skin synthesis of vitamin D. This was supported by the geographical differences in serum vitamin D levels that paralleled the degree of sunlight exposure [1].

Sun exposure is considered the major source of vitamin D in humans. Vitamin D is synthesized in the skin under the influence of UV light exposure and subsequently hydroxylated in the liver to 25-OH vitamin D and in the kidneys and peripheral tissue to the active metabolite 1,25-OH vitamin D. 25-Hydroxylation (in contrast to 1-hydroxylation) is not tightly regulated, making 25-OH vitamin D the best surrogate of vitamin D status [2]. Furthermore, the half-life of 25-OH vitamin D is about 3 weeks, and thus, its measurement may reflect an individual's status over several weeks to months.

Several case control studies have shown an association between 25-OH vitamin D deficiency and colorectal cancer [3-7]. Despite the association between vitamin D status and risk of colorectal cancer, scant information exists on vitamin D and colorectal cancer progression across stages I–IV. Furthermore, no data exists regarding the interaction between vitamin D status and colorectal cancer treatment, especially chemotherapy. One study investigated 25-OH vitamin D and 1,25-OH vitamin D status across stages I–IV of colorectal cancer [8]. Surprisingly, 25-OH vitamin D levels in colon cancer cases were higher than the controls in this study [8]. Furthermore, 25-OH D3 levels did not change across the various stages of colorectal cancer, while 1,25-OH vitamin D decreased with increasing stage [8]. The results from this study seem at odds with the results of prior case-controlled studies that show a role for 25-OH vitamin D status in colorectal carcinogenesis but not for 1,25-OH vitamin D [4,9, 10]. Given the limited information on vitamin D status across various stages of colorectal cancer and in view of emerging clinical data supporting an impact of vitamin D status on cancer outcome [11], we investigated vitamin D status in 315 patients with colorectal cancer treated in a single institute.

Materials and methods

Given the general health benefits associated with normal vitamin D status and the known association between vitamin D deficiency and colorectal cancer, we have implemented the practice of routine 25-OH vitamin D assays in all medical oncology colorectal cancer patients starting April 2006. Patients with vitamin D levels <30 ng/ dl were offered vitamin D3 supplementation. Over a period of 1 year, more than 300 patients with colorectal cancer were tested for a baseline 25-OH vitamin D. A retrospective study of this population was performed to evaluate the relation between vitamin D status, stage, patient demographics, and

chemotherapy treatment. The study was approved by the Institutional Review Board at Roswell Park Cancer Institute (RPCI).

Study conduct

Medical records of all patients treated in the Colorectal Medical Oncology Clinic at RPCI between April 1st of 2006 and January 31st of 2007 were reviewed. All patients with a 25-OH vitamin D level were identified. Only patients without pharmacological vitamin D replacement (>400 IU of vitamin D) at the time of assay were included. Patients receiving a multivitamin or 400 IU or less of vitamin D per day were included in the analysis. Demographic data including age, sex, stage of disease at the time of 25-OH vitamin D levels, body mass index, date of 25-OH vitamin D assay, and treatment history, were collected. The first 25-OH vitamin D assay was used as the baseline in patients with multiple 25-OH vitamin D testing. Chemotherapy status was documented in all patients. Colorectal cancer patients were divided into two categories. The first category was labeled “no chemotherapy group.” This included all patients who did not receive any chemotherapy or whose last chemotherapy treatment was at least 3 months prior to 25-OH vitamin D assay. The second category was labeled “chemotherapy group.” This included all patients whose baseline 25-OH vitamin D level was obtained during chemotherapy treatment or within 3 months after last dose of chemotherapy. All colorectal cancer cases were located in the same general geographical area (Western New York).

Vitamin D assay

25-OH vitamin D in colorectal cancer patients was assayed by a standard commercially available Immunochemiluminometric Assay (ICMA)[1]. The lower normal threshold on this assay is 32 ng/ml. This is largely based on the maximum suppression of parathyroid hormone (PTH) above this threshold [12]. The normal recommended 25-OH vitamin D levels using this assay are 32 to 100 ng/ml.

Statistical analysis

The association of age, sex, race, BMI, primary site, stage of disease, chemotherapy status, and date of vitamin D assay on vitamin D status was initially investigated by univariate analysis. Continuous variables such age and BMI were categorized. The odds ratio was defined as the ratio of odds for a subject with “very low” (≤15 ng/ml) 25-OH vitamin status at one level of a specific variable with respect to the default or reference level. As one or more of the cell frequencies are lower than or equal to 5, the reported *p* values were by exact Pearson Chi-square test; otherwise, Chi-square tests. To simultaneously consider the impact of age, sex, race, BMI, primary site, stage of disease, and time on vitamin D status, multiple logistic regression was performed by fitting the log of odds (with “very low” 25-OH vitamin status) on the explanatory variables described above. The computation of *p* values and the confidence intervals for odds ratio was based on individual Wald tests.

Results

Patient demographics

Three hundred and fifteen patients with CRC had a baseline 25-OH vitamin D assayed between April 1st of 2006 and January 31st of 2007. Fifty-five percent were males. The median age of the population was 61 years (range 31 to 91 years). Most patients had metastatic disease (57%), reflecting a typical medical oncology practice. About 70% of the patients had colon, and 30% had rectal cancer. More than half (59.4%) of the samples were obtained in the Summer/Fall

[1]http://www.labcorp.com/datasets/labcorp/html/chapter/mono/sr004600.htm, last accessed on January 05, 2008

(June 1st to November 30th), and the rest (40.6%) were drawn in Winter/Spring (December 1st to May 31st). The mean and median 25-OH vitamin D levels in the overall colorectal population were 23.7 and 21.3 ng/ml, respectively. Patient demographics are summarized in Table 1.

Impact of patient demographics on vitamin D status

For the purpose of this study, 25-OH vitamin D status was dichotomized into two categories "very low" and "low to normal." The "very low" category was defined as ≤15 ng/ml and the "low to normal" category was defined at >15 ng/ml. Levels below 15 ng/ml have been historically considered as low. Furthermore, ≤15 ng/ml corresponds to the lowest quartile of our population. Variables investigated included age, sex, race, body mass index (BMI), primary site (colon vs. rectum), stage of disease (stages I–III vs. IV), and date of 25-OH vitamin D assay. Stage, primary site, and chemotherapy were found to be associated with vitamin D status on univariate analysis (Table 2). Stage IV disease and rectal cancer were 1.7 and 1.8 times more likely to be associated with low 25-OH vitamin D levels than stages I–III and colon cancer, respectively. Patients in the chemotherapy group were 3.2 times more likely to have very low 25-OH vitamin D levels than patients not receiving chemotherapy ($p<0.0001$). Only primary site and chemotherapy status maintained their statistically significant influence on vitamin D status on multivariate regression analysis (Table 2). Chemotherapy status remained the most important prognostic variable for very low 25-OH vitamin D levels on multivariate analysis (OR=4; 95% CI=1.9–7.35), followed by a rectal primary diagnosis (OR=2.6; 95% CI=1.4–4.5).

Discussion

Several preclinical and clinical studies support a protective role for vitamin D from colorectal carcinogenesis. Vitamin D Receptor (VDR) is expressed in normal intestinal epithelium and in colonic polyps but its expression steadily decreases with colorectal tumor progression [13-17]. VDR is the target of the active vitamin D compound 1,25-OH vitamin D (1,25-OH D3), and the binding of this compound to VDR results in antiproliferative and differentiating activities [18,19]. Vitamin D3 antiproliferative effects on colonic epithelium have been demonstrated clinically. The supplementation of vitamin D3 in combination with calcium carbonate was shown to reduce the proliferative index and increase VDR expression in colonic polyps and mucosa [20]. Furthermore, an inverse relationship between serum 25-OH vitamin D levels and whole-crypt proliferative index has been documented [21]. Epidemiological data lends further support to the importance of 25-OH vitamin D status in colorectal carcinogenesis. Three studies have shown a lower incidence of colorectal adenomas in patients with higher 25-OH vitamin D levels [9,22,23]. Similar associations have been confirmed in later stages of colorectal carcinogenesis [3-7,24]. Garland et al. matched 67 controls to 34 cases with colorectal cancer identified among a population cohort of 25,620 volunteers in Maryland, USA [3]. This 8-year prospective study showed a reduction in the risk of colorectal cancer by 75% and 80% in the third and fourth quintile of serum 25-OH vitamin D in comparison to the lowest quintile. However, a subsequent follow-up study based on the same population cohort did not support the same association [25]. The negative results on the follow-up study may have been attributed to prolonged lag period (10–17 years) between serum vitamin D assays and development of colorectal cancer. It is unclear if the cases or controls would have maintained the same vitamin D status over a course exceeding a decade. Four subsequent nested case control studies (Finnish clinical trial cohort, Nurses' Health Study, Women Health Initiative Study, and the Health Professional Follow-up Study) showed a clear protective effect of 25-OH vitamin against the risk of colorectal cancer [4-7]. This has been supported further by a metanalysis of five case-controlled studies that suggested a 50% lowering of the risk of

colorectal cancer in association with 25-OH vitamin D levels ≥33 ng/ml compared to levels ≤12 ng/ml [24].

Despite the strong evidence linking vitamin D deficiency and an increased risk of colorectal cancer, no substantial information is available on the vitamin D status across different stages of colorectal cancer or its interaction with chemotherapy in this population. We have evaluated vitamin D status in 315 colorectal cancer patients in various stages of disease through the measurement of 25-OH vitamin D. As expected, 25-OH vitamin D level in this population was low; the median level was 21.3 ng/ml which is considerably lower than the optimal threshold of 32 ng/ml. In a univariate and multivariate regression analysis, chemotherapy treatment was associated with a significant increase in the risk of vitamin D deficiency. The odds of having severe vitamin D deficiency (25-OH vitamin D≤15 ng/ml) in a patient receiving chemotherapy was fourfold higher than a patient with colorectal cancer who never received chemotherapy or completed chemotherapy at least 3 months prior to their vitamin D assay. The chemotherapy regimens used in our study patients were irinotecan-based in 43% of patients (irinotecan plus 5-FU and leucovorin with or without bevacizumab or irinotecan plus cetuximab), oxaliplatin-based in 39% of patients (oxaliplatin plus 5-FU and leucovorin with or without bevacizumab), and a fluoropyrimidine in 18% of patients (5-FU plus leucovorin or capecitabine with our without bevacizumab). We did not investigate the effect of the dosing or chemotherapy regimen on 25-OH vitamin D levels for two reasons. First, given the various numbers of regimens, the number of patients receiving chemotherapy would not be powered adequately to detect significant differences among various regimens. Second, a large number of patients receiving chemotherapy had received more than one line of chemotherapy treatment making it difficult to attribute the association of the vitamin D deficiency to one chemotherapy regimen versus another. Given the retrospective nature of this study, it is impossible to explore potential causes of this deficiency. It is plausible that patients undergoing chemotherapy are less likely to participate in outdoor activities and thus experience less sunlight exposure. It is also possible that chemotherapy administration results in dietary modifications such as reduction or elimination of milk products (milk is fortified with vitamin D) as part of the management of chemotherapy-induced diarrhea. It is also possible that patients undergoing chemotherapy do not absorb dietary vitamin well due to subclinical mucositis. Lastly, it is possible that chemotherapy induces the metabolism of 25-OH vitamin D into inactive compounds such as 24,25 OH vitamin through the activation of CYP3A4 or other metabolizing enzymes. We are currently performing a prospective supplementation study of 2,000 IU/day of vitamin in patients with colorectal cancer to determine the impact of chemotherapy administration on response to vitamin D3 supplementation. Irrespective of the mechanism of the deficiency, the association between chemotherapy and 25-OH vitamin D deficiency has significant clinical significance. The established role of vitamin D status in bone health and fracture prevention, muscle strength, immune system modulation, diabetes, and cancer prevention has been recently reviewed [2]. Review of the epidemiological data suggests that an optimal level of vitamin D for bone health and colorectal cancer prevention is a level exceeding 30 ng/ml, and possibly 40 ng/ml [2]. Only about one quarter of our colorectal cancer population had levels exceeding the 30 ng/ml threshold. We should also note that vitamin D status may be of significant importance in cancer outcome. A recent study analyzed the outcome of colorectal cancer patients who had a baseline vitamin D level (RIA) at least 2 years prior to cancer diagnosis through a retrospective analysis of the NHS and NPFS studies [26]. Three hundred and four colorectal cancer cases were identified. Stages I–IV of colorectal cancer were equally distributed among all four quartiles of 25(OH)D. Yet, the mortality rate was the lowest in the highest quartile of 25(OH)D. Compared to the lowest quartile, the highest quartile had an adjusted HR for overall mortality of 0.52 (95% CI, 0.29–0.94). The HR for colorectal cancer mortality was 0.61 (95% CI, 0.31–1.19) for the highest 25(OH)D quartile compared to the lowest [26]. This study strongly suggests a correlation between vitamin D status and the risk of death from colorectal cancer. Whether this association is a cause–effect association or

signifies a common association between a more replete vitamin D status and other factors that positively impact colorectal cancer outcome remains to be determined. Similar findings have been replicated in lung cancer. Patients with early stage non-small-cell lung cancer with vitamin D deficiency suffered from a worse overall survival in comparison to a vitamin-D-replete population [11].

There is no clear explanation for the increased risk of “very low” 25-OH vitamin D in the rectal cancer population in comparison to the colon cancer population. However, a greater increase in the risk of rectal cancer in lower sunlight regions has been described for rectal cancer than for colon cancer [27]. Furthermore, a recent Japanese case-control study has shown an increased risk of rectal cancer among patients with low 25-OH vitamin D levels and failed to show the same among colon cancer patients [28]. It is possible that the carcinogenesis process in the left colon and rectum is more susceptible to vitamin D deficiency. It is known that colorectal tumors with microstatellite instability involve predominantly the right colon [29]. These tumors have a variant carcinogenesis pathway that may not be dependent on vitamin D status [30,31].

Our study suffers from significant limitations. We did not factor in for multivitamin intake of for 25-OH vitamin D supplements of ≤400 IU in our population. We do not believe that this amount of replacement would have significant impact on our study as the prevalence of this practice is likely even across different subgroups. More importantly, such replacement strategy would be expected to have a minimal impact on 25-OH vitamin D levels [2]. The retrospective nature of our study does not factor in sun exposure and dietary difference among various subgroups, both of which are known to significantly affect vitamin D status.

This study should raise awareness to the common vitamin D deficiency status among colorectal cancer patients, especially those receiving chemotherapy. With a large number of patients receiving adjuvant chemotherapy and achieving a cure, this population may eventually suffer from an increased risk of osteoporosis and fracture with long-term follow-up, highlighting the need for vitamin D status optimization. Furthermore, the emerging role of vitamin D in immune-mediated response supports the need to investigate and optimize vitamin D status in the general population and especially those at risk for infection secondary to chemotherapy [32]. Prospective and well-controlled retrospective evaluation of vitamin D status effect on bone health, toxicity, and overall survival in patients with colorectal cancer as well as other cancers should be conducted. Aggressive vitamin D replacement strategies with dosages exceeding 400 IU/day should be considered in deficient patients.

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Table 1

Colorectal cancer patient characteristics

Characteristics	**Study sample (*N*=315)**
Median age	61 years
Mean age	60.73±12.97 (years)
Gender	
Male	54.92%(173 patients)
Female	45.08%(142 patients)
Mean BMI	28.08±6.33
Mean 25-OH vitamin D level (ng/ml)	23.66±13.71
Race	
White	90.79%(286 patients)
African American	7.62% (24 patients)
Other	1.59% (5 patients)
Colon cancer	70.16%(221 patients)
Rectal cancer	29.84% (94 patients)
Treatment status	
Chemotherapy	48.57%(153 patients)
No chemotherapy	51.43%(162 patients)
Stage of disease	
Stages I–III	42.86% (135 patients)
Stage IV	57.14% (180 patients)
Season	
Summer/Fall[a]	59.37% (187 patients)
Winter/Spring[b]	40.63% (128 patients)

BMI body mass index

[a] June to November

[b] December to May

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Table 2

Univariate and multivariate data analysis for colorectal cancer cases

Category		**Serum vitamin D level**		**Univariate analysis Odds ratio[a] (confidence interval)**	**Multivariate analysis Odds ratio[a] (confidence interval)**
n=315		**<15 ng/ml**	**>15 ng/ml**		
Age	≤65	60	145	1.0	1.0
	>65	27	83	0.79 (0.46, 1.33)	1.04 (0.58, 1.86)
Race	White	76	210	1.0	1.0
	Black	9	15	1.66 (0.70, 3.95)	1.67 (0.64, 4.34)
	Other	2	3	1.84 (0.30, 11.24)	3.36 (0.49, 23.20)
Gender	Male	42	131	1.0	1.0
	Female	45	97	1.45 (0.88, 2.38)	1.61 (0.93, 2.76)
BMI	<25 Normal	29	75	1.0	1.0
	25–30 Overweight	26	87	0.77 (0.42, 1.43)	1.09 (0.55, 2.13)
	>30 Obese	32	66	1.25 (0.69, 2.29)	1.87 (0.95, 3.70)
Chemo	None	27	135	1.0	1.0
	Chemotherapy	60	93	3.23 (1.91, 5.46)	3.74 (1.90, 7.35)
Primary_Site	Rectal	34	60	1.0	1.0
	Colon	53	168	0.56 (0.33, 0.94)	0.39 (0.22, 0.71)
Stage	I, II, III	29	106	1.0	1.0
	IV	58	122	1.74 (1.04, 2.91)	1.07 (0.57, 2.0)
Season	Summer/Fall[b]	41	146	1.0	1.0
	Winter/Spring[c]	46	82	2.0 (1.21, 3.29)	1.22 (0.68, 2.17)

[a] Odd is defined as the ratio of the number of subjects having vitamin D level ≤15 to the number of subjects having vitamin D level >15

[b] June to November

[c] December to May