

## Retrospective Cohort Study

## Association between serum vitamin D levels and gastric cancer: A retrospective chart analysis

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### Abstract

#### AIM

To determine whether there is an increased risk of gastric adenocarcinoma associated with vitamin D deficiency (VDd).

#### METHODS

A retrospective case control study was performed of all patients diagnosed with gastric adenocarcinoma between 2005 and 2015. After we excluded the patients without a documented vitamin D level, 49 patients were included in our study.

#### RESULTS

The average age of patients with gastric adenocarcinoma and documented vitamin D level was 64 years old (95%CI: 27-86) and average vitamin D level was 20.8 mg/dL (95%CI: 4-44). Compared to a matched control group, the prevalence of VDd/insufficiency in patients with gastric adenocarcinoma was significantly higher than normal vitamin D levels (83.7% vs 16.3%). Forty-one patients (83.7%) with adenocarcinoma showed VDd/insufficiency compared to 18 (37%) patients with normal vitamin D level without gastric cancer (OR: 8.8, 95%CI: 5-22,  $P$  value < 0.0001). The average age of males with gastric adenocarcinoma diagnosis was 60 years old vs 68 years old for females ( $P$  = 0.01). Stage

II gastric adenocarcinoma was the most prevalent in our study (37%).

### CONCLUSION

We reported a positive relationship between VDd and gastric adenocarcinoma, that is to say, patients with decreased VDd levels have an increased propensity for gastric adenocarcinoma.

**Key words:** Gastric cancer; Adenocarcinoma; Vitamin D

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**Core tip:** In recent years, vitamin D deficiency (VDd) has been associated with several gastrointestinal malignancies largely mediated by vitamin D receptors. It affects multiple cellular processes such as inhibiting differentiation, metastasis, proliferation and inducing apoptosis and cell cycle arrest. All these mechanisms support vitamin D's anti-cancer role. VDd removes the tumorigenic activity that it elicits from regulating cell cycle, inhibiting cellular proliferation, angiogenesis and molecular signaling. Several studies have revealed that vitamin D<sub>3</sub> substantially promotes apoptosis in undifferentiated gastric malignant cells, specifically HCG-27. A retrospective research was conducted to find an association between vitamin D serum levels and gastric cancer.

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## INTRODUCTION

Vitamin D is a fat soluble secosteroid responsible for enhancing intestinal absorption of several key nutrients such as calcium, magnesium, iron and phosphate. It is known to affect intestinal, skeletal and biologic pathways such as immune cells and tumor microenvironment. Vitamin D exists in two forms - vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol), which is obtained from foods such as fortified dairy products, eggs, fish and liver<sup>[1]</sup>. The development of vitamin D<sub>3</sub> also stems from the conversion process of 7-hydrocholesterol in the dermis after exposure to sunlight (ultraviolet-B radiation)<sup>[2]</sup>. Vitamin D<sub>2</sub> and D<sub>3</sub>, whether from diet or dermal synthesis, is considered biologically inactive. The activation process begins in the liver where hydroxylation occurs by enzyme 25-hydroxylase, which results in 25-hydroxy vitamin D [25(OH)D]<sup>[1-3]</sup>. Next, 25(OH)D travels to the kidneys to become the active form of vitamin D; 1,25(OH)<sub>2</sub>D<sub>3</sub> by 1 alpha hydroxylase<sup>[2,3]</sup>. Subsequently, vitamin D<sub>3</sub> is released to serum where it

acts on receptors of the intestine, bone and kidney to regulate calcium metabolism<sup>[2,4,5]</sup>.

Measurement of 25(OH)D level is the highly indicative for overall vitamin D status. 25(OH)D accounts for sunlight exposure, dietary intake and conversion from adipose tissue<sup>[3,6,7]</sup>. Vitamin D deficiency (VDd) is defined as 25(OH)D < 15-20 mg/dL and sufficient range > 30 mg/dL.

In recent years, VDd has been associated with a multitude of gastrointestinal malignancies largely mediated by vitamin D receptors (VDRs). It affects multiple cellular processes such as inhibiting differentiation, metastasis, proliferation and inducing apoptosis and cell cycle arrest. All these mechanisms support vitamin D's anti-cancer role. Numerous studies have associated colon cancer with low vitamin D, however limited data suggests an association with gastric cancer<sup>[8-11]</sup>.

Gastric adenocarcinoma is considered the fourth most common cancer worldwide. A major risk factor for development of gastric adenocarcinoma is *Helicobacter pylori* (*H. pylori*) infection<sup>[2]</sup>. Other risk factors include smoking and alcohol use. However, recent studies show that VDd is associated with poor prognosis in gastric adenocarcinoma<sup>[3]</sup>. Recent cohort studies revealed that increased serum vitamin D levels are linked to a decreased risk of gastric cancer.

VDd removes the tumorigenic activity that it elicits from regulating cell cycle, inhibiting cellular proliferation, angiogenesis and molecular signaling<sup>[12]</sup>. Current research illustrates that vitamin D<sub>3</sub> increases apoptosis in undifferentiated gastric malignant cells, specifically HCG-27 cell lines<sup>[3]</sup>. In order to find a correlation between serum levels of vitamin D and gastric adenocarcinoma a retrospective research was conducted.

## MATERIALS AND METHODS

### Study design

A retrospective, single-centered study was performed of all subjects diagnosed with gastric adenocarcinoma between 2005 and 2015. This study was conducted at a tertiary medical center in one of the most diverse communities in the United States, which provided a significant cultural and epidemiological advantage. This study was approved by Icahn School of Medicine at Mount Sinai, Institutional Review Board.

### Selection criteria

Among 3200 patients with gastrointestinal malignancies diagnosed between 2005 and 2015, 304 patients had gastric adenocarcinoma. Patients who did not have a vitamin D level were excluded. Of the 304 patients with gastric adenocarcinoma, 49 patients had documented vitamin D levels, documented gastric pathology by pathologist report and were over the age of 18. Vitamin D levels were defined as following: 25(OH)D deficiency (< 20 ng/mL), insufficiency (20-29 ng/mL) and normal 25(OH)D level (≥ 30 ng/mL).

Demographic data such as age, gender and ethnicity

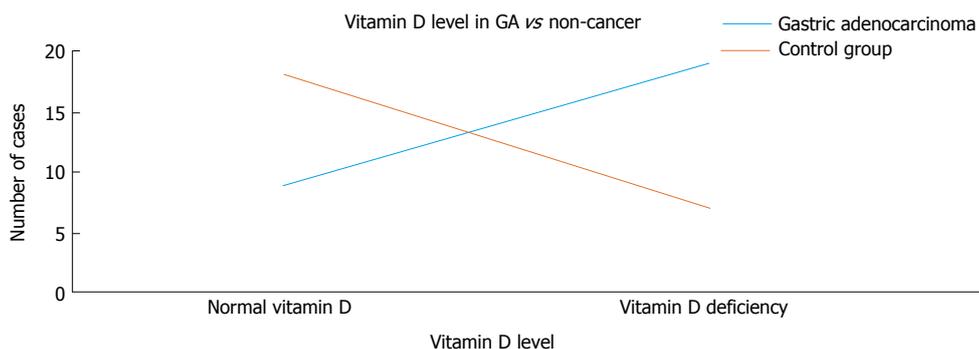


Figure 1 Average vitamin D level in gastric adenocarcinoma vs control group. GA: Gastric adenocarcinoma.

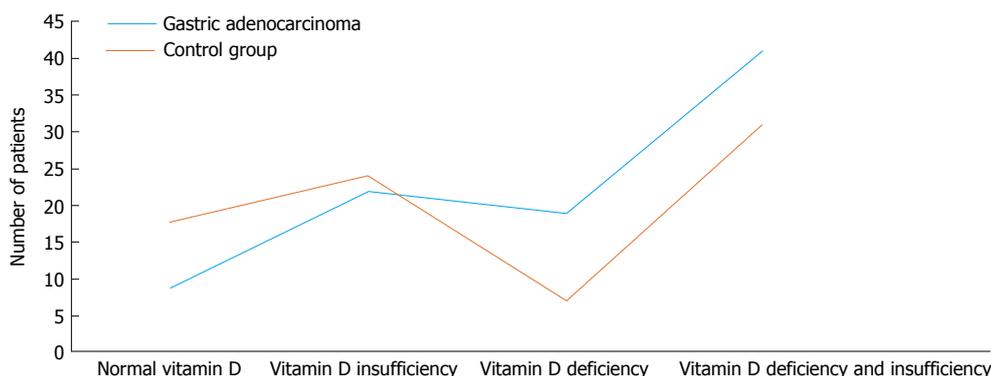


Figure 2 Vitamin D level distribution among gastric cancer adenocarcinoma and control group.

**Table 1** Baseline characteristics of gastric adenocarcinoma and control group

Characteristics	Case (gastric adenocarcinoma) (n = 49)	Control (n = 49)
Age, yr	63.9%	60.43%
Male	24 (49%)	24 (49%)
Female	25 (51%)	25 (51%)
Hispanic	30 (61.2%)	30 (61.2%)
Body mass index	24 kg/m <sup>2</sup>	25 kg/m <sup>2</sup>
	SD (22-27)	SD (23-28)
Vitamin D deficiency	19 (38.8%)	7 (14.3%)
Vitamin insufficiency	22 (44%)	24 (49.0%)
Combined vitamin D deficiency and insufficiency	41 (83.68%)	31 (63.27%)

as well as smoking, body mass index, *H. pylori* infection and stage of adenocarcinoma were assessed. Our cohort was compared to a matched control group of subjects who had no known history of cancers and with documented level of vitamin D (Table 1).

For all statistical analyses, the results were considered significant when two-tailed *P*-values were < 0.05. The distributions of demographic information and baseline comorbidity were compared between both groups.

## RESULTS

The average age of patients with gastric adenocarcinoma and documented vitamin D level was 64 years old

(95%CI: 27-86) and average vitamin D level was 20.8 (95%CI: 4-44). Compared to the matched controls, the prevalence of VDd and vitamin D insufficiency in patients who had gastric adenocarcinoma was significantly higher than in patients with normal vitamin D levels (83.7% vs 63.27%). There were 41 gastric adenocarcinoma patients with VDd/insufficiency (83.7%) compared to 18 (37%) patients with normal vitamin D level without gastric adenocarcinoma (OR: 8.8, 95%CI: 5-22, *P* value < 0.0001) (Figure 1).

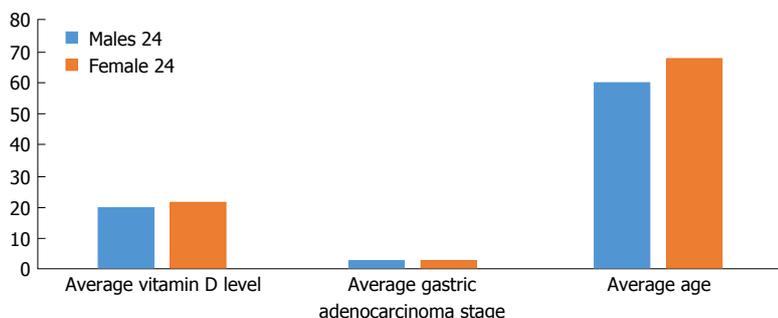
Furthermore, patients with VDd had an OR that was 2.7 times higher for gastric adenocarcinoma compared to the normal vitamin D population (95%CI: 1.4-5, *P* value 0.002), while patients with VDd had a 1.4 OR. However, endpoints did not achieve statistical significance (*P* value 0.1) (Figure 2).

Among gastric adenocarcinoma groups, stage II gastric adenocarcinoma was most common (37%) followed by stages III (25%), I (20%) and IV (18%). The vitamin D level did not differ between different cancer stages. There were higher rates of Hispanics (61%) followed by the East Asian population (13%) (Table 2). The average age in males with a gastric adenocarcinoma diagnosis was 60 years old vs 68 years old for females (*P* = 0.01). There was no significant difference in average vitamin D level (20 ng/mL in males vs 22 ng/mL in females) or stage of cancer (Figure 3).

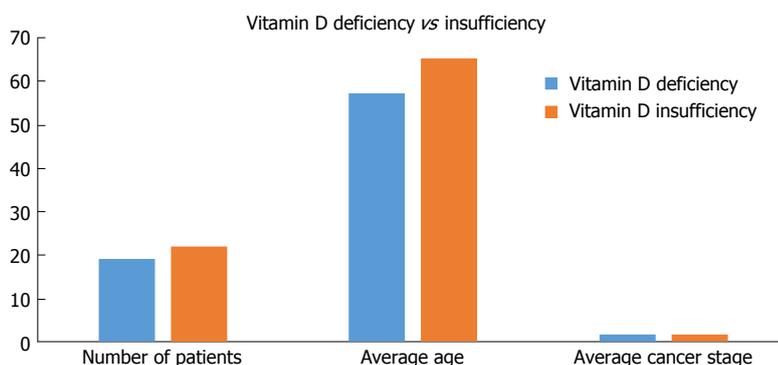
We sub grouped the patients with an abnormal vitamin D values into VDd and insufficiency; the average age of gastric adenocarcinoma in the deficiency group

**Table 2** Average vitamin D level, age and gastric adenocarcinoma cancer stage based on ethnicity

	Number of patients	Average vitamin D level	Average age	Average adenocarcinoma stage
Hispanic	30 (61%)	20	63	3
East Asian	13 (27%)	20	60	2
Middle Eastern	4 (8%)	21	70	3
Indian	2 (4%)	30	75	3



**Figure 3** The average vitamin D level, age and stage of gastric adenocarcinoma between males and females.



**Figure 4** Vitamin D deficiency vs insufficiency among gastric adenocarcinoma group.

was 57.7 years old vs 65.5 years old in the insufficiency group ( $P = 0.07$ ). There were no differences in gastric adenocarcinoma stage between the two groups (Figure 4).

## DISCUSSION

In our study, our inclusion criteria were patients diagnosed with gastric adenocarcinoma with a vitamin D level. We had 49 patients as part of our cohorts. These cases were then matched to a cohort of similar age, gender and ethnicity with measured serum vitamin D level and no history of cancer. The mean age of the cases were 64 as opposed to the control group at 60. Gender ratio was similar - 49% male and 51% female. The predominant ethnicity was Hispanic, accounting for 61.2%. This can be attributed to the increased Hispanic patient population at Elmhurst Hospital Center. The diagnoses of gastric adenocarcinoma were by biopsy: 18% with stage IV, 25% with stage III, 37% with stage II and finally 20% with stage I. For our case group, the vitamin D value recorded was the one measured at the time of diagnoses and prior to repletion. We defined

vitamin D levels in association with widely accepted thresholds. VDd is defined as  $< 20$  mg/dL, insufficiency 20-29 mg/dL and sufficiency was  $\geq 30$  mg/dL.

The prevalence of VDd was compared between the gastric adenocarcinoma group and matched control group, using ORs and 95%CI. Our finding showed an increased prevalence of VDd in the case group as compared to the matched group - 39% vs 14% respectively. The primary end point suggests an association between VDd and gastric adenocarcinoma; however, the study also found no correlation between the degree of deficiency and the stage of gastric adenocarcinoma.

In general, there is now accumulating evidence of VDd associated with multiple malignancies due to its anticancer effects. There has been increasing data for the association of VDd with colon cancer<sup>[2,5,10]</sup>. More recently, there is some new research suggesting an association with esophageal, pancreatic and liver cancer as well<sup>[2]</sup>. However, there is limited data showing gastric adenocarcinoma. The anticancer biochemical role of vitamin D is largely mediated by the VDR. VDR is a steroid in the thyroid hormone receptor family. Free

1,25 D<sub>3</sub> binds to the VDR causing phosphorylation of the receptor then the ligand activated VDR interacts with the retinoid X receptor (RXR) to form a heterodimer<sup>[8,9,11-14]</sup>. Subsequently, the heterodimer 1,25-VDR-RXR complex translocate to the nucleus and thus binds to vitamin D response elements (VDREs) in multiple regulatory regions located in the promoters of target genes<sup>[5,8,9,11-14]</sup>. The receptor signaling between RXR and VDR is a vital step for VDR transcriptional activity. VDREs are also utilized to initiate gene transcription. The RXR-VDR complex recruit specific coactivator molecules such as steroid receptor coactivators, histone acetyltransferases and its mediators. The significance of the RXR-VDR complex translocating to the nuclei and binding to VDREs is to allow for promotion or suppression of precise cellular events of tumorigenesis<sup>[2,4,5,15]</sup>.

The most common malignancy of the stomach is adenocarcinomas arising from gastric epithelium. Gastric adenocarcinoma is the fourth most common malignancy worldwide. In the United States, gastric adenocarcinoma accounts for 1.5% of new cancer cases and 1.8% of cancer deaths. The 5-year relative survival rate for gastric cancer increased from 14.3% in 1975 to 29.3% from 2006-2011<sup>[16]</sup>. The 5-year observed survival rate for gastric adenocarcinoma patients after surgery ranges from 71% for stage IA to as low as 4% for stage IV<sup>[17]</sup>.

Most gastric cancer patients are elderly when diagnosed with a median age of 69 in the United States. Less than 2% of gastric cancer cases arise in patients under 35 years of age. Asia and South America have higher rates of gastric cancer than in the United States. Gastric adenocarcinoma is marginally more prominent in males in the United States, whereas in Japan, it is the most common cancer diagnosed in men. However, worldwide, gastric cancer rates are twice as high in men compared to women. American Cancer Society's estimates for stomach cancer in the United States for 2015 revealed that approximately 24590 cases will be diagnosed (15540 in men and 9050 in women) and that 10720 people will die from this type of cancer (6500 men and 4220 women).

Gastric adenocarcinoma is often asymptomatic, but some non-specific symptoms reported include indigestion, abdominal discomfort and appetite loss. Later in the disease phase there is bleeding which leads to anemia. Although causes of gastric cancer are multifactorial, *H. pylori* infections are an essential risk factor<sup>[17]</sup>. However, only 2% of people with *H. pylori* infections develop stomach cancer<sup>[18]</sup>. Duodenal ulcers are most likely due to inflammation of the pyloric antrum, whereas inflammation of the corpus causes gastric ulcers and gastric carcinoma<sup>[19]</sup>. There is a counter correlation between low socioeconomic status and this disease due to factors such as poor nutrition, poor sanitation and scarce treatment and conservation of food and water. Individuals who maintain diets high in fruits, green vegetables, beta-carotene and ascorbic acid are less at risk. There is also research that indicates decreased use of nitrites in prepared foods reduces the

risk as well. It has also been well studied that dietary factors such as smoked foods and red meat<sup>[20]</sup> also increase the risk. With respect to vitamin D, there is now supporting evidence for the association of deficient levels and an increase risk for gastric adenocarcinoma. Several *in vitro* studies proved that 1,25-dihydroxyvitamin D<sub>3</sub> has the anticarcinoma effects of anti-proliferation, promoting apoptosis<sup>[9,20-22]</sup>. More specifically, it has been demonstrated that vitamin D<sub>3</sub> substantially stimulates apoptosis in the undifferentiated gastric cancer cell line HCG-27<sup>[3,23]</sup>. Moreover, specific to gastric adenocarcinoma, vitamin D<sub>3</sub> inhibits gastric cancer cell growth and induces cell cycle arrest<sup>[9,20,23]</sup>. Bao *et al.*<sup>[12]</sup> found that direct usage of 1,25 dihydroxy vitamin D<sub>3</sub> induces cellular apoptosis in gastric cancer cells and also increases the expression of VDR, further supporting the antitumor role that vitamin D may activate in gastric adenocarcinoma<sup>[2]</sup>. One of the limitations of our study is the small population number as not every patient with gastric adenocarcinoma had documented vitamin D level. Another limitation that must be addressed is the role malnutrition in cancer patients. There are several pathogenesis of cancer associated malnutrition. The primary reason is decreased food intake due to systemic effects of the disease, local tumor effects, psychological effects or adverse effects of treatment. Other contributing factor is the malignancy releasing inflammatory markers systemically such as procytokines have been linked to malnutrition and cachexia<sup>[24]</sup>. However, this study is unable to assess the nutrition status of the patients included in this study but one must be aware malnutrition which includes low vitamin D could be a result of the malignancy itself.

The question becomes, can vitamin D supplementation decrease incidence of gastric adenocarcinoma? It is reasonable to suggest the role of supplementation of vitamin D in deficient patients because of indirect etiologies related to gastric adenocarcinoma. Patients who underwent gastrectomy subsequently altered vitamin D metabolism, especially amongst those who received total gastrectomy<sup>[3,25]</sup>. Supplementation is also recommended for patients who have malnutrition and malabsorption disorders, which is a consequence of malignancy or diseases such as celiac sprue. Lastly, there is new evidence that high doses of vitamin D plus calcium show significant reduction in cancer incidence in women<sup>[26]</sup>. With expanding evidence of vitamin D supplementation and its benefits as mentioned above, avoiding deficiency or adding vitamin D supplements might be an economical and safe way to reduce cancer incidence, or act as a supplement to chemotherapeutic agents<sup>[9,11,24,27]</sup>. Overall, VDD can be easily corrected by taking supplements, changing dietary habits or increasing sunlight exposure, which is why it is a practical reason for clinicians to assess vitamin D status. To further assess this association, additional prospective research should be done to clarify the benefit of vitamin D supplementation and possible prevention of gastric adenocarcinoma.

In summary, there is increasing research on the role of vitamin D and gastrointestinal cancers, but there is still limited data on the association of vitamin D and gastric adenocarcinoma. Our study showed VDd has an increased predisposition for gastric adenocarcinoma. There is however no correlation between the severity of VDd and stage of gastric adenocarcinoma.

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## COMMENTS

### Background

In recent years, vitamin D deficiency (VDd) has been associated with a multitude of gastrointestinal malignancies. It affects multiple cellular processes such as inhibiting differentiation, metastasis, proliferation and inducing apoptosis and cell cycle arrest. All these mechanisms support vitamin D's anticancer role. Numerous studies have associated colon cancer with low vitamin D, however limited data suggests an association with gastric cancer.

### Research frontiers

Vitamin D is a fat soluble secosteroid that is known to affect intestinal, skeletal and biologic pathways such as immune cells and tumor microenvironment. Vitamin D is related to many cancers and the current research hotspot is the potential use of vitamin D screening and supplementation to prevent or slow the progression of malignancy.

### Innovations and breakthroughs

Understand the pathogenesis of vitamin D anticancer role. Several studies have found a link between low vitamin D levels and gastrointestinal malignancy. However, there is limited data suggesting a relationship between VDd/insufficiency in gastric adenocarcinoma.

### Applications

This study showed VDd has an increased predisposition for gastric adenocarcinoma. Further studies are warranted to assess this association and the possible risk stratification of vitamin D supplementation in preventing or slowing the progression of gastric adenocarcinoma.

### Terminology

The anticancer biochemical role of vitamin D is largely mediated by the vitamin D receptor (VDR). VDR is a steroid in the thyroid hormone receptor family. Free 1,25 D<sub>3</sub> binds to the VDR causing phosphorylation of the receptor then the ligand activated VDR interacts with the retinoid X receptor to form a heterodimer. This allows for the suppression or promotion of specific cellular events of tumorigenesis.

### Peer-review

It is interesting that the VDd is associated with gastric adenocarcinoma. The article fits in perfectly with the global trend.

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