Study of the relationship between colorectal cancer and vit D defficiency

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Background
Colorectal cancer is currently the third most common cancer in both men and women. The high prevalence of vitamin D deficiency, combined with the discovery of increased risk for certain types of cancer in those who are deficient, suggests that vitamin D deficiency may play a role in the development and progression of colon, breast, ovarian, and prostate cancers. Many studies suggest a possible relationship between sufficient vitamin D status and lower risk for cancer.

Aim of the work
The aim of this study was to determine vitamin D status in a sample of Egyptian patients with cancer of the colon.

Study design
We conducted a case–control study on 40 participants, 20 cases of colon cancer and 20 healthy adults matched for age. The cases were recruited from the general surgery wards and outpatient clinics at Ain Shams University Hospital, before surgical intervention or receiving oncological treatment. All participants were subjected to full medical history taking and thorough clinical examination. Fasting blood samples were drawn in the morning for evaluating haemoglobin, total Ca, phosphorus, Mg++, alkaline phosphatase, alanine transaminase, aspartate transaminase, carcinoembryonic antigen, and 25 hydroxyvitamin D. For the patients, chest radiography, pelvic and abdominal ultrasound, and colonoscopy and biopsy were performed.

Results
Egyptian patients with cancer of the colon showed a statistically significantly lower serum concentration of vitamin D (6.4 ± 3.912 ng/dl) compared with healthy controls (14.4 ± 9.838) ($P = 0.002$). There was a highly significant difference between the two groups as regards alkaline phosphatase, with a mean of 381.500 ± 73.721 in patients with cancer of the colon and a mean of 194.300 ± 88.838 in healthy controls ($P < 0.001$).

Conclusion
Vitamin D is lower in Egyptian patients with colorectal cancer, which may point to the possible protective role of vitamin D against cancer colon.

Keywords:
calcium, cancer colon, vitamin D

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Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world. It is the third most common cancer worldwide, and the fourth most common cause of death. It is more common in men than in women [1].

Most CRCs are due to lifestyle factors and increasing age, with only a small number of cases due to underlying genetic disorders. Risk factors include diet, obesity, smoking, and not enough physical activity [2].

CRC survival is highly dependent upon the stage of disease at diagnosis, and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage, 70% for regional cancer to 10% for people diagnosed with distant metastatic cancer. In general, the earlier the stage at diagnosis, the higher the chance of survival [3].

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods and is available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis [4].

In addition to the known role of vitamin D in promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate

mineralization of bone and preventing hypocalcemic tetany, vitamin D is being increasingly recognized as an important immunomodulator; low vitamin D has been prospectively associated with disease onset for many autoimmune diseases such as multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis [5].

Vitamin D might also play an important part in cancer control by modulating cellular growth and apoptosis and by reducing angiogenesis [6]. The hypothesis that vitamin D status is related to CRC has received strong experimental support over the past two decades [7].

Aim of the work

The aim of this study was to determine vitamin D status in Egyptian patients with colon cancer to evaluate the possible association between circulating vitamin D level and risk for development of cancer of the colon.

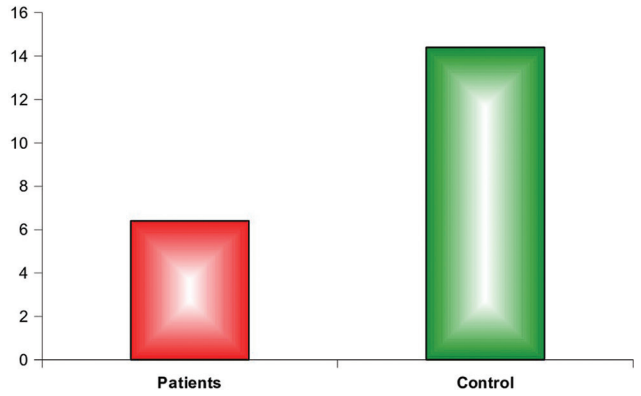
Subjects and methods

The present case–control study was conducted on 40 participants: 20 cases of colon cancer (34–85 years) and 20 healthy adults matched for age (32–75 years). The cases were recruited from the general surgery wards and outpatient clinics at Ain Shams University Hospital, before surgical intervention or receiving oncological treatment. All participants were subjected to full medical history taking, emphasizing on sun exposure, clothing pattern, dietary intake, and supplements of calcium and vitamin D, and thorough clinical examination, including blood pressure, pulse, and temperature. Fasting blood samples were drawn in the morning for evaluating haemoglobin, total Ca, phosphorus, Mg++, alkaline phosphatase (ALP), alanine transaminase, aspartate transaminase, carcinoembryonic antigen, and 25-hydroxy vitamin D level (enzyme-linked immunosorbent assay). For the patients, chest radiography, pelvic and abdominal ultrasound, and colonoscopy and biopsy were performed. Patients with renal failure, liver cell failure, malabsorption, hypoparathyroidism, or patients receiving drugs that might affect vitamin D and serum calcium level, such as corticosteroids or anti epileptic dru gs, were excluded from our study (Figs. 1–5 and Tables 1–5).

Statistical analysis

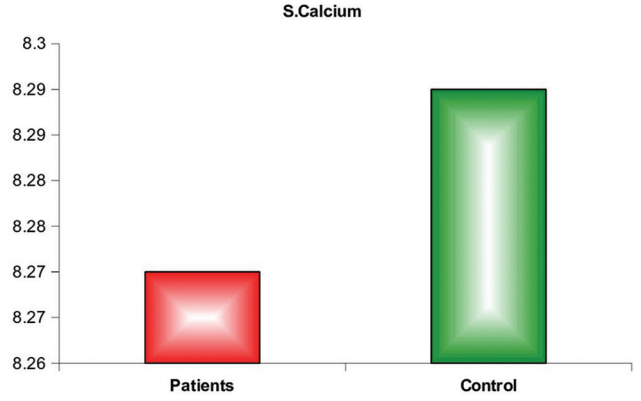
After data collection, revision, and tabulation, statistical analysis was performed and data were expressed as mean ± SD. The one-way analysis of variance test was used to compare parametric and quantitative variables between groups. All quantitative data were correlated with each other using Pearson's correlation coefficient (r). An receiver operating characteristic curve was plotted to assess the predictive accuracy of vitamin D as a risk factor for CRC.

Figure 1



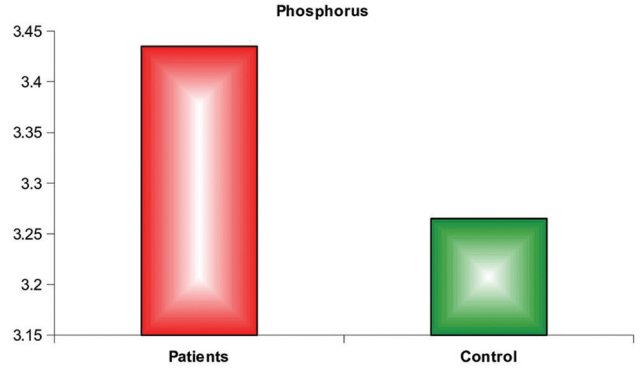
Comparison between the patient and control group as regards serum 25(OH) vitamin D.

Figure 2



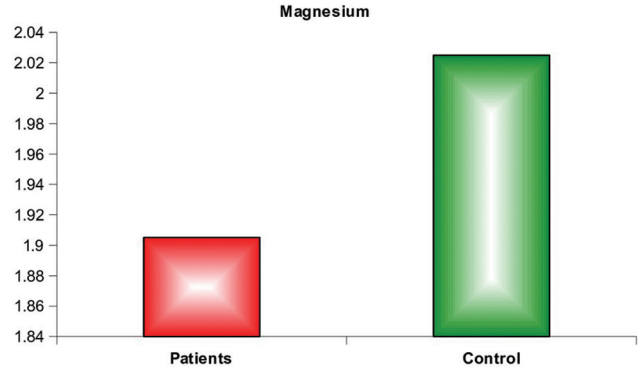
Comparison between the patient and control groups as regards serum calcium.

Figure 3



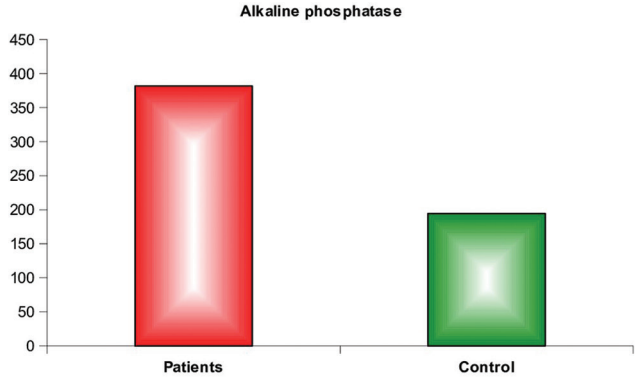
Comparison between the patient and control groups as regards serum phosphorus.

Figure 4



Comparison between the patient and control groups as regards serum magnesium.

Figure 5



Comparison between the patient and control groups as regards serum alkaline phosphatase.

Table 1 Comparison between the patient and control groups as regards serum 25(OH) vitamin D

Groups	Serum 25 vitamin D (ng/ml)		*t*-test	
	Range	Mean±SD	*t*	*P* value
Patient	3-18	6.400±3.912	−3.379	0.002*
Control	4-34	14.400±9.838		

*Significant. SD, standard deviation.

Table 2 Comparison between the patient and control groups as regards serum calcium

Groups	Serum calcium (mg/dl)		*t*-test	
	Range	Mean±SD	*t*	*P* value
Patient	7.6-11	8.270±0.732	−0.107	0.915
Control	7.7-9.3	8.290±0.405		

SD, standard deviation.

Table 3 Comparison between the patient and control group as regards serum phosphorus

Groups	Phosphorus (mg/dl)		*t*-test	
	Range	Mean±SD	*t*	*P* value
Patient	1.7-4.6	3.435±0.625	0.981	0.333
Control	2.5-4.1	3.265±0.458		

SD, standard deviation.

Table 4 Comparison between the patient and control group as regards serum magnesium

Groups	Magnesium (mg/dl)		*t*-test	
	Range	Mean±SD	*t*	*P* value
Patient	1.3-3.2	1.905±0.356	−1.323	0.194
Control	1.7-2.3	2.025±0.194		

SD, standard deviation.

Table 5 Comparison between the patient and control groups as regards serum alkaline phosphatase

Groups	Alkaline phosphatase		*t*-test	
	Range	Mean±SD	*t*	*P* value
Patient	275-570	381.500±73.721	7.252	<0.001*
Control	110-415	194.300±88.838		

*Significant. SD, standard deviation.

Results

In the present study, we found that vitamin D level was lower in patients with colon cancer, with a significant difference between group 1 (CRC patients) and the control group (P = 0.002). Vitamin D level was 3–18 ng/dl (mean 6.4 ± 3.912) in the patient group and 4–34 ng/dl (mean 14.4 ± 9.838) in the control group. There was a highly significant difference between group 1 (CRC patients) and group 2 (the control group) with regard to ALP (P < 0.001): 275–750 (mean 381.500 ± 73.721) in the patient group and 110–415 (mean 194.300 ± 88.838) in the control group.

There was no statistically significant difference between the two groups as regards age (0.150); the age range was 34–84 years (mean 60.35 ± 11.226) in the patient group and 32–75 years (mean 54.900 ± 12.226) in the control group (i.e. age-matched controls). There was no significant difference between the two groups as regards serum Ca (P = 0.915): 7.6–11 mg/dl (mean 8.270 ± 0.732) in the patient group and 7.7–9.3 mg/dl (mean 8.290 ± 0.405) in the control group. There was no significant difference between the two groups as regards serum phosphorus (P = 0.333): 1.7–4.6 mg/dl (mean 3.435 ± 0.625) in the patient group and 2.5–4.1 mg/dl (mean 3.265 ± 0.458) in the control group.

On correlating vitamin D with different parameters, we found that there was a negative nonsignificant correlation between level of vitamin D and CEA (P = 0.670; r = −0.102), AST (P = 0.495; r = −0.162), and ALP (P = 0.307; r = −0.240), but there was no significant correlation between level of vitamin D and other parameters.

Discussion

In this case–control study, our results confirmed that there was a significant difference between Egyptian

patients with CRC and healthy controls with regard to vitamin D status (P = 0.002); it was lower in patients with CRC than in controls.

Moreover, receiver operating characteristic curve in the assessment of the predictive accuracy of vitamin D as risk factor for CRC showed that vitamin D value with a cutoff value of 9 ng/ml or less has a sensitivity of 85% and specificity of 70% with a predictive accuracy of 80% (Figs. 6 and 7 and Tables 6 and 7).

Table 6 Correlation between serum 25(OH) vitamin D and different parameters

Parameters	Serum 25(OH) vitamin D	
	r	*P* value
CEA	−0.102	0.670
Hb	0.330	0.155
AST	−0.162	0.495
ALT	0.059	0.805
Serum creatinine	0.210	0.374
Serum calcium	0.173	0.464
Phosphorus	0.127	0.592
Magnesium	0.304	0.192
Alkaline phosphatase	−0.240	0.307

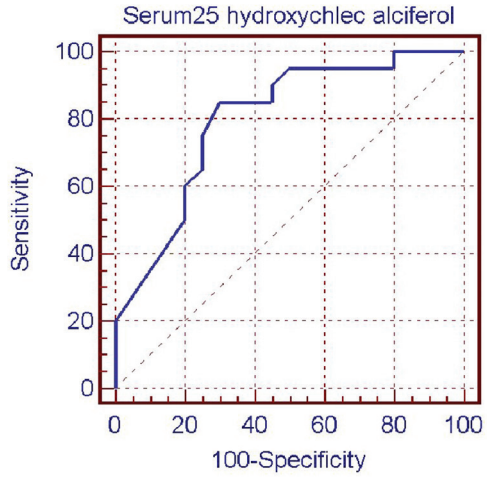
There was a negative correlation between level of vitamin D and CEA (r=−0.102), AST (r=−0.162), and alkaline phosphatase (r=−0.240).ALT, alanine transaminase; AST, aspartate transaminase; CEA, carcinoembryonic antigen; Hb, haemoglobin.

Table 7 The predictive accuracy of vitamin D as a risk factor for colorectal cancer

Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy (%)
≤9	85.0	70.0	73.9	82.4	80

NPV, negative predictive value; PPV, positive predictive value.

Figure 6



An ROC curve plotted to assess the predictive accuracy of vitamin D as a risk factor for colorectal cancer. The results show that vitamin D value with a cutoff value of 9 ng/ml or less has a sensitivity of 85% and specificity of 70% with a predictive accuracy of 80%. ROC, receiver operating characteristic.

These results are in agreement with the studies that reported that vitamin D was lower in the cases of colorectal carcinoma [8,9].

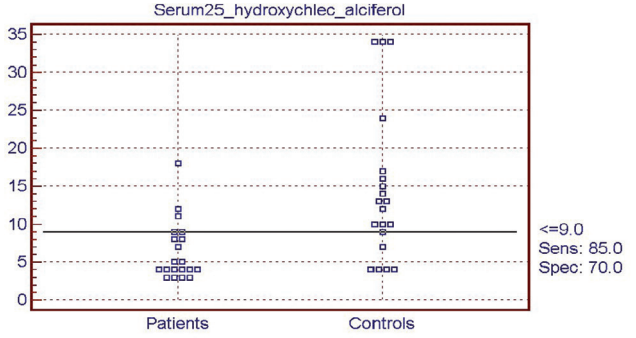
In a meta-analysis, it had been found that an increase of 84 nmol/l in serum 25(OH) vitamin D level led to a 50% reduction in the incidence of CRC [10].

Individually, the four largest studies were from the European Prospective Investigation into Cancer and Nutrition study, a combined analysis of the Nurses' Health Study and Health Professionals Follow-Up Study [11].

In the European Prospective Investigation into Cancer and Nutrition study, 1248 CRC cases were identified and matched to 1248 controls by age, sex, study center, follow-up time, fasting status, and time of day of blood donation [12]. Compared with a serum 25(OH) D concentration of 20–29 ng/ml, lower levels of 25(OH) D were associated with an increase in CRC risk [<10 ng/ml: odds ratio (OR)=1.32; 95% confidence interval (CI): 0.87 – 2.01; 10–19 ng/ml: OR = 1.28; 95% CI: 1.05 – 1.56], whereas higher concentrations were associated with a decreased risk for CRC (30–39 ng/ml: OR = 0.88; 95% CI: 0.68 – 1.13; ≥40 ng/ml: risk reduction (RR) = 0.77; 95% CI: 0.56 – 1.06). The association was stronger in the colon compared with the rectum.

In the combined results from the Health Professionals Follow-Up Study and the Nurses' Health Study, higher plasma 25(OH) D levels were associated with decreased risks for both rectal cancer [RR = 0.66; 95% CI: 0.42 – 1.05; P (trend)=0.01] and colon cancer [RR = 0.54; 95% CI: 0.34 – 0.86; P (trend)=0.002] [11].

Figure 7



An ROC curve plotted to assess the predictive accuracy of vitamin D as a risk factor for colorectal cancer. The results show that vitamin D value with a cutoff value of 9 ng/ml or less has a sensitivity of 85% and specificity of 70% with a predictive accuracy of 80%. ROC, receiver operating characteristic.

The Women's Health Initiative was based on a total of 322 cases of CRC. In that study, an inverse association was observed between baseline 25(OH) D level and CRC risk; however, detailed analyses on potential confounders were not reported [13].

Our results are not in agreement with The Japan Public Health Center based Prospective Study, in which a case–control study of 375 incident cases of CRC during 11.5 years of follow-up after blood collection had been performed. Two controls were matched per case as regards sex, age, study area, date of blood draw, and fasting time. The multivariate analysis was further adjusted for smoking, alcohol consumption, body mass index, physical exercise, vitamin supplement use, and family history of CRC. Plasma 25(OH) D was not significantly associated with CRC, but the lowest category of plasma 25(OH) D was associated with an elevated risk for rectal cancer in both men (RR = 4.6; 95% CI: 1.0 – 20) and women (RR = 2.7; 95% CI: 0.94 – 7.6), compared with the other quartiles combined [14].

These results that suggest inverse relationship between vitamin D status and CRC could be explained by that vitamin D and its metabolites reduce the incidence of various cancers through several mechanisms at the cellular level, such as inhibition of cell proliferation, sensitization to apoptosis, induction of epithelial differentiation and cell detoxification metabolism, and inhibition of angiogenesis [15].

Vitamin D metabolites also help to maintain a standard calcium gradient in the various colonic epithelial cells. High levels of blood serum 25(OH) D3 are associated with a noticeable decrease in proliferation of noncancerous cells [16].

Vitamin D had been found to have a role in apoptosis sensitization in colorectal adenoma, and carcinoma cells involve the upregulation of the proapoptotic protein BAK and the downregulation of the nuclear antiapoptotic protein BAG-1 [17].

The antiproliferative effect of vitamin D is attained by inducing G1 cell-cycle arrest, which is probably mediated by upregulation of cell cycle inhibitors. Vitamin D modulates the activation of these cell cycle-related genes through various mechanisms. Vitamin D also exerts anticarcinogenic effects by interfering with the synthesis of growth factors and cytokines and by modulating their signaling pathways. In addition to the growth inhibitory effects, vitamin D induces the differentiation of colon cancer cells. The 1, 25(OH) D3 and its analogs exert anticarcinogenic activities in human colon cancer cells by inhibition of proliferation and induction of differentiation and apoptosis [18].

In CRC cells, 1,25(OH) D3 has specific and multiple prodifferentiation effects. It increases the expression and/or activity of several brush border enzymes, such as ALP and maltase, and enhances the formation of microvilli [7]. In addition, 1, 25(OH) D3 increases the expression of several components of cell adhesion structures that are essential for the maintenance of the epithelial phenotype [19].

The angiogenic capacity of CRC cells may be affected by 1,25(OH) 2D3, as it represses the expression and transcriptional activity of hypoxia-inducible factor-1, a key transcription factor involved in hypoxia-induced angiogenesis [20]. In addition, 1, 25(OH) 2D3 regulates the expression of vascular endothelial growth factor and thrombospondin-1, two major opposing factors that control tumor angiogenesis [21].

Finally, polymorphisms in vitamin D receptors may play a role in colon cancer risk. The polyA (short), BsmI (BB), and TaqI (tt) variants of the vitamin D receptor (VDR) gene were found to be in linkage disequilibrium in a mostly White population. These variants were associated with reduced risk for colon cancer [22]. Moreover, VDR genotypes are associated with anticancer activity in CRC. There are several VDR genotypes. For example, the most important VDR genotype is Bsm I, which has three variants: BB, Bb, and bb in America. The bb genotype is associated with lower concentrations of circulating 1, 25(OH) 2D3, leading to an increased incidence of CRC [23].

Moreover, the present study found that there was a significant difference between CRC cases and healthy controls as regards ALP, being higher in the cases.

As the cases at the time of diagnosis do not have bone metastasis, this result could be attributed to lower vitamin D levels, as there is inverse relationship between vitamin D and ALP as it is well known that vitamin D deficiency causes an increase in bone resorption [24].

In conclusion, our results revealed that serum vitamin D is lower in Egyptian patients with colorectal cancer compared with healthy controls, a result which may suggest a potential role for vitamin D in the prevention of colorectal cancer in future interventional study.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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