Original Article

Evaluation of Serum Calcium, Vitamin D, Vitamin E, and CEA Levels in Patients with Colorectal Cancer

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Abstract

Background: Colorectal cancer (CRC) is a widespread illness that begins with unusual growth of the inner colon or rectum and progresses to the entire thickness of the epithelial lining before spreading to nearby lymph nodes and tissues and eventually distant metastases. High vitamin D concentrations are correlated with a decreased risk of recurrence and all-cause death in CRC patients. The serum carcinoembryonic antigen is not created in large amounts after birth, but it is raised in CRC. Antioxidant micronutrients (vitamin E) have anticancer effects. The role of vitamin E in reducing CRC risk is still debated. **Objective:** The study's goal is to determine the clinical importance of calcium, vitamin D, vitamin E, and carcinoembryonic antigen (CEA) levels in patients with CRC. **Materials and Methods:** The participants of the study were 180 cases, comprising patients and healthy individuals, separated into two categories. The first category had 90 patients: 47 men and 43 women. The second group had 90 healthy individuals, including 56 men and 34 women. **Results:** The results show a significantly high decrease ($P < 0.01$) in the concentrations of serum calcium, vitamin D, and vitamin E in CRC compared to healthy controls. Meanwhile, the results show a significantly high increase ($P = 0.013$) in the level of serum CEA in CRC compared to healthy controls. **Conclusion:** Low calcium, vitamin D, and vitamin E levels are strongly associated with a greater chance of CRC, according to the findings.

Keywords: Calcium, CEA, colorectal cancer, vitamin D, vitamin E

Introduction

Colorectal cancer (CRC) is the most frequent kind of cancer. This is the third most frequent cancer in males and the second most prevalent cancer in females in the world. Males have a much greater incidence than females.[1] WHO predicts that by 2030, there will be 27 million new cases of CRC. CRC is a tumor of malignant epithelial origin in the large intestine. Over 90% of CRCs are adenocarcinomas, which develop from glandular structures in epithelial tissue; this might trigger alterations in the intestinal microenvironment that contribute to colorectal carcinogenesis.[2,3] Most individuals with CRC die from organ metastasis. The prognosis varies widely across individuals and is highly dependent on metastatic patterns.[4] CRC is caused by a complicated interaction of inherited susceptibility and environmental factors.[5]

Cancer patients usually suffer from electrolyte imbalances. They might negatively influence cancer patients' prognosis, whereas a quick adjustment seems to be beneficial.[6] Calcium is the most prevalent mineral in the body. It is essential for normal and pathological cellular function. Apoptosis and gene expression are some of its primary roles.[7] It is found in the blood in three forms: free ionized Ca (50%) and protein-bound Ca (40%) with a small quantity of Ca complexed with other molecules like citrate and phosphate.[8] Calcium as a nutrient is most commonly associated with the formation and metabolism of bone. As well as needed during muscular function, intracellular signaling, hormone secretion, neuronal

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transmission, and other body functions.[9,10] Calcium has been shown to protect epithelial cells from toxic effects by binding ionized fatty acids and secondary bile acids in the colon. The relationships between dietary vitamin D and calcium consumption and the risk of CRC remained inconclusive.[11]

Vitamin D is a fat-soluble vitamin produced mostly in the skin exposed to sunlight. Vitamin D is a hormone, not a vitamin since it is created in the skin and is the primary source of the vitamin in most cases.[12,13] It is produced in the body when a cholesterol precursor molecule (7-dehydrocholesterol) is exposed to ultraviolet radiation. The first form is provitamin D3 (cholecalciferol). Vitamin D3 is hydroxylated to 25(OH)D3 in the liver and then converted to 1,25-dihydroxycholecalciferol (calcitriol) in the kidney.[14,15] The active form (calcitriol) of vitamin D has been found to regulate calcium and phosphate homeostasis and bone metabolism. Eating a lot of vitamin D to keep calcium balanced may lessen cancer risk.[13,16]

However, vitamin D may also influence CRC risk by binding to the vitamin D receptor, inhibiting epithelial cell proliferation, and possesses anti-carcinogenic characteristics, such as inducing apoptosis, differentiation, immunomodulation, and inhibiting angiogenesis.[17] Research suggests that having higher vitamin D levels in the blood may reduce a person's chance of developing CRC, although results are inconsistent. Clinical research has not identified a link between daily vitamin D intake and the risk of adenomas or CRC. Recent meta-analysis studies discovered that higher vitamin D levels were associated with a lower risk of CRC, whereas insufficiency was associated with a 37% increased risk of CRC.[11] The anticancer properties of antioxidant micronutrients (vitamin E) are mediated by decreasing protein kinase C and reducing reactive oxygen species formation.[18] It also helps to keep cell membranes fluid by maintaining their fluidity. Tocopherols and tocotrienols are two families of compounds capable of expressing vitamin E. D-α-tocopherol is the most active of the antioxidants.[19] A recent study revealed that consumption of vitamin E lowered the likelihood of developing CRC by 16.8% for each milligram consumed per week.[20]

A blood-based tumor marker such as glycoprotein carcinoembryonic antigen (CEA) may have an impact on the prognosis, therapy, and follow-up of patients with CRC.[21] In gastrointestinal cancer, determining particular tumor marker levels in the blood is critical for screening, diagnosis, treatment management, and monitoring advanced illness.[22,23] CEA has prognostic significance, with greater CEA levels related to a worse preoperative fate.[24] CEA is also useful in surgical follow-up and the early diagnosis of recurrent disease.[25] Because of its limited sensitivity in early cancer stages, CEA can not be utilized for screening. It may also be increased in benign conditions.[26] Preoperative CEA elevation predicted increasing overall survival in CRC, with a 62% mortality risk compared to normal CEA levels.[27] CEA levels should fall exponentially after the therapeutic operation and, hence, the removal of the cause of CEA. CEA levels that did not return to normal after the operation were indicative of chronic or recurring illness.[28] The study's goal is to determine the clinical importance of calcium, vitamin D, vitamin E, and CEA levels in patients with CRC.

Materials and Methods

The participants in this study were 180 cases, comprising patients and healthy people, separated into two groups: The first group included 90 patients, comprising 47 males and 43 females. The second group had 90 healthy individuals, 56 of whom were men and 34 of whom were women. A venous blood sample was taken from each of the subjects, where it was permitted to clot before being centrifuged for 10 min at 3000 rotations per minute. All tube samples were kept at (−20°C) deep-freezing until they were analyzed. Serum vitamin D and CEA levels were measured by Cobas E411 (Roche Diagnostics, Germany), and the concentration of serum calcium was measured by dry chemistry in the Fujifilm method. Enzyme-linked immunosorbent assay was used to measure vitamin E.

The data from the study were analyzed using IBM Statistical Package for Social Sciences Statistics software, version 27. All statistical comparisons were conducted using independent *t*-tests, one-way analysis of variance, and numeric variables were reported as means and standard deviation, while the chi-square (χ^2) test was used to compare frequency with P value < 0.05 considered statistically significant. High significance at P value ≤ 0.01.

Results

Table 1 shows the statistical distribution (frequency and percentage) of study groups (patients and control) by their sex and age. The participants in this study were 180 cases, comprising patients and healthy individuals, separated into two groups: The first group included 90 patients, comprising 47 males and 43 females. The second group had 90 healthy individuals, 56 men and 34 women. The descriptive statistics and differences of study groups by sex showed significant differences between the patient and control groups (P value = 0.175). The same table revealed that the highest percentage of the age subgroup is 65–74 years, which constituted 24 (26.66%) patients.

Age is the most important factor in determining the risk of CRC development. The patient's age ranged from 25 to 74 years. The distribution of patients among age groups was as follows: (25–34 years) included 18 (20%) patients, (35–44 years) included 11 (12.22%) patients, (45–54 years)

Table 1: Demographic characteristics of study groups (patients and healthy controls)

Character	Category	Groups		Calculated *P* value
		Healthy (*N* = 90)	Patients (*N* = 90)	
Sex, No. (%)	Male	56 (62.22)	47 (52.22)	0.175
	Female	34 (37.77)	43 (47.77)	
Age (year), No. (%)	25–34	22 (24.44)	18 (20)	0.277
	35–44	18 (20)	11 (12.22)	
	45–54	19 (21.11)	16 (17.77)	
	55–64	16 (17.77)	21 (23.33)	
	65–74	15 (16.66)	24 (26.66)	

High significant at $P \leq 0.01$, significant difference at $P < 0.05$

Table 2: Serum concentrations of CEA, vitamin D, vitamin E, and calcium between colorectal cancer patients and healthy group

Parameters	Groups		*P* value
	Healthy (*N* = 90)	Patients (*N* = 90)	
	Mean ± SD	Mean ± SD	
CEA (ng/mL)	1.66 ± 0.04	28.44 ± 0.51	0.013
Vit. D (ng/mL)	25.25 ± 0.92	16.7 ± 1.44	<0.01
Vit. E (nmol/L)	49.93 ± 1.15	40.73 ± 0.81	<0.01
Ca^{+2} (mmol/L)	2.48 ± 0.14	1.95 ± 0.02	<0.01

CEA: carcinoembryonic antigen, Vit. D: vitamin D, Vit. E: vitamin E, Ca^{+2}: Calcium

Table 3: Serum concentrations of carcinoembryonic antigen (CEA), vitamin D, vitamin E, and calcium according to the sex among colorectal cancer patients

Parameters	Category		*P* value
	Male (*N* = 47)	Female (*N* = 43)	
	Mean ± SD	Mean ± SD	
CEA (ng/mL)	34.26 ± 17.15	22.08 ± 11.65	0.566
Vitamin D (ng/mL)	17.84 ± 2.38	15.65 ± 1.71	0.451
Vitamin E (nmol/L)	41.31 ± 1.05	40.09 ± 1.25	0.458
Ca^{+2} (mmol/L)	2.1 ± 0.21	1.8 ± 0.18	0.256

Non-significant at *P* value > 0.05

included 16 (17.77%) patients, (55–64 years) included 21 (23.33%) patients, and (65–74 years) included 24 (26.66%) patients. Table 1 demonstrated that there was no significant ($P < 0.277$) difference in the age of the patients' group compared to the control group.

Table 2 exhibited the differences in the measurements of CEA, vitamin D, vitamin E, and calcium between CRC patients and the control group. The mean CEA concentration in the CRC patient group (28.44 ± 0.51) was significantly increased ($P = 0.013$) compared to the healthy control group (1.66 ± 0.04), while the mean serum vitamin D and vitamin E concentrations in the CRC patient group were significantly decreased ($P = <0.01$) compared to the healthy control group. In addition, the mean serum calcium in the CRC patient group (1.95 ± 0.02) was significantly decreased ($P = <0.01$) compared to the healthy control group (2.48 ± 0.14).

Table 3 shows that the mean serum CEA, vitamins (D and E), and calcium concentration in male CRC patients were not significantly different from that in female CRC patients.

Table 4 shows that there were non-significant differences in the serum biomarkers CEA, vitamin D, vitamin E, and calcium concentration according to age among CRC patients (*P* value < 0.05).

Discussion

The descriptive statistics and differences in study groups by sex. Table 1 demonstrated that there were no significant differences between the patients and control groups (*P* value = 0.175). CRCs are less common in women, and colonoscopy studies show that females have fewer colorectal adenomas.[29,30] The occurrence of bleeding in colon lesions differs by sex[31]; few colorectal adenomas and carcinomas were correlated with low amounts of hemoglobin in feces. It is still a well-known fact that women have very little hemoglobin in their feces compared to men.[32,33]

Age is the most important factor in determining the risk of CRC development. Table 1 demonstrated that there was no significant ($P < 0.277$) difference in the age of the patient group compared to the control group. According to the present findings, the age category with the greatest proportion is 65–74 years. The current investigation supported the findings of Wong *et al.*[34] who found a link between CRC risk and advanced age. On the contrary, the results disagreed with Gondran *et al*.[35] who claimed that the age-specific incidence of CRC rose dramatically among those aged 35–64 years compared with those aged ≥65 years. Similarly, Singh *et al*.[21] have observed that most CRC patients were males, aged 40–60 years, with 30% being under 40 years old. Patients with CRC under the age of 50 exhibited higher survival rates than their older counterparts at all stages of diagnosis. On the contrary, individuals <65 years had the lowest survival rates due to age-related disadvantages such as comorbidity.[36]

Table 4: Serum concentrations of carcinoembryonic antigen (CEA), vitamin D, vitamin E, and calcium according to the age among colorectal cancer patients

Parameters	Category (year)					*P* value
	25–34	35–44	45–54	55–64	65–74	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
CEA (ng/mL)	11.27 ± 4.39	9.34 ± 2.72	8.09 ± 2.95	46.01 ± 2.11	48.27 ± 0.78	0.532
Vitamin D (ng/mL)	14.52 ± 1.77	16.78 ± 5.52	16.52 ± 3.24	17.79 ± 3.6	17.45 ± 2.8	0.958
Vitamin E (nmol/L)	40.8 ± 1.73	39.12 ± 2.19	42 ± 2.3	38.4 ± 1.34	42.5 ± 1.69	0.394
Ca^{+2} (mmol/L)	2.5 ± 0.35	2.1 ± 0.38	1.86 ± 0.35	1.87 ± 0.32	1.69 ± 0.22	0.395

Non-significant at *P* value > 0.05

Comparison of serum biomarkers between patients and control. Table 2 demonstrates that the results showed a significantly high increase ($P = 0.013$) in the measurement of the serum biomarker (CEA). Additionally, there was a significantly high decrease ($P < 0.01$) in the levels of serum vitamin D, vitamin E, and Ca^{+2} between CRC patients and the control group.

The variations in the serum biomarker (CEA) between CRC patients and the control group. The mean serum CEA concentration in the CRC patient group was considerably higher than that of the healthy control group. However, Singh *et al.* and Dang *et al.*[21,37] deduced that the joint evaluation of four tumor markers of TK1, CEA, CA 19–9, and CA 72–4 scored even better, which may be significant for the early diagnosis of CRC. On the contrary, Al-Saigh *et al*.[38] It has been found that serum from people with CRC had higher levels of CEA than serum from healthy people, as demonstrated (83.6%) for patients with equal to or more than 5 ng/mL, and may be utilized as a tumor marker for the diagnosis of CRC. CEA is an oncofetal glycoprotein, that is, generally produced by mucosal cells. It is overexpressed in several cancers. It is most typically linked with prognostic relevance in patients with CRC, particularly with hepatic metastases.[4] However, other malignancies may also raise it, such as the breast, liver, stomach, and pancreas. Changes in CEA depend on the stage, grade, location, and dissemination of CRC to the liver.[21] The clinical importance of this finding is that CEA might be used as a prognostic indicator for advanced or metastatic CRC and does not seem to be a good marker for early-stage disease.[39] These findings are corroborated by Kim *et al*.[40] who observed that higher CEA levels were related to advanced CRC stages and poor clinical outcomes.

The mean serum concentration in CRC patients was highly significantly lower in vitamin D, vitamin E, and calcium than that of the healthy control group. Accumulating data suggest that vitamin D can regulate the entire process of tumorigenesis, from initiation to metastasis and cell–microenvironment interactions.[14] In agreement with Al-Ghafari *et al.*,[41] the present investigation found highly significant variations in blood total vitamin D and calcium levels between CRC patients and controls ($P < 0.001$). Prior clinical studies that support our study found lower vitamin D levels in colon cancer patients compared to healthy controls. Vitamin D levels have been demonstrated to avoid the onset of CRC, but the exact mechanism behind this role is unknown.[42,43] Another study done by Morales-Oyarvide *et al.*[44] evaluated the effect of vitamin D and physical activity as intervention methods for CRC prevention and treatment. He found that CRC patients with vitamin D levels in the highest quantiles improved overall survival rates compared to those in the lowest quantiles.

In aspects of vitamin E in developing countries, the most common cause of vitamin E deficiency is inadequate dietary intake, disorders that cause fat malabsorption, and a rare genetic form of vitamin E deficiency.[45] Relationship between serum vitamin E levels and the risk of CRC, this study disagrees with the Italian cohort study, which found no association between chosen antioxidants, such as vitamin E, on CRC risk.[46] A meta-analysis of supplementary antioxidant consumption, which included 20 randomized trials on vitamin E and beta-carotene supplementation, found no protective benefit.[47] A case–control study with 816 CRC patients in Japan found no evidence of a preventive effect of dietary vitamin E on CRC risk.[48] Studies done by Dong *et al.*[49] found contradictory results. On the contrary, this study agrees with Brannon,[16] who studied the relationship between CRC and diet using data from 64 CRC patients and 123 sex- and age-matched controls. Consumption of vitamin E was shown to be a preventive factor, with each milligram of vitamin E consumed per week lowering the risk of CRC by 16.8%. This study also agrees with Dong *et al.*,[49] who found that individuals with CRC had lower serum vitamin E serum concentrations than healthy controls. These findings are also consistent with previous case–control studies in China and Jordan that found a protective effect of dietary vitamin E consumption.[14,50] However, prospective studies are required to confirm the influence of serum vitamin E on CRC risk.

In talking about Ca^{+2} consumption, several causes can induce hypocalcemia in cancer patients, for example, malnutrition due to anorexia or bowel obstruction, malabsorption related to bowel tumor infiltration or

previous intestinal surgery, drugs, or abnormal liver function due to liver metastasis might promote the development of hypoalbuminemia and subsequent hypocalcemia. Furthermore, malabsorption and malnutrition might frequently cause vitamin D deficiency and then hypocalcemia in cancer patients.[6,51] Calcium was inversely associated with CRC risk in a study of 922 Korean CRC patients.[52] Another recent study found that CRC patients with high CEA levels had lower serum Ca^{+2} levels than low-level tumor markers.[53] However, prospective studies are required to confirm the influence of serum calcium on CRC risk.

Differences in biomarkers according to the sex among CRC patients. Table 3 shows that there were non-significant differences in the levels of serum biomarkers between male and female CRC patients.

The mean serum CEA concentration in the male patients was not significantly different from that of the female patients ($P = 0.566$), as illustrated in Table 3. The findings are consistent with Naicker *et al*.[39] who found no significant ($P = 0.8$) link between CEA levels and sex. On the contrary, the results disagree with Al-Saigh *et al*.[38] who reported that the male patients exceeded female patients by a statistically significant ($P \leq 0.01$) ratio. The mean serum vitamin D concentration in the male patients was not significantly different from that of the female patients ($P = 0.451$). The variety of factors affecting vitamin D levels in various countries, such as sunlight exposure, clothing styles, nutrition, and study season, variance in vitamin D low prevalence. Therefore, among the most significant elements that influence vitamin D levels in women are clothing routines, the detrimental effects of the sun on the skin, and ignorance about the need for sunlight for vitamin D synthesis. More research with an appropriate number of participants is required. The mean serum calcium concentration in the male patients was not significantly different from that in the female patients ($P = 0.256$).

Differences in biomarkers according to age among CRC patients. Table 4 exhibits the differences in biomarker levels among different age subgroups of CRC patients. The results showed no significant differences in the levels of all biomarkers in this study with the age of CRC patients.

The present findings coincide with Naicker *et al*.[39] who found no significant change in CEA and vitamin E levels throughout old age ($P = 0.6$). In a large Korean study, serum CEA was revealed to be a major risk factor for the development of advanced colorectal neoplasms in both young (50 years) and old (>50 years) patients.[40] A case series study of 956 CRC patients between the ages of 25 and 50 showed that they were significantly ($P \leq 0.01$) more likely to suffer than those between the ages of >50 years or <25 years.[38] According to vitamin D and calcium, this study found no significant change in vitamin D levels with age ($P = 0.958$).

Conclusion

There was a highly significant relation between CEA, vitamin D, vitamin E, calcium levels, and CRC, but non-significant association between these levels and the age and sex of the patients.

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Conflicts of interest

There are no conflicts of interest.

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