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Assessing the Impact of Serum Calcium, 25-Hydroxy Vitamin D, Ferritin, and Uric Acid Levels on Colorectal Cancer Risk

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Abstract

Background: The aim of this study is to investigate whether vitamin D, calcium, ferritin, and uric acids play a beneficial biomarker role in the prevention of colorectal cancer (CRC) risk.

Methods: The case-control design was employed, including 650 CRC cases and 650 controls aged 35 to 70 years, comprising both men and women. The study encompasses sociodemographic data, clinical information, radiological diagnoses, and biochemical measurements.

Results: Statistically significant differences were observed between CRC and controls in terms of age, diagnostic radiology, tomography, positron emission tomography/computed tomography (PET/CT), colonoscopy, CRC awareness, risk factors, age, genetics, exposure to chemicals, inadequate nutrition, smoking, hookah and alcohol use. Significant differences were also identified in intestinal inflammations, obesity, processed foods ($P < 0.001$), abdominal pain and cramps, diarrhea, constipation, blood in stool, bloating (gas), irritable bowel, nausea/vomiting, anemia, stress, fatigue, weakness, and weight loss. Regarding biochemical parameters, statistically significant differences were found between CRC and controls in terms of hemoglobin, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), vitamin D, neutrophil level, red blood cell (RBC), white blood cell (WBC), platelet level, platelet count, hematocrit, potassium, sodium (Na), calcium, creatinine, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), bilirubin, uric acid, iron (Fe), ferritin, C-reactive protein (CRP), total protein, systolic blood pressure (SBP), and diastolic blood pressure (DBP) parameters ($P < 0.001$). Multivariate stepwise regression analysis was performed to find the best risk factors for the diagnosis of CRC as the dependent variable. As a result of the analysis, intestinal inflammation ($P < 0.001$), nausea/vomiting ($P < 0.001$), stomach pain ($P = 0.003$), hookah-smoking ($P = 0.034$), uric acid ($P < 0.001$), bilirubin ($P < 0.001$), cigarette smoke exposure ($P = 0.033$), processed food consumption ($P = 0.002$), calcium levels ($P = 0.029$), vitamin D deficiency ($P < 0.001$), and ferritin ($P < 0.001$) levels were identified as significant determinants for CRC.

Conclusions: The current study demonstrated that vitamin D, calcium, ferritin, and uric acids play a beneficial biomarker role in reducing the risk of CRC prevention. The increase in CRC rates may be associated with lifestyle, environmental and hereditary factors, nutrition, alcohol consumption, hookah use, and cigarette smoking.

Keywords: Epidemiology; Colorectal; Calcium; Vitamin D; Uric acids; Lifestyle; Cigarette smoking; Nargile-hooker and alcohol use

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, ranking as the third most frequent cancer in males and the second most frequent cancer in females [1]. In the year 2020 alone, there were over 1.9 million new cases of CRC reported. However, the morbidity and mortality of CRC vary significantly from country to country [1-3]. While the highest incidence rates of CRC are found in the wealthiest developed countries, the lowest rates are observed in some of the poorest developing nations. This geographical diversity is primarily linked to differences in nutrition, lifestyle, genetics, and environmental factors [3-7]. Specifically

identified diet risk factors for CRC include the consumption of red meat, processed meat, high-fat diets, and alcohol intake [2, 3]. Conversely, diets rich in plant-based fiber, as well as the consumption of whole grains or dairy products, have been shown to provide protection against CRC development [2-4], Nonetheless, in developing countries, CRC rates are rapidly increasing, potentially attributed to the adoption of Western lifestyles by these societies [5-7]. An increase in the incidence of early-onset CRC, defined as CRC diagnosed before the age of 50, has been globally confirmed within the past 50 years [1-8].

It is known that vitamin D and calcium reduce CRC incidence by influencing cell proliferation, differentiation, and apoptosis [8-14]. Studies have reported that higher serum levels of vitamin D may reduce the risk of CRC, and findings also suggest that calcium intake plays a beneficial role in reducing the incidence of CRC [11-13]. However, there are few intervention studies defining the relationship between vitamin D, calcium, and CRC [11-15].

Previous reviews on colon cancer have focused on specific risk factors such as lifestyle [7, 16-21], iron [16], obesity [17], physical inactivity [18], dietary fiber intake [22-24], red meat consumption [25, 26], and hereditary CRC [5, 19]. Currently, there are no prospective studies that have explored the impact of vitamin D, calcium, ferritin, and uric acid on the formation of CRC [27, 28]. Nevertheless, the clinical evidence regarding the preventive role of vitamin D, calcium, ferritin, and uric acid supplementation in CRC remains uncertain [10-14]. The aim of this study is to investigate whether vitamin D, calcium, ferritin, and uric acids play a beneficial biomarker role in the prevention of CRC risk.

Materials and Methods

Participants

A cross-sectional investigation was carried out involving participants aged 35 to 70 years who sought medical care at the Oncology and Gastrointestinal Clinics, as well as Out-Patient Clinics, at the Istanbul Medipol University Hospital. The study adhered to the principles outlined in the Declaration of Helsinki (1964) and obtained ethical clearance and approval from the Ethics Committee (RP# and IRB# E-10840098-772.02-2645).

The determination of the sample size was based on the anticipated proportion in controls (P = 0.01), assumed odds ratio (OR = 4), confidence interval (CI = 0.99), and power = 0.80. Consequently, the final sample comprised 650 subjects with CRC compared to 650 controls (without CRC), encompassing both males and females aged 35 - 70 years.

The study encompassed diverse demographic factors, including age, gender, body mass index (BMI), smoking and alcohol habits, physical activity, intestinal inflammations, abdominal pain and cramps, diarrhea, constipation, irritable bowel, blood in the stool, and pre-existing health conditions. Patient evaluation was conducted through magnetic resonance angiography (MRA), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), and colonoscopy.

Biochemical and vitamin D assessment

Biochemical parameters measured in the study included hemoglobin, serum ferritin, magnesium, potassium, phosphorous, creatinine, fasting glucose levels, glycated hemoglobin (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, albumin, triglyceride, uric acid, bilirubin, triglyceride, systolic and diastolic blood pressure (SBP and DBP). The serum levels of vitamin D in the participants were measured using competitive radioimmunoassay (RIA) with the 25-hydroxy vitamin D test, which was conducted using DiaSorin method as described in previous studies [9, 10, 15].

Statistical analysis

Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. OR and 95% CI were calculated by using Mantel-Haenszel test. The stepwise logistic regression analysis was performed to find out the best predictors for diagnosis of malignancy as dependent variable. The level $P < 0.05$ was considered as the cut-off value for significance.

Results

There were statistically significant differences between CRC and control groups in terms of age, diagnostic radiology, tomography, PET/CT, colonoscopy, CRC awareness, risk factors, age, genetics, exposure to chemicals, inadequate nutrition, smoking, hookah/nargile, and alcohol use, intestinal inflammations, obesity, and processed foods ($P < 0.001$). Demographic and clinical characteristics comparisons of risk factors between CRC and control subjects are presented in Table 1.

Table 2 presents statistically significant differences in the comparison of functional gastrointestinal disorders (FGID) symptoms between CRC and control groups: abdominal pain, abdominal cramps, diarrhea, constipation, blood in stool, bloating (gas), irritable bowel, nausea/vomiting, anemia, stress, feeling of fatigue, weakness, and weight loss ($P < 0.001$).

When compared with control subjects, CRC subjects showed a significant decrease in hemoglobin, vitamin D, red blood cell (RBC), white blood cell (WBC), lymphocyte, platelet levels, hematocrit, potassium, sodium (Na), creatinine, cholesterol, HDL, LDL, bilirubin, iron (Fe), ferritin, C-reactive protein (CRP) levels, while HbA1c, fasting blood glucose (FBG), neutrophil level, platelet, calcium, triglyceride, uric acid, total protein, SBP, and DBP increased significantly. Statistical analysis revealed a correlation of $r = 0.278$ and $P < 0.001$ between carcinoembryonic antigen (CEA) and 6-month follow-up. Comparisons of clinical biochemistry parameters between CRC and control subjects are presented in Table 3.

Multivariate stepwise regression analysis was conducted to identify the best risk factors for patients diagnosed with

Table 1. Sociodemographic and Lifestyle Habits by CRC and Control (N = 1,300)

Variables	CRC (n = 650), n (%)	Control (n = 650), n (%)	OR (95% CI)	P value
Age groups (in years)				
< 55	258 (39.7)	105 (16.2)	1.41 (2.63 - 4.43)	0.001
> 55	392 (62.3)	545 (63.8)	1.0	
Gender				
Male	341 (52.5)	340 (52.3)	1.06 (0.81 - 1.23)	0.956
Female	309 (47.5)	310 (47.7)	1	
BMI (kg/m^2)				
Normal (< 25 kg/m^2)	158 (25.8)	192 (29.5)	1	
Overweight (29 - 30 kg/m^2)	266 (40.9)	288 (44.3)	1.06 (0.81 - 1.38)	0.690
Obese (> 30 kg/m^2)	216 (33.2)	170 (26.2)	1.45 (1.09 - 1.94)	0.011
Tomography (last 6 months)				
Yes	524 (89.6)	168 (26)	5.13 (4.36 - 6.02)	0.001
No	126 (9.4)	472 (74)	1.0	
PET/CT (last 6 months)				
Yes	190 (29.2)	50 (7.7)	1.82 (1.66 - 2.00)	0.001
No	460 (70.8)	600 (92.3)	1.0	
Colonoscopy (last 6 months)				
Yes	623 (95.8)	113 (17.4)	17.68 (12.22 - 25.58)	0.001
No	27 (4.2)	537 (82.6)	1.0	
CRC awareness				
Yes	537 (82.6)	163 (25.1)	4.07 (3.43 - 4.83)	0.001
No	113 (17.4)	487 (74.9)	1.0	
Risk factor of colon cancer				
Genetic factors				
Yes	137 (21.1)	54 (8.3)	1.55 (1.39 - 1.73)	0.001
No	513 (78.9)	590 (91.7)	1.0	
Exposure to chemicals				
Yes	62 (9.5)	27 (4.2)	1.43 (1.23 - 1.66)	0.001
No	588 (90.5)	623 (95.8)	1.0	
Malnutrition				
Yes	125 (19.2)	78 (12.0)	1.74 (1.28 - 2.37)	0.001
No	525 (80.8)	572 (88.0)	1.0	
Smoking				
Yes	120 (18.5)	60 (9.2)	2.22 (1.59 - 3.10)	0.001
No	530 (81.5)	590 (90.8)	1.0	
Hookah/nargileh use				
Yes	75 (11.5)	40 (6.2)	1.98 (1.35 - 2.96)	0.001
No	575 (88.5)	610 (93.8)	1.0	
Alcohol use				
Yes	85 (13.1)	60 (9.2)	1.42 (1.10 - 2.01)	0.001
No	565 (86.9)	590 (90.8)	1.0	
Intestinal inflammations				
Yes	207 (31.8)	82 (12.6)	3.23 (2.43 - 4.30)	0.001
No	443 (68.2)	568 (87.4)	1.0	
Obesity				
Yes	109 (16.8)	64 (9.8)	1.84 (1.32 - 2.56)	0.001
No	541 (83.2)	586 (90.2)	1.0	
Processed foods				
Yes	145 (22.3)	84 (12.9)	1.93 (1.44 - 2.59)	0.001
No	505 (77.7)	566 (887.1)	1.0	

CRC: colorectal cancer; BMI: body mass index; PET/CT: positron emission tomography/computed tomography; OR: odds ratio; CI: confidence interval.

Table 2. Comparison of CRC Developing Functional Gastrointestinal Symptoms With Controls (N = 1,300)

Variables	CRC (n = 650), n (%)	Control (n = 650), n (%)	OR (95% CI)	P value
Pain in abdomen				
Yes	162 (24.9)	79 (10.3)	2.39 (1.78 - 3.22)	0.001
No	488 (75.1)	571 (87.7)	1.0	
Cramp in abdomen				
Yes	151 (23.2)	94 (14.5)	1.79 (1.34 - 2.37)	0.001
No	499 (76.8)	556 (84.5)	1.0	
Diarrhea				
Yes	160 (24.6)	114 (17.5	1.53 (1.17 - 2.10)	0.001
No	490 (75.4)	536 (82.5)	1.0	
Constipation				
Yes	184 (28.3)	67 (10.3)	3.43 (2.53 - 4.66)	0.001
No	466 (71.7)	583 (89.7)	1.0	
Blood in the stool				
Yes	128 (19.7)	75 (11.5)	1.88 (1.38 - 2.58)	0.0011
No	522 (80.3)	575 (88.5)	1.0	
Bloating (flatulence)				
Yes	172 (26.5)	112 (17.2)	1.72 (1.32 - 2.26)	0.001
No	478 77.5)	538 (88.8)	1.0	
Irritable bowel				
Yes	122 (18.8)	62 (9.5)	2.19 (1.57 - 3.04)	0.001
No	578 (81.2)	587 (90.5)	1.0	
Nausea/vomiting				
Yes	154 (23.7)	81 (12.5)	12.18 (1.62 - 2.92)	0.001
No	496 (76.3)	569 (87.5)	1.0	
Anemia				
Yes	146 (22.5)	99 (15.2)	1.61(1.21 - 2.13)	0.001
No	504 (77.5)	5517 (84.8)	1.0	
Stress				
Yes	148 (22.8)	61 (9.4)	2.84(2.06 - 3.92)	0.001
No	502 (77.2)	589 (90.6)	1.0	
Feeling fatigue weakness				
Yes	170 (26.2)	110 (16.9)	1.73 (1.32 - 2.27)	0.001
No	488 (73.8)	540 (83.1)	1.0	
Weight loss				
Yes	125 (19.2)	61 (9.4)	2.29 (1.65 - 3.9)	0.002
No	525 (80.8)	589 (90.6)	1.0	
Physical exercise				
Yes	143 (22.0)	189 (29.1)	1.20 (1.07 - 1.34)	0.003
No	507 (78.0)	461 (70.9)	1.0	

CRC: colorectal cancer; OR: odds ratio; CI: confidence interval.

CRC as the dependent variable. In the analysis, intestinal inflammation ($P < 0.001$), nausea/vomiting ($P < 0.001$), stomach pain ($P \leq 0.003$), hookah/nargile use ($P = 0.034$), uric acid ($P < 0.001$), bilirubin ($P < 0.001$), cigarette smoke ($P = 0.033$), processed foods ($P = 0.002$), calcium ($P = 0.029$), vitamin D deficiency ($P < 0.001$), and ferritin ($P < 0.001$) were identified

Table 3. Clinical Biochemistry Baseline Value Among CRC and Control Subjects (N = 1,300)

Variables	CRC (n = 650), mean ± SD	Control (n = 650), mean ± SD	P value
Hemoglobin (g/dL)	12.76 ± 0.78	13.00 ± 1.06	0.001
HbA1c (%)	6.37 ± 0.64	6.14 ± 0.46	0.001
Fasting blood glucose (mmol/L)	6.53 ± 0.78	6.32 ± 0.54	0.001
Vitamin D (mmol/L)	16.03 ± 7.21	21.35 ± 8.07	0.009
Neutrophil level (× 10^9/L)	6.33 ± 0.24	5.66 ± 0.18	0.001
Red blood cell (RBC) (× 10^{12}/L)	4.18 ± 0.49	4.386 ± 0.46	0.001
White blood cell (WBC) (× 10^9/L)	7,723.7 ± 1,502	8,344.9 ± 2,049	0.001
Lymphocyte (× 10^3/µL)	1.62 ± 0.93	2.06 ± 0.83	0.038
Platelet (/mm^3)	222.1 ± 93.6	207 ± 102	0.001
Hematocrit (%)	34.70 ± 6.54	37.1 ± 5.61	< 0.001
Aspartate transaminase (U/L)	26.10 ± 13.0	25.8 ± 11.3	0.644
Alanine transaminase (U/L)	21.00 ± 0.93	20.4 ± 7.4	0.470
Potassium (mEq/L)	3.72 ± 0.91	4.46 ± 0.76	0.001
Na (mEq/L)	133.6 ± 4.59	136.1 ± 4.89	0.001
Calcium (mg/dL)	5.19 ± 0.50	3.59 ± 0.45	0.001
Creatinine(mmol/µL)	57.45 ± 16.90	70.4 ± 26.5	0.001
Cholesterol (mmol/L)	3.740 ± 0.43	6.04 ± 0.77	0.011
HDL (mmol/L)	1.39 ± 0.14	3.55 ± 0.58	0.001
LDL (mmol/L)	2.78 ± 0.64	5.02 ± 0.43	0.001
Bilirubin (µmol/L)	6.19 ± 2.09	10.71 ± 3.16	0.001
Triglyceride (mmol/L)	2.59 ± 0.38	1.75 ± 0.49	0.058
Uric acid (mg/L)	4.32 ± 0.49	4.18 ± 0.52	0.001
Fe (µg/L)	66.7 ± 20.51	71.3 ± 24.9	0.001
Ferritin (µg/L)	82.1 ± 15.44	99.2 ± 14.38	0.001
C-reactive protein (CRP) (µg/L)	0.79 ± 0.08	0.92 ± 0.09	0.001
Total protein (µg/L)	6.37 ± 0.89	6.16 ± 0.818	0.027
Systolic blood pressure (mm Hg)	128.82 ± 12.48	125.53 ± 12.00	0.001
Diastolic blood pressure (mm Hg)	79.29 ± 10.82	77.64 ± 9.81	0.002

CRC: colorectal cancer; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

as significant determinants for CRC. Risk factors in CRC subjects are provided in Table 4.

Discussion

CRC is one of the most prevalent cancers worldwide. In numerous evidence-based studies, dietary patterns, dairy and dairy products, meat, vegetables, milk, cheese, smoking and e-cigarettes, hookah/nargile, BMI, obesity, alcohol consumption, physical activity and exercise, and sedentary lifestyle have been well established as risk factors for CRC [5-9]. This is the first prospective case-control study investigating the relationship between CRC and levels of vitamin D, calcium, ferritin, and uric acids. These clinical biochemistry parameters may play a useful marker role in reducing the risk of CRC for participant patients. Therefore, in addition to these modifiable risk factors, the clinical observation and statistical evaluation of biochemical parameters are crucial in preventing CRC risk. Most recently study reported that healthy lifestyle was strongly inversely associated with CRC risk [7]. This is consistent and confirmative with our current reported study.

While identifiable hereditary factors are found in approximately 20% of CRC diagnoses, specific germline mutations characterize about 5% of all colon cancer cases [29, 30]. The estimated incidence of Lynch syndrome, the most common hereditary syndrome, is 5-7% of all CRC cases [5, 7, 21, 29]. The current study revealed that genetic risk is statistically associated with CRC at 1.55 (1.39 - 1.73), P > 0.001 (Table 1).

There is evidence supporting the relationship between lifestyle factors such as diet, smoking, alcohol consumption, obesity, and exercise with CRC [7, 18, 19]. Various studies have shown that smoking is significantly associated with CRC incidence and mortality in individuals, and it also increases the

Table 4. The Predictor Risk of CRC Using Multivariate Stepwise Regression Analysis (N = 1,300)

Independent variables	Regression coefficients	Standard error	Wald value	P value	Exp (B)	95% CI
Intestinal inflammation	1.064	0.228	21.704	0.001	2.897	1.852 - 4.532
Nausea/vomiting	0.896	0.247	13.210	0.001	2.451	1.511 - 3.974
Stomach pain	0.766	0.256	8.961	0.003	2.151	1.303 - 3.553
Nargileh/hookah use	0.564	0.267	4.478	0.034	1.758	1.042 - 2.964
Uric acids	0.556	0.112	24.387	0.001	1.740	1.397 - 2.168
Bilirubin	0.530	0.035	234.430	0.001	1.699	1.587 - 1,818
Cigarette smoke	0.487	0.228	4.571	0.033	1.628	1.041 - 2.545
Processed foods	0.420	0.139	9,148	0.002	1.521	1.159 - 1.997
Calcium	0.404	0.185	4.746	0.029	1.497	1.041 - 2.153
Vitamin D deficiency	0.080	0.012	45.177	0.001	1.083	1.058 - 1,109
Ferritin	0.150	0.050	10.423	0.001	1.015	1.006 - 1.024

CRC: colorectal cancer; CI: confidence interval.

risk of CRC development [20-26]. Smoking, hookah use, and alcohol consumption are risk factors for CRC [31-33]. Smoking increases CRC risk in a dose-dependent manner with intensity and duration, and quitting smoking reduces CRC risk [31, 32]. In our study, CRC risk linearly increased with smoking intensity and duration. Physical activity reduces CRC risk [34], but the available evidence is primarily derived from self-reported recreational and occupational activity, with less known about the contribution of other areas of physical activity, such as transportation and home-related activities. Engaging in 1 h of exercise per week was associated with a lower prevalence of CRC [34].

Iron deficiency anemia is the most common symptom in CRC patients. While malignancy leads to functional iron deficiency, chronic blood loss can cause absolute iron deficiency and depletion of iron stores [35, 36]. In our study, hematocrit, RBC, WBC, and hemoglobin levels were significantly decreased in CRC patients. The decrease in Fe and ferritin levels in the CRC group indicates a significant reduction in hematopoiesis. Additionally, bilirubin, a byproduct of hemoglobin breakdown and an endogenous antioxidant believed to have cancer-preventive properties, was found to be significantly decreased in the CRC group in our study (Table 3).

Evaluation and treatment of biochemical parameters are of great importance in patients with CRC. Studies have reported a higher risk of CRC associated with lower HDL and higher triglycerides (TG, dyslipidemia markers) levels [6]. In our study, cholesterol, HDL, and LDL levels were significantly decreased in CRC patients. Considering that vitamin D synthesis occurs through cholesterol, our study revealed a significant decrease in vitamin D levels in the CRC group compared to the control group alongside the decreased cholesterol levels (Table 3).

Increased levels of FBG, along with increased HbA1c, have been previously reported as a risk factor in CRC patients [37]. Increased FBG not only directly affects the cardiovascular system but also affects the gastrointestinal system by causing epithelial dysfunction. An increase in platelet levels, which are procoagulant markers, accompanies increased neutrophil levels in tissues [38]. Our study supports this hypothesis, as we observed an increase in HbA1c, FBG, neutrophil levels, platelet levels, and calcium levels in CRC patients (Table 3).

Furthermore, the increase in calcium levels in CRC patients in our study may be a consequence of the decrease in vitamin D levels. Serum uric acid may play a significant role in the emergence of CRC in both men and women [27]. In a recent large-scale cohort study [28], authors found a positive relationship between serum uric acid and the risk of CRC occurrence, especially in men, in young and middle-aged individuals (≤ 65 years), and in normal individuals. Although the results vary among compiled studies, the outcomes of the meta-analysis suggest that, as in our study, elevated serum uric acid may be associated with an increased risk of CRC in the adult population [28].

Serum vitamin D levels in CRC patients indicate disruptions in steroid and lipid metabolism. The increase in LDL, platelet, and HbA1c levels, along with the accompanying rise in SBP and DBP, signifies the presence of epithelial tissue damage, as seen in cardiovascular diseases. Furthermore, the decrease in ferritin and uric acid levels, described as endogenous antioxidants in CRC patients, suggests that nutritional habits and environmental factors, including smoking, hookah (nargile) use, and alcohol consumption, are crucial contributors to damage at the core (Table 4).

Study strengths and limitations

The current study has several limitations. Firstly, the design of current study is not ideal matched case and control study. The results could not establish a causal relationship between vitamin D, calcium, uric acids, and CRC because of its observational nature. Second, the present study could not evaluate the effect of biochemistry lab parameters alterations on tumors over time, as they were measured only twice. Third, the study may not reach to the target patients in population as a bias, which is very hard to avoid. Fourth, the clinical assessment and test performed for the CRC might be misclassified; therefore, the results should be interpreted with great caution, even though they are based on a large sample size.

Conclusions

The current study revealed that vitamin D, calcium, ferritin and uric acids play a useful role as markers in reducing the risk of CRC in patients. The rising rates of CRC can be attributed to lifestyle, cigarette smoking, nargileh use, alcohol consumption, as well as dietary, environmental, and hereditary factors.

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Financial Disclosure

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Conflict of Interest

The author(s) declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent

All data published here are under the consent for publication. Written informed consent was obtained from all individual participants included in the study.

Author Contributions

Study design and conceptualization: AB, AEO, UVU, AFA, CCB. Data curation and supervision: AB, AEO, AFA. Project administration: AB, AEO, AFA, CCB. Formal analysis and validation: AB, AEO, UVU, ASD. Writing - original draft review and editing: AB, AEO, UVU, AFA, ASD. Approval of final manuscript: AB, AEO, UVU, CCB, ASD.

Data Availability

The authors declare that data supporting the findings of this study are available within the article. The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Abbreviations

CRC: colorectal cancer; OR: odds ratio; CI: confidence interval; BMI: body mass index; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RIA: radioimmunoassay; FGID: functional gastrointestinal disorder; RBC: red blood cell; WBC: white blood cell; CRP: C-reactive protein; FBG: fasting blood glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; Ca: calcium; Na: sodium; Fe: iron

References

1. Global Cancer Observatory. January 24, 2024. Available online: https://gco.iarc.fr/.
2. Vernia F, Longo S, Stefanelli G, Viscido A, Latella G. Dietary factors modulating colorectal carcinogenesis. Nutrients. 2021;13(1):143. doi pubmed
3. O'Sullivan DE, Sutherland RL, Town S, Chow K, Fan J, Forbes N, Heitman SJ, et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2022;20(6):1229-1240. e1225. doi pubmed
4. Barrubes L, Babio N, Becerra-Tomas N, Rosique-Esteban N, Salas-Salvado J. Association between dairy product consumption and colorectal cancer risk in adults: a systematic review and meta-analysis of epidemiologic studies. Adv Nutr. 2019;10(suppl_2):S190-S211. doi pubmed
5. Bener A. Colon cancer in rapidly developing countries: review of the lifestyle, dietary, consanguinity and hereditary risk factors. Oncology Reviews. 2011;5(1):5-11.
6. Fang Z, He M, Song M. Serum lipid profiles and risk of colorectal cancer: a prospective cohort study in the UK Biobank. Br J Cancer. 2021;124(3):663-670. doi pubmed
7. Chen X, Ding J, Li H, Carr PR, Hoffmeister M, Brenner H. The power of a healthy lifestyle for cancer prevention: the example of colorectal cancer. Cancer Biol Med. 2022;19(11):1586-1597. doi pubmed
8. Munoz A, Grant WB. Vitamin D and cancer: an historical overview of the epidemiology and mechanisms. Nutrients. 2022;14(7):1448. doi pubmed
9. Lopez-Caleya JF, Ortega-Valin L, Fernandez-Villa T, Delgado-Rodriguez M, Martin-Sanchez V, Molina AJ. The role of calcium and vitamin D dietary intake on risk of colorectal cancer: systematic review and meta-analysis of case-control studies. Cancer Causes Control. 2022;33(2):167-182. doi pubmed
10. Wi YJ, Na SY. [Calcium, Vitamin D, and Colorectal Cancer]. Korean J Gastroenterol. 2023;82(2):47-55. doi pubmed
11. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354(7):684-696. doi pubmed
12. Carroll C, Cooper K, Papaioannou D, Hind D, Pilgrim H, Tappenden P. Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clin Ther. 2010;32(5):789-803. doi pubmed

13. Baron JA, Barry EL, Mott LA, Rees JR, Sandler RS, Snover DC, Bostick RM, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. N Engl J Med. 2015;373(16):1519-1530. doi pubmed
14. Huang D, Lei S, Wu Y, Weng M, Zhou Y, Xu J, Xia D, et al. Additively protective effects of vitamin D and calcium against colorectal adenoma incidence, malignant transformation and progression: A systematic review and meta-analysis. Clin Nutr. 2020;39(8):2525-2538. doi pubmed
15. Bener A, Al-Hamaq A, Zughaier SM, Ozturk M, Omer A. Assessment of the role of serum 25-Hydroxy vitamin D level on coronary heart disease risk with stratification among patients with type 2 diabetes Mellitus. Angiology. 2021;72(1):86-92. doi pubmed
16. Anderson KJ, Cormier RT, Scott PM. Role of ion channels in gastrointestinal cancer. World J Gastroenterol. 2019;25(38):5732-5772. doi pubmed
17. Lee J, Kim SY. [Obesity and Colorectal Cancer]. Korean J Gastroenterol. 2023;82(2):63-72. doi pubmed
18. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713-732. doi pubmed
19. Carr PR, Weigl K, Edelmann D, Jansen L, Chang-Claude J, Brenner H, Hoffmeister M. Estimation of absolute risk of colorectal cancer based on healthy lifestyle, genetic risk, and colonoscopy status in a population-based study. Gastroenterology. 2020;159(1):129-138.e129. doi pubmed
20. Bradbury KE, Murphy N, Key TJ. Diet and colorectal cancer in UK Biobank: a prospective study. Int J Epidemiol. 2020;49(1):246-258. doi pubmed
21. Bener A, Moore MA, Ali R, El Ayoubi HR. Impacts of family history and lifestyle habits on colorectal cancer risk: a case-control study in Qatar. Asian Pac J Cancer Prev. 2010;11(4):963-968. pubmed
22. Chang VC, Cotterchio M, De P, Tinmouth J. Risk factors for early-onset colorectal cancer: a population-based case-control study in Ontario, Canada. Cancer Causes Control. 2021;32(10):1063-1083. doi pubmed
23. Adamek MU, Bergmann L, Adamek HE. [Exercise and diet in colorectal cancer prevention and therapy]. Z Gastroenterol. 2023;61(7):818-826. doi pubmed
24. Lee YC, Hsu CY, Chen SL, Yen AM, Chiu SY, Fann JC, Chuang SL, et al. Effects of screening and universal healthcare on long-term colorectal cancer mortality. Int J Epidemiol. 2019;48(2):538-548. doi pubmed
25. Niedermaier T, Gredner T, Hoffmeister M, Mons U, Brenner H. Impact of reducing intake of red and processed meat on colorectal cancer incidence in Germany 2020 to 2050 - a simulation study. Nutrients. 2023;15(4):1020. doi pubmed
26. Alegria-Lertxundi I, Bujanda L, Arroyo-Izaga M. Role of dairy foods, fish, white meat, and eggs in the prevention of colorectal cancer: a systematic review of observational studies in 2018-2022. Nutrients. 2022;14(16):3430. doi pubmed
27. Mi N, Huang J, Huang C, Lin Y, He Q, Wang H, Yang M, et al. High serum uric acid may associate with the increased risk of colorectal cancer in females: A prospective cohort study. Int J Cancer. 2022;150(2):263-272. doi pubmed
28. Li W, Liu T, Siyin ST, Zhang Q, Wang Y, Cao L, Qu J. The relationship between serum uric acid and colorectal cancer: a prospective cohort study. Sci Rep. 2022;12(1):16677. doi pubmed
29. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044-2058. doi pubmed
30. Bener A, El Ayoubi HR, Chouchane L, Ali AI, Al-Kubaisi A, Al-Sulaiti H, Teebi AS. Impact of consanguinity on cancer in a highly endogamous population. Asian Pac J Cancer Prev. 2009;10(1):35-40. pubmed
31. Botteri E, Borroni E, Sloan EK, Bagnardi V, Bosetti C, Peveri G, Santucci C, et al. Smoking and colorectal cancer risk, overall and by molecular subtypes: a meta-analysis. Am J Gastroenterol. 2020;115(12):1940-1949. doi pubmed
32. Huang YM, Wei PL, Ho CH, Yeh CC. Cigarette smoking associated with colorectal cancer survival: a nationwide, population-based cohort study. J Clin Med. 2022;11(4):913. doi pubmed
33. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, Negri E, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol. 2011;22(9):1958-1972. doi pubmed
34. Mahmood S, English DR, MacInnis RJ, Karahalios A, Owen N, Milne RL, Giles GG, et al. Domain-specific physical activity and the risk of colorectal cancer: results from the Melbourne Collaborative Cohort Study. BMC Cancer. 2018;18(1):1063. doi pubmed
35. Chardalias L, Papaconstantinou I, Gklavas A, Politou M, Theodosopoulos T. Iron deficiency anemia in colorectal cancer patients: is preoperative intravenous iron infusion indicated? A narrative review of the literature. Cancer Diagn Progn. 2023;3(2):163-168. doi pubmed
36. Seyed Khoei N, Jenab M, Murphy N, Banbury BL, Carreras-Torres R, Viallon V, Kuhn T, et al. Circulating bilirubin levels and risk of colorectal cancer: serological and Mendelian randomization analyses. BMC Med. 2020;18(1):229. doi pubmed
37. Meng Q, Yu Y, Wang K, Zhang Z, Zhao J, Wang Y, Hao D, et al. The prognostic role of fasting plasma glucose levels on survival in advanced colorectal cancer patients with type II diabetes mellitus: a retrospective cohort study. J Gastrointest Oncol. 2022;13(6):3080-3089. doi pubmed
38. Zhang Y, Wang C, Yu M, Zhao X, Du J, Li Y, Jing H, et al. Neutrophil extracellular traps induced by activated platelets contribute to procoagulant activity in patients with colorectal cancer. Thromb Res. 2019;180:87-97. doi pubmed

