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Risk factors for colorectal cancer in Albania: a case-control study

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Informed consent: all patients gave informed consent after being informed about the aim and procedures of the study.

Patient consent for publication: all participants provided written consent for the publication of anonymized data derived from this study.

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Abstract
The prevalence of colorectal cancer (CRC) has increased significantly in recent years in many countries worldwide, including Albania, a transitional Mediterranean country in the Western Balkans. This study aimed to identify dietary patterns among CRC Albanian patients. This was a case-control study conducted during 2011-2016, including 262 patients histologically confirmed with a diagnosis of CRC and 289 sex- and age-matched controls who were family members of patients hospitalized for acute, non-neoplastic conditions unrelated to digestive tract diseases. Structured interviews employing standardized questionnaires were administered by trained personnel. Comparisons of dietary patterns were performed using the analysis of variance test for continuous variables and the χ^2 test for categorical variables. A dietary model characterized by a low intake of whole-grain bread, fruits, and olive oil was encountered more frequently among CRC patients. Our study indicates that diets rich in fruits, whole-grain bread, and olive oil exert a protective role against CRC development. The findings from this study are important for promoting protective diets, especially in areas with limited medical screening facilities.

Introduction

The prevalence of colorectal cancer (CRC) has increased significantly in recent years. In 2022, the World Health Organization estimated CRC as the 3rd most common cancer worldwide, with 1.9 million new cases, and the 2nd leading cause of death, with 900,000 deaths.[1] There is a wide global geographical variation; the highest rates are found in developed countries in North America and Europe, and the lowest rates in developing countries in Africa.[1] These differences suggest that environmental factors such as lifestyle and diet play an important role in carcinogenesis. Recently, there has been a growing amount of data that reports an increasing incidence of CRC in developing countries in Eastern Europe, Eastern Asia, and even in countries in Western Asia.[2] Due to limited resources available in these countries, this high incidence is associated with an increased rate of mortality and the burden of cancer.[2] In the Balkan area, which encompasses only 0.3% of the world population, the CRC mortality rate is about 5% of the estimated global mortality.[3] Albania, an upper-middle-income country,[4] experienced an increase of 249.17% in CRC incidence over 30 years, between 1990 and 2019. It is estimated that this rate will continue to grow by 2030 unless prevention strategies are implemented.[3] It is suggested that the tendency of diet and lifestyle westernization in these regions may be the reason for this incidence in low- and middle-income countries. Thus, the identification of dietary habits in CRC patients may play an important role in the development of education and prevention strategies. To our knowledge, there are no studies in Albania aiming to identify dietary models in CRC patients.

Materials and Methods

Study participants

Case selection

All cancer cases were incident and histologically confirmed diagnoses of CRC. These cases were identified and recruited from the University Hospital Center Mother Teresa, the Clinic of Gastrohepatology, Surgery Clinic, and the Oncology Clinic during the period 2011-2016.

Controls selection

Controls were sex- and age-matched individuals who were family members of patients hospitalized for acute, non-neoplastic conditions unrelated to digestive tract diseases.

Data collection

Data were collected using structured interviews and standardized questionnaires administered by trained personnel. The questionnaire covered a broad range of variables, including demographic variables [age, gender (male, female), place of residence (urban, rural)], socioeconomic variables [education level (0-8 years, 9-12 years, ≥13 years), economic level (low, middle, high)] and presence of family history for gastrointestinal cancer. Anthropometric indices were measured, including weight, height, body mass index (BMI), waist circumference, and hip circumference. Lifestyle factors included alcohol consumption (yes or no), frequency of alcohol consumption (once daily or more, ≥once per week, <once per week), smoking status (current smoker, former smoker, or never smoker), number of cigarettes per day, years of smoking, and physical activity level (low, intermediate, or high).

Dietary habits were evaluated by asking participants about the frequency of consumption of various food items (once daily or more, ≥once/week, <once/week), including fruits, vegetables, whole-grain bread, red meat, and olive oil.

Statistical analysis/assessment of dietary patterns

The answers from the questionnaire were initially combined into five different food groups as follows: vegetables, fruits, wholegrain bread, red meat, and olive oil. For each item patients and controls were asked the average frequency of consumption (less than 1 time/a week, > than 1 time/a

week but < than 1 time a day, > than 1 time a day). Cluster analysis was used to identify groups with similar characteristics. The number of clusters was defined using the SPSS direct marketing method (segment my contacts into clusters). Two dietary patterns (diet 1 and diet 2) were identified by cluster analysis. The silhouette coefficient, used to measure the quality of clustering results was fair. Comparisons of dietary patterns were performed using the analysis of variance test for continuous variables and χ^2 test for categorical variables. Continuous variables were presented as means with standard deviations and compared using independent samples *t*-tests. Categorical variables were expressed as frequencies and percentages, and the differences between them were analyzed using the chi-square test. Statistical significance was accepted for two-sided $p \leq 0.05$. All data management and analyses were performed with the SPSS version (IBM, Chicago, IL, USA).

Results

The demographic and lifestyle characteristics of the study population are presented in Table 1. The mean age was higher among CRC patients than controls ($p<0.001$), while the gender distribution was similar in both groups. The cases had lower education and economic level ($p<0.001$), and a higher proportion of CRC familial history. With regard to alcohol intake, our patients consume more ($p<0.001$) but in a more moderate way than controls ($p=0.024$). The proportion of current smokers was higher among controls (20.4% *vs*. 15.3%), while that of former smokers was higher among cases (21.9% *vs.* 12.5%). The number of cigarettes per day was similar in both groups, with higher duration of smoking (years) among cases than controls (25.6±9.6 *vs.* 24.2±13.9; $p=0.581$). Low physical activity was encountered more frequently among cases (70.2 *vs.* 51.9%), while intermediate and high physical activity were found more frequently in the control group (44.6 *vs.* 29.4 and 3.5 *vs.* 0.4 respectively; $p<0.001$). Considering weight, height, and BMI, no statistically significant differences were found between groups, while waist and hip circumference were significantly higher in the control group (97.8±14.7 *vs.* 94.2±12.2; $p=0.002$ and 109.4±14.3 *vs.* 106.9±11.4; $p=0.001$, respectively).

Based on diet, socioeconomic level (economic and education level), and lifestyle habits (alcohol intake and smoking), we have created 3 subgroups for cases and controls. For each group, we have built a score created by the mean individual values for each category (Figure 1). Cases have lower education and economic level than controls (<0.001), consume statistically more alcohol and cigarettes ($p= 0.001$), and fewer food units (0.041).

Two major dietary patterns (diet 1 and diet 2) were identified by cluster analysis in the study population (Table 2). Most food groups exhibited significant differences between the two clusters (Table 3). The first cluster (diet 1), denominated as urbanized, was characterized by a significantly lower intake of whole grain bread, fruits, and olive oil compared to the second one (diet 2), denominated as traditional, and was encountered significantly more frequently in the CRC group (Table 4).

Discussion and Conclusions

This study confirms, to an extent, that the traditional Albanian dietary pattern may play a protective role in CRC. A dietary pattern/model characterized by a low intake of whole-grain bread, fruits, and olive oil was encountered more frequently in our CRC patients. Albanian cuisine is traditionally categorized as “Mediterranean”, which is mainly characterized by low consumption of meat and high consumption of fruit, vegetables, and olive oil.[4] In fact, in our study, the consumption of red meat is almost the same in both groups. The relationship between red meat intake and CRC has been evaluated by numerous studies. Based on these studies, the World Cancer Research Fund/American Institute for Cancer Research established a strong association between a high consumption of red and processed meat and an increased risk of CRC.[5] Also, similarly, the International Agency for Research on Cancer has classified processed red meat as a human carcinogen, while suggesting that red meat may be a probable cause of CRC.[6,7] As there is a general consensus on regard of carcinogenetic of

processed red meat, there is a lack of consensus on the risk associated with unprocessed red meat intake. A systematic review and meta-analysis of 148 studies showed that high red meat and processed meat intake were positively associated with the risk of CRC cancer.[8] On the other hand, a case-control study from Italy and Switzerland reported that processed meat, but not total red meat, was associated with a 56% increased risk of early-onset CRC.[9] Moreover, the Burdon of Proof study, which evaluated the link between unprocessed red meat intake and CRC cancer, found weak evidence of an increased risk for this cancer.[10] This inconsistency may be attributed to the lack of distinction between processed and unprocessed red meat.[11] Additionally, recent studies have emphasized that the way of cooking red meat is also important in determining the risk of CRC.[12,13] In regard to our findings, although it is not specified in the questionnaire that we used, we should keep in mind that the most common red meat used in Albania is the unprocessed one. It is reasonable to assume that this may be one of the reasons that red meat did not represent a risk factor for CRC in our cohort. This finding could also have to do with foods that are consumed in conjunction with red meat as part of the overall dietary pattern.

When comparing the intake patterns of fruits, vegetables, and whole-grain bread in patient and control groups, our data are consistent to an extent with other studies, which found an inverse relationship with CRC risk.[14] Fruits and vegetables rich in fiber exercise their protective effect through several mechanisms: speeding up the transit of food through the colon, inducing the production of short fatty acids such as butyrate, and reducing secondary bile acids, which altogether have demonstrated changes in colon microbiota and colonic proliferation.[15] Besides the fiber content, there are also other compounds in fruits and vegetables that play an important role in CRC prevention, such as β-carotene and lycopene.[16] In our study, the consumption of vegetables was higher among the CRC group. The European Prospective Investigation into Cancer and Nutrition study, with a cohort of 452,755 participants, found no association between vegetables alone and CRC risk. When combined, fruits and vegetables show a weak inverse relationship with colon cancer, but not with rectal cancer. Moreover, vegetable consumption by current smokers showed a positive relationship with CRC risk.[17] Similar results were found by Vogtmann *et al*. in a study that encompassed more than 60,000 participants. They found that only fruit consumption was inversely associated with CRC risk. In regard to vegetables, no association was found even when they were categorized into different subgroups.[18] These findings may suggest that not all kinds of fruits and vegetables exercise a protective effect against CRC, and this protective effect may be diminished with concomitant use of other risk factors for CRC.

In this study, the intake of whole-grain bread is less frequent in CRC patients. This finding is similar to other reports that observed an inverse association of whole grains with CRC incidence.[19,20] Whole grain, rich in fiber, helps to prevent CRC cancer as other sources of fiber by increasing stool bulk, diluting possible carcinogens, reducing stool transit time through the bowel, and indirectly by reducing CRC risk factors such as weight gain and type 2 diabetes.[21] Hullings *et al.*, in a prospective study, investigated more than 10,000 incident cases of CRC, focusing on the role of dietary fiber, along with whole grains, in CRC risk. The inverse relationship was found only with whole grain intake.[22] This result may be explained by numerous compounds found in whole grains, such as B vitamins, minerals, phenols, antioxidants, and phytoestrogens, which may protect against CRC.[23] This result emphasizes once again that it is probably the combination of fiber and the related nutrients found in whole grains that confer protection against CRC risk.

Studies show that olive oil is rich in high-value health compounds such as monounsaturated free fatty acids, squalene, phytosterols, and phenols, which exert protective effects on carcinogenesis through diverse mechanisms.[24] Comparing olive oil intake in both groups, we found that controls consume it significantly more frequently. This finding is in line with other studies, which identified olive oil, even when used for frying, as a protective factor against CRC.[25]

This study has some limitations. Firstly, the dietary intakes were assessed using a food frequency questionnaire, which may not be accurate in estimating the absolute quantity and all the subgroups of

each food category. In addition, the possibility of selection bias is difficult to avoid. Moreover, case-control studies are susceptible to recall bias, and cases are more likely to recall perceived unhealthy dietary habits compared with controls. We tried to minimize this by recruiting cases as soon as possible after diagnosis, at most within the first month, and administering FFQs by trained interviewers under similar conditions to both cases and controls in a hospital setting.

In summary, our study adds to the body of evidence that diets rich in fruits, whole-grain bread, and olive oil have a protective role against CRC. The lack of association with red meat may suggest that at the local level, it is consumed unprocessed, in the absence of harmful subproducts resulting from meat processing. The loss of the protective effect of a traditional diet seems more important than the adoption of a Western diet, rich in processed red meat, refined cereals, and sweets. These findings may be important in promoting this protective diet, especially in areas where screening strategies are limited. These findings can be used to support public health in developing policies to slow down the increasing rate of CRC in our country and region.

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Table 1. Characteristics of the study population.

Variable	Cases: 262	Controls: 289	p-value
Age	62.7±11	58.9±11	<0.001
Gender, n (%)			0.218
Male	147 (56.1)	147 (50.9)	
Female	115 (43.9)	142 (49.1)	
Place of residence, n (%)			0.487
Urban	176 (67.2)	186 (64.4)	
Rural	86 (32.8)	103 (35.6)	
Education level, n (%)			<0.001
Low	100 (38.2)	79 (27.3)	
Intermediate	122 (46.5)	134 (46.4)	
High	40 (15.3)	76 (26.3)	
Economic level, n (%)			<0.001
Low	101 (38.5)	41 (14.2)	
Intermediate	147 (56.1)	222 (76.9)	
High	14 (5.3)	26 (9)	
Family history of cancer, n (%)			0.001
Yes	17 (6.5)	4 (1.4)	
No	245 (93.5)	285 (98.6)	
Alcohol consumption, n (%)			<0.001
Yes	143 (54.6)	122 (42.2)	
No	119 (45.4)	167 (57.8)	
Alcohol frequency, n (%)			0.024
Once daily or more	34 (23.8)	47 (38.5)	
≥once/week	66 (46.2)	50 (41)	
<once/week	43 (30)	25 (20.5)	
Smoking, n (%)			0.009
Current smoker	40 (15.3)	59 (20.4)	
Former smoker	57 (21.9)	36 (12.5)	
Never smoker	165 (63)	194 (67.1)	
Cigarettes per day	18±10.4	20.4±12.5	0.319
Smoker (years)	25.6±9.6	24.2±13.9	0.581
Physical activity, n (%)			<0.001
Low	184 (70.2)	150 (51.9)	
Intermediate	77 (29.4)	129 (44.6)	
High	1 (0.4)	10 (3.5)	
Anthropometric indices, n (%)			
Weight (kg)	74.3±10.4	75.6±11.7	0.113
Height (cm)	168.2±8	168.3±8.7	0.982
Body mass index	26.2±3	26.7±3.7	0.193
Waist circumference (cm)	94.2±12.2	97.8±14.7	0.002
Hip circumference (cm)	106.9±11.4	109.4±14.3	0.001

Table 2. Distribution of food patterns/models among our study group.

Dietary model (pattern)	Cases (%)	Controls (%)	Total (%)	P-Value
Model 1 (Urbanized/transitional)	233 (89)	111 (38.4)	343 (62.5)	<0.001
Model 2 (Traditional/prudent)	29 (11)	178 (61.6)	206 (37.5)	
Total	262 (100)	289 (100)	549 (100)	

Table 3. Characteristics of the two diet models/patterns.

Food categories	**Diet 1 (n=343)**	**Diet 2 (n=206)**	**P-value**
Fruits	2.17±0.631*	2.84±0.368†	<0.001
Vegetables	2.19±0.752	1.86±0.908	<0.001
Whole-grain bread	1.60±0769	2.13±0.590	<0.001
Red meat	1.80±0.469	2.55±0.835	<0.001
Olive oil	2.08±0.859	2.36±0.859	<0.001

*mean ± standard deviation.

Table 4. Frequency of different food categories in our study population.

Variable	Cases: 262	Controls: 289	P-value
Fruits, n (%)			<0.001
Once daily or more	97 (37.2)	178 (61.8)	
≥once/week;< once daily	128 (49)	102 (35.4)	
<once/week	36 (13.8)	8 (2.8)	
Vegetables, n (%)			<0.001
Once daily or more	129 (49.4)	79 (27.4)	
≥once/week;< once daily	126 (48.3)	44 (15.3)	
<once/week	6 (2.3)	165 (57.3)	
Whole-grain bread, n (%)			<0.001
Once daily or more	71 (27.2)	40 (13.9)	
≥once/week;< once daily	19 (7.3)	198 (68.8)	
<once/week	171 (65.5)	50 (17.3)	
Red meat, n (%)			<0.001
Once daily or more	31 (11.9)	139 (48.3)	
≥once/week;< once daily	164 (62.8)	90 (31.3)	
<once/week	66 (25.3)	59 (20.5)	
Olive oil, n (%)			<0.001
Once daily or more	131 (50.2)	137 (47.6)	
≥once/week;< once daily	34 (13)	82 (28.4)	
<once/week	96 (36.8)	69 (24)	

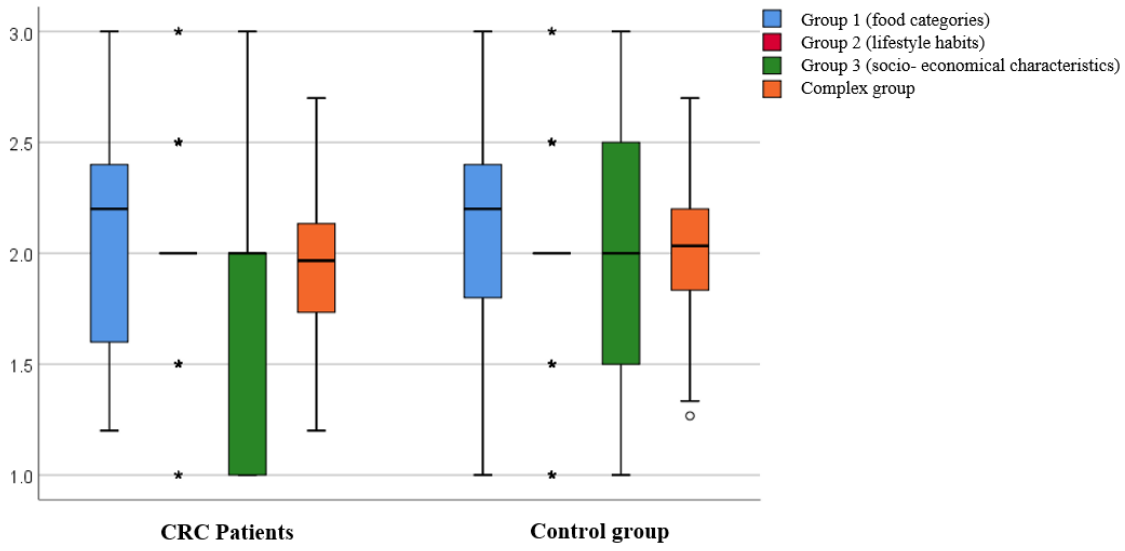

Figure 1. Food scores, lifestyle habits, and socio-economic status in our study group. CRC, colorectal cancer.