Ref: Ro Med J. 2024;71(1)
DOI: 10.37897/RMJ.2024.1.2

Variable role of diet-related risk factors for colorectal cancer – A cross-sectional analysis of regional differences

Tara Rolić[1,2], Iva Lukić[1,2], Sanja Mandić[1,2], Ilijan Tomaš[3,4], Ines Banjari[5]

[1]Department for Chemistry, Biochemistry and Clinical Chemistry, Faculty of Medicine, "Josip Juraj Strossmayer" University of Osijek, Osijek, Croatia
[2]Institute of Clinical Laboratory Diagnostics, University Hospital Centre Osijek, Osijek, Croatia
[3]Department of Oncology, University Hospital Center Osijek, Osijek, Croatia
[4]Department of Nuclear Medicine and Oncology, Faculty of Medicine, "Josip Juraj Strossmayer" University of Osijek, Osijek, Croatia
[5]Department of Food and Nutrition Research, Faculty of Food Technology, "Josip Juraj Strossmayer" University of Osijek, Osijek, Croatia

ABSTRACT

Background and objectives. Diet is the crucial environmental factor in sporadic colorectal cancer. Its complexity and diversity reflect our cultural and historical background, and could potentially explain why the existing public health strategies focused on colorectal cancer are failing.

Materials and methods. An observational cross-sectional study encompassed 60 non-metastatic CRC patients to assess dietary factors related to colorectal cancer, with regard to their traditional diet i.e. the region they come from. Patients were recruited from two regions (30 patients per region), in one (Slavonia) traditional diet is abundant in well-known dietary risk factors for colorectal cancer, and in the second (Dalmatia) traditional diet is the Mediterranean type.

Results. Based on the logistic regression analysis, patients from Dalmatia have a 24% higher risk for the high-risk diet in comparison to patients from Slavonia (OR = 1.240, 95% CI 1.195 – 9.990, P=0.022). Identified independent risk factors include weight loss in the last 3 months along with daily alcohol consumption which were found to increase CRC risk by 61.4% and 53.1%, respectively.

Conclusions. Our results support statistical data showing that colorectal cancer incidence is higher in the Mediterranean region, suggesting a shift in the Mediterranean dietary pattern, which in our case were higher obesity rates, daily alcohol consumption and abundance of unfavorable dietary habits.

Keywords: colorectal cancer, diet, regional differences, alcohol consumption, body weight

Abbreviations (in alphabetical order):

BMI	– Body Mass Index	CRC	– Colorectal Cancer
CI	– Confidence Interval	OR	– Odds Risk

INTRODUCTION

Colorectal cancer is the third most common cancer globally and the second cause of death due to cancer [1]. Burden of cancer is immense and affects not only individuals but also entire societies, either directly or indirectly, and the burden of CRC is becoming more intense in people under 50 years of age [2].

For spontaneous CRC cases (around 70% of all cases) [3], diet and physical activity are the most important environmental factors involved in its pathology

Corresponding author:
Ines Banjari
E-mail: ibanjari@ptfos.hr

Article History:
Received: 25 September 2023
Accepted: 29 March 2024

[4]. Their effect has such a profound role in CRC pathology that overcome positive genetic family history or diagnosis of the inflammatory bowel diseases [3].

Out of all diet-related risk factors for CRC, consumption of processed and red meat [4], and excessive alcohol consumption [5,6] stand out. Daily consumption of 50 g of processed meat (in a form of salted and smoked meat) increase the risk for CRC by 18%, and regular consumption of red meat (beef, pork and game meat) increase the risk by 12% [4]. Alcohol consumption shows a dose-dependent relation to CRC risk. Excessive alcohol consumption (≥ 50 g/day for men, ≥25 g/day for women) increase the risk for CRC between 21% and 52%, but also the risk of CRC mortality [5]. Additionally, lifetime average alcohol consumption of ≥25 g/day showed strong association for early-onset CRC [6]. Alcohol's negative impact seem to be more strongly accentuated in men, people with positive family history and obesity (BMI over 30 kg/m^2) [5].

Despite a number of convincing research findings, there are many showing null or negative association. Potential reason for that may lie in the diversity of diet. Culinary diversity is a global phenomena [7], visible not only between countries but within regions of the same country. Our previously published findings support this idea [8].

The aim of this study was to determine diet-related risk factors for CRC in colorectal cancer patients from two regions with different traditional dietary patterns.

MATERIALS AND METHODS

Study type and participants

An observational cross-sectional study encompassed non-metastatic CRC patients, diagnosed with either colon or rectal cancer for at least 6 months. Men and women of at least 40 years of age were eligible for inclusion, without any additional recruitment criteria. Patients were recruited through patient registry of General hospital Zadar (N=30) and University Hospital Centre Osijek (N=30), with equal distribution between men and women from each region (16 men and 14 women).

Ethics approval was obtained from both study centres. Patients who signed informed consent form were contacted via telephone to complete the study-specific questionnaires.

Questionnaires

First part of the study-specific questionnaire included general questions (e.g. age, gender), socio-demographic questions (e.g. education level, employment, income,), questions regarding health and CRC diagnosis (e.g. constipation, weight change, medication use, supplement use), and questions regarding general dietary and lifestyle habits (e.g. number of meals per day, meal skipping, smoking, alcohol consumption, physical activity). Patients' diet was analysed for energy, macro and micronutrient intake by using one 24-hour dietary recall. MeDietetic Software (MeDietetic, 2022) was used for all nutrition calculations.

Body Mass Index was calculated on the basis of self-reported weight and height and was used to categorize CRC patients according to their nourishment status as underweight (BMI ≤ 24.9 kg/m^2) or overweight/obese (BMI ≥ 25 kg/m^2) [9].

Statistical analysis

Statistical analysis was performed with Statistica 14.0, and MS Office Excel 2016 package was used for graphical presentation of study results.

Non-parametric Kolmogorov-Smirnov test was used to test the normality of the data by comparing medians, arithmetic means and histogram plotting. Parametric statistical tests were used, and level of significance used was 0.05. For the comparison of cathegorical data, Pearson's correlation test, student's t-test for independent variables and Chi square test were used. Logistic regression was used to test differences between regions. To calculate odds ratios between regions as binary variables in relation to one or more independent variables related to CRC risk univariate and multiple logistic regression were used, respectively. For the latter, only significant independent factors from univariate logistic regression were retained. The accepted probability of alpha error was 0.05.

RESULTS

General characteristics of patients are shown in table 1. All three patients < 50 years were from Dalmatia, while patients from Slavonia were mostly between 50 and 65 years old. There was no statistical difference between the distribution of patients according to their BMI, but more patients from Slavonia had BMI ≤ 24.9 kg/m^2, while more patients from Dalmatia had BMI ≥ 25 kg/m^2 (73.3% vs 56.7%, Table 1). More patients from Slavonia were using enteral nutrition, and these patients also had a lower BMI.

The majority of CRC patients from both regions lost up to 5 kg from the diagnosis; 30% from Slavonia and 40% from Dalmatia (Figure 1). However, more patients from Dalmatia reported losing more than 20 kg from the diagnosis, while one patient from Slavonia reported loosing 40 kg after the diagnosis which was the highest weight loss reported. Significantly more patients lost weight in the last 3 months from Slavonia ($p=0.020$) while significantly more patients from Dalamtia did not change their weight ($p<0.001$) (Figure 2).

TABLE 1. Basic characteristics of CRC patients from Slavonia (n=30) and Dalmatia (n=30)

Characteristics	Slavonia (n=30)	Dalmatia (n=30)	p[a]
	Mean ± SD (Min–Max)	Mean ± SD (Min–Max)	
Age <50 years (n/ %)	(0/ 0.0)	(3/ 10.0)	/
Age 50-65 years (n/ %)	(24/ 80.0)	(8/ 26.7)	
Age > 65 years (n/ %)	(6/ 20.0)	(19/ 63.3)	
BMI (kg/m^2)	26.3 ± 4.3 (20.7 – 36.6)	27.6 ± 4.4 (18.6 – 39.5)	0.272
BMI ≤ 24.9 kg/m^2 (n/ %)	(13/ 43.3)	(8/ 26.7)	0.279
BMI ≥ 25.0 kg/m^2 (n/ %)	(17/ 56.7)	(22/ 73.3)	
Using oral enteral nutrition (n/ %)	(14/ 46.6)	(7/ 23.3)	0.004*
BMI of patients on OEN (kg/m^2)	25.2 ± 3.3	27.9 ± 4.6	0.019*

BMI – Body Mass Index, SD – standard deviation, Min – minimum value, Max – maximum value
*a – T test for independent samples or Chi square test; *statistically significant at p<0.05*

TABLE 2. Cross-sectional analysis of indicators correlated with CRC risk between the two regions (multivariate logistic regression)

Variable	Category	OR	95% CI	P
Age	Per year	1.073	**0.992 – 1.161**	**0.079**
Weight change in the last 3 months	1=loss, 2=same, 3=gained	0.386	0.176 – 0.846	0.017*
Alcohol consumption	1=daily, 2=2-3 times per week, 3=monthly	0.469	0.238 – 0.923	0.028*
Protein contribution to the total daily energy intake	Per %	0.951	0.800 – 1.132	0.573
Analysis of the overall dietary risk	1=low risk, 2=high risk	2.851	0.729 – 11.145	0.132
Constant		0.273		0.675

**statistically significant at p<0.05; OR - Odds Ratio; CI - Confidence Interval*

In order to determine which indicators independently influence CRC risk between the two regions, we tested selected variables with logistic regression. Variables tested include age, BMI, weight loss, change in weight in the last 3 months, smoking habit, frequency of alcohol consumption, amount of alcohol consumed per day, daily energy intake, contribution of proteins, fats and carbohydrates to the total energy intake, dietary fiber consumption, preference towards spicy foods and the overall assessment of diet in regard to CRC risk as the high-risk or the low-risk diet (literature-identified important diet-related risk factors for CRC) [4]. Variables confirmed to be significant in the univariate model were

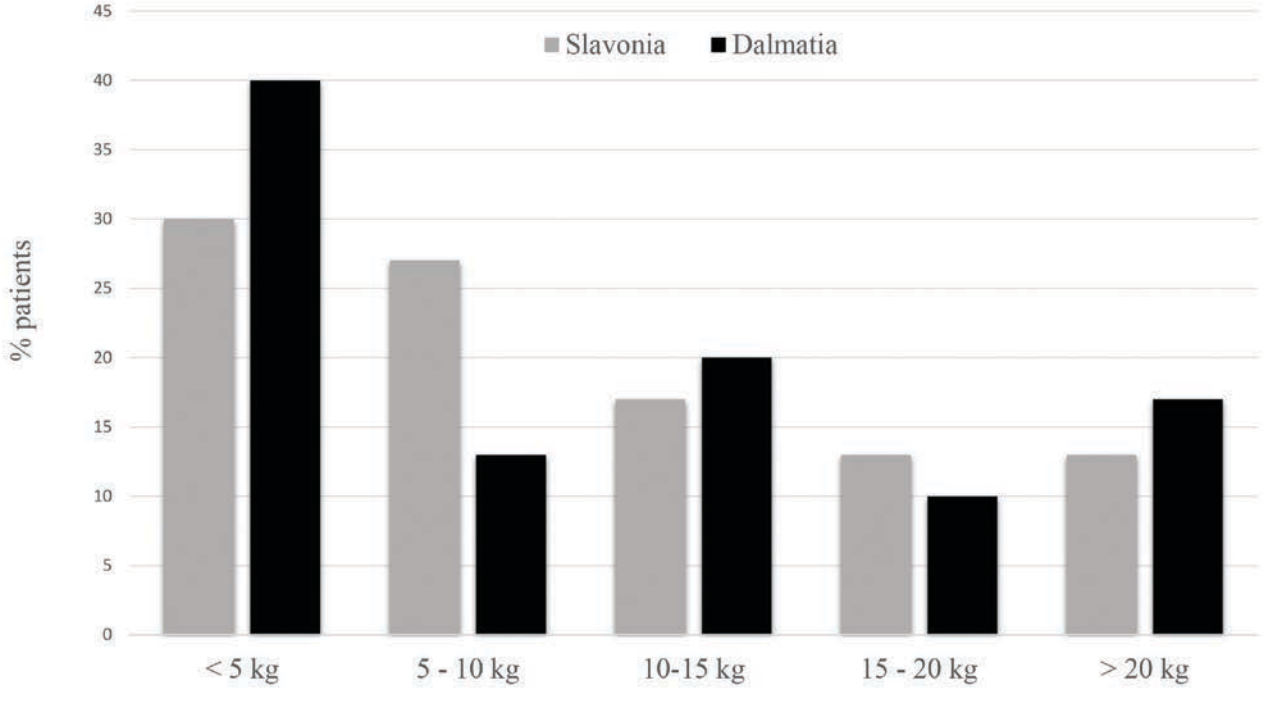

FIGURE 1. Weight loss among CRC patients after the diagnosis from Slavonia (n=30) and Dalmatia (n=30)

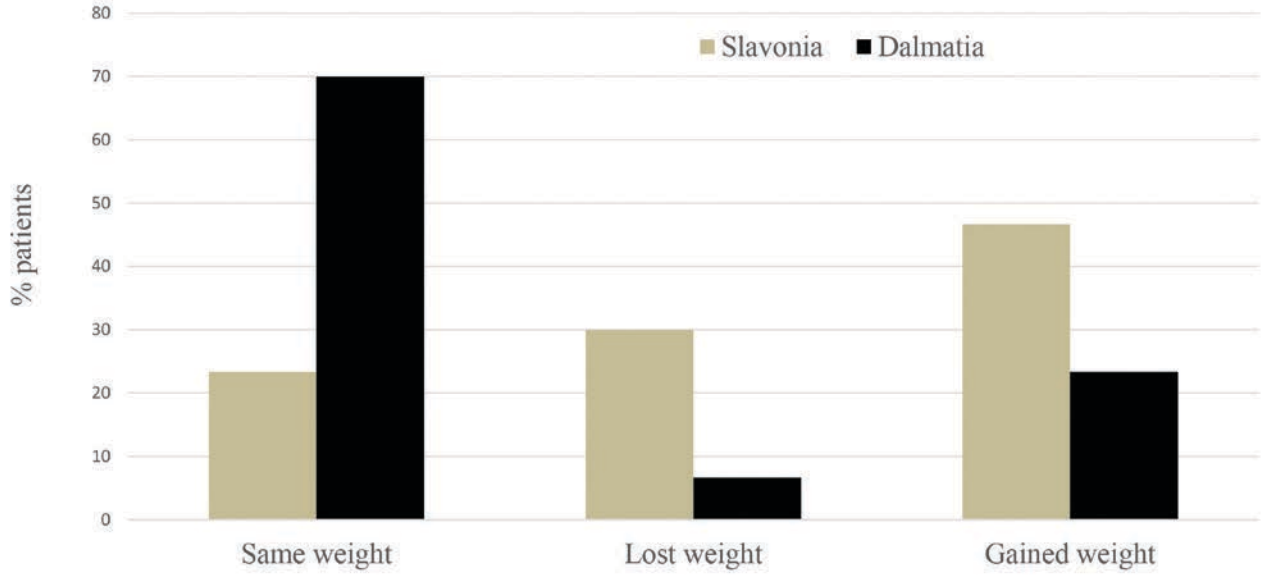

FIGURE 2. Self-assessment of weight change within the last 3 months among CRC patients from Slavonia (n=30) and Dalmatia (n=30)

included in the multivariate model (Table 2). Patients from Dalmatia have a 24% higher risk for the high-risk diet in comparison to patients from Slavonia (OR = 1.240, 95% CI 1.195 – 9.990, P=0.022). Identified independent risk factors include weight loss in the last 3 months along with daily alcohol consumption which were found to increase CRC risk by 61.4% and 53.1%, respectively (Table 2).

DISCUSSION

Risk for CRC increases with age, but rising trends among people under the age of 50 years [2] indicated that other factors overcome the effect of age. Also, a more aggressive form of CRC is found in patients under 50 years of age, but they have better survival rates in comparison to patients of 50+ years of age [4]. In our research, only three patients, all from Dalmatia were < 50 years old, but generally, the average age of our patients (Table 1) supports global statistics about the rising trend of CRC in people under the age of 65 [4]. In Croatia, 32% of CRC patients are younger than 65 years, but their share in the total number of the newly diagnosed is on the rise [10].

The problem of overweight and obesity is more than evident (Table 1), especially in Dalmatia. Overweight and obesity seem to be an especially pronounced risk in men, while generally, between 30 and 70% of CRC has been linked to increased body weight [11]. The risk for CRC increases significantly after BMI > 27 kg/m^2 [4], and more aggressive form of CRC is expected in a patient who is obese at the time of the diagnosis [12].

Weight change is an important indicator of survival; survival lowers by 25% with every 5 kg of weight lost [12], while weight gain did not show to be important indicator of either outcome or survival [13]. The majority of patients from both regions lost up to 5 kg post diagnosis (Figure 1), but there were some who lost > 20 kg, which can reflect negatively on the treatment and survival. At the time of the diagnosis and after the diagnosis, the majority of patients stay in their usual BMI category [12], which was the case among patients from Dalmatia while patients from Slavonia either gained or lost weight in the last 3 months (Figure 2). It should be noted that the average weight loss in CRC patients is about 7 kg, which has been fund to increase the risk of developing cancer cachexia [14]. Enteral nutrition is a good strategy to prevent cancer cachexia, and by applying it early in the postoperative course (within 48 h postoperatively) it improves patient's recovery, reduces the number of complications, improves treatment outcome, prevents muscle loss and improves immune response [14]. Our research findings suggest that enteral nutrition was introduced to improve patients' overall nutritional status (Table 1), as a mean to improve treatment and recovery.

The first region (Slavonia) due its specific geographic location in its diet reflects culinary influences from Turkey and Hungary. Traditionally, people in the first region consume a lot of red and processed meat, with high preference towards spicy foods, large contribution of saturated fats, but with abundancy of fermented dairy and fresh vegetables [8]. This is completely opposite from the second region (Dalmatia), located on the Adriatic coast, in which the traditional dietary pattern is the Mediterranean diet. The Mediterranean diet is considered to be superior, with proven beneficial effect on CRC too [4,7]. However, CRC incidence rates do not follow these traditional dietary characteristics. According to the latest availa-

ble statistics for Croatia [10], incidence rates for C18 (colon cancer excluding rectum) per 100 000 population are higher in Dalmatia than in Slavonia (60.0 to 69.9 in Dalmatia in comparison to 43.3 in Slavonia). Additionally, obesity rates in Croatia are among the highest in the world, and continue to rise [9]. Regions mostly affected with obesity are coastal regions [15], proving that the traditional diet in the Mediterranean region is changing [7].

Detailed nutrition analysis between the two regions was published elsewhere, but no difference was found in energy or micronutrient consumption [3]. Logistic regression analysis revealed that patients from Dalmatia had a 24% higher risk for the high-risk diet in comparison to patients from Slavonia, and independent risk factors for CRC include weight loss in the last 3 months and daily alcohol consumption (Table 2), all known risk factors for CRC. Alcohol is especially problematic when combined with other risk factors, particularly obesity [5]. Alcohol is a possible cause of the metastatic disease due to changes in folate metabolism in the liver it causes [5].

A combination of daily alcohol consumption, diet abundant in risk factors for CRC and higher obesity rates make adults from Dalmatia at an increased risk for CRC in comparison to adults from Slavonia. Yet, our results suggest that patients from Slavonia have a more severe form of CRC, which, given the poor nutritional status (lower BMI, more weight loss) of these patients, require more attention in regard to treatment and recovery.

CONCLUSION

The results clearly show that for people from different regions within one country, the diet-related risk factors for CRC have variable levels of importance. Our results support a number of research findings on unfavorable changes in the Mediterranean dietary pattern. In this case, these unfavorable changes are reflected in higher CRC incidence rates in comparison to a region which should, by its traditional dietary pattern, have a higher risk for CRC. Findings from this study should encourage researchers from countries known for its diverse dietary habits across regions to conduct similar research and explore the role of culinary diversity in CRC risk.

Conflict of interest:
The authors have no conflict of interest to disclose.

Financial support: none declared

Author's contributions:
Conceptualization, T.R. and I.L.; methodology, I.B.; validation, S.M., I.T. and I.B..; formal analysis, I. B.; investigation, T.R., I.L. and I.T.; writing—original draft preparation, T.R.; writing—review and editing, S.M., and I.B.; visualization, I.L.; supervision, S.M. and I.B.. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. World Health Organization. International Agency for Research on Cancer (2020): GLOBOCAN Cancer Today Data. https://gco.iarc.fr/today/home.
2. Voigtländer S, Hakimhashemi A, Grundmann N, Rees F, Meyer M, Algül H, et al. Trends of colorectal cancer incidence according to age, anatomic site, and histological subgroup in Bavaria: A registry-based study. *Front Oncol.* 2022;12:904546. doi: 10.3389/fonc.2022.904546.
3. Kunac M, Tomaš I, Telesmanić Dobrić V, Balkić Widmann J, Stokanović Cvijetić M, Banjari I. Dietary habits of colorectal cancer patients – comparison between Slavonia and Dalmatia. *Hrana u zdravlju i bolesti* 2023;12(1):1-6.
4. World Cancer Research Fund/ AICR, American Institute for Cancer Research (2018): Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. https://www.wcrf.org/sites/default/files/Colorectal-cancer-report.pdf.
5. Rossi M, Jahanzaib Anwar M, Usman A, Keshavarzian A, Bishehsari F. Colorectal Cancer and Alcohol Consumption-Populations to Molecules. *Cancers* (Basel). 2018;10(2):38. doi: 10.3390/cancers10020038.
6. Chen X, Li H, Guo F, Hoffmeister M, Brenner H. Alcohol consumption, polygenic risk score, and early- and late-onset colorectal cancer risk. *E Clinical Medicine.* 2022;49:101460. doi: 10.1016/j.eclinm.2022.101460.
7. Mertens E, Kuijsten A, Dofková M, Mistura L, D'Addezio L, Turrini A, et al. Geographic and socioeconomic diversity of food and nutrient intakes: a comparison of four European countries. *Eur J Nutr.* 2019; 58(4):1475-1493. doi: 10.1007/s00394-018-1673-6.
8. Banjari I, Kožić S. Dietary intake of vitamin B12 in relation to diet and lifestyle characteristics in a population at high risk for colorectal cancer. *Cent Eur J Public Health.* 2018;26(4):253-259. doi: 10.21101/cejph.a4585.
9. World Obesity. Global Obesity Observatory. https://data.worldobesity.org/country/croatia-51/.
10. Croatian Institute of Public Health. Croatian National Cancer Registry. Cancer Incidence in Croatia 2019. Bulletin No. 44. Zagreb: Croatian Institute of Public Health, 2021.
11. Duraiyarasan S, Adefuye M, Manjunatha N, Ganduri V, Rajasekaran K. Colon Cancer and Obesity: A Narrative Review. *Cureus*. 2022;14(8):e27589. doi: 10.7759/cureus.27589.
12. Kocarnik JM, Hua X, Hardikar S, Robinson J, Lindor NM, Win AK, et al. Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: The Colon Cancer Family Registry. *Cancer*. 2017;123(23):4701-4708. doi: 10.1002/cncr.30932.
13. Cong Z, Wang D, Cao Y. The relationship between body mass index changes during chemotherapy and prognosis of patients with advanced colorectal cancer: A retrospective cohort study. *Medicine* (Baltimore). 2018;97(22):e10843. doi: 10.1097/MD.0000000000010843.
14. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers.* 2018;4:17105. doi: 10.1038/nrdp.2017.105.
15. Fister K, Kolcić I, Milanović SM, Kern J. The prevalence of overweight, obesity and central obesity in six regions of Croatia: results from the Croatian Adult Health Survey. *Coll Antropol.* 2009;33 Suppl 1:25-9.