

## Coincidence of colorectal cancer and diverticular disease of the colon

### *Koincidencija kolorektalnog karcinoma i divertikuloze kolona*

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#### Summary

Background: Diverticular disease (DD) of the colon and colorectal cancer (CRC) have common characteristics (e.g. more common in the westernized world and in the elderly, similar dietary features implicated for both diseases) and a casual relationship between them has been suggested. Our aim was to evaluate the coincidence of CRC and DD in continental and coastal Croatia as a dietary variability observed in our population – low fiber diet in the continent and Mediterranean diet on the coast creates a favourable situation for the investigation of diseases with suspected nutritional aetiology. Methods: Medical histories of 710 patients from the continental region and 406 from the coastal region diagnosed with CRC from 2011 to 2016 were analyzed with regard to the prevalence of DD. The groups were furthermore divided in different age and sex groups and the prevalence of DD in each group was calculated and compared. Distribution of DD and CRC in the colon for the groups of CRC in concomitance with DD were also analyzed. Results: The prevalence of DD among the CRC group in the coastal region was 32.3% and in the continental region 11.5%. The prevalence of DD in the coastal region was significantly higher in the overall number compared to the continental region as well as in the overall number of men and women, and in the age-stratified group > 65. The left colon was affected more often with DD and CRC in both groups. Conclusions: Our findings suggest that patients with CRC and DD could derive from distinct groups and the effect of the diet has yet to be established.

**Key words:** colorectal cancer, diverticular disease, low-fiber diet, Mediterranean diet

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#### Sažetak

Uvod: Divertikuloza (DK) debeloga crijeva i karcinom debeloga crijeva (KDC) imaju neke zajedničke karakteristike (npr. češći su u zapadnom dijelu svijeta i kod starijih osoba, slične prehrambene značajke uključene su u obje bolesti) a povremena povezanost između njih je ispitivana. Naš cilj je bio procijeniti ko incidenciju KDC-a i DK u kontinentalnoj i primorskoj Hrvatskoj, kao i prehrambenu varijabilnost u našoj populaciji - prehrana s manjim udjelom vlakana u kontinentalnoj Hrvatskoj i mediteranska prehrana u primorskoj Hrvatskoj stvara povoljnu situaciju za istraživanje bolesti sa sumnjom na prehrambenu etiologiju. Metode: Analizirane su medicinske povijesti 710 bolesnika iz kontinentalne regije i 406 bolesnika iz primorske regije s dijagnozom KDC od 2011. do 2016. godine s obzirom na prevalenciju DK. Skupine su nadalje podijeljene prema različitim dobnim i spolnim skupinama, a prevalencija DK u svakoj skupini izračunata je i uspoređena. Analizirane su i distribucije DK i KDC-a za skupine KDC u usporedbi s DK. Rezultati: Prevalencija DK u skupini KDC u obalnom području iznosila je 32,3%, a u kontinentalnoj regiji 11,5%. Prevalencija DK u primorskom području bila je znatno veća u ukupnom broju u usporedbi s kontinentalnom regijom, kao i u ukupnom broju muškaraca i žena, te u dobno stratificiranoj skupini > 65. Lijevi kolon je češće zahvaćen s DK i KDC u obje skupine. Zaključci: Naši podaci upućuju da bolesnici s KDC i DK mogu proizaći iz različitih ispitivanih skupina, a učinak prehrane tek treba ustanoviti.

**Ključne riječi:** kolorektalni karcinom, divertikularna bolest, dijeta s malo vlakana, mediteranska dijeta

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## Background

The diverticular disease (DD) of the colon and colorectal cancer (CRC) have common characteristics: they share a similar increase in incidence, there is an increase in both entities with advancing age, they are more common in the westernized world and similar dietary features (such as a diet consisting of low fiber content and rich in dietary fat) have been implicated for both diseases.<sup>1</sup> The prevalence of both diseases increases in populations moving from low-risk to high-risk areas within the first generation.<sup>2,3</sup> Therefore, it is not surprising that a casual relationship between these two entities has been suggested. Epidemiologic studies found a more frequent rectosigmoid localization of neoplastic lesions (advanced adenoma and CRC) in patients with diverticulosis as compared with controls, particularly in those with a previous diverticulitis episode or with an extensive disease. However, data are still controversial, with other studies failing to confirm this observation. Such discrepancy could be referred to the high heterogeneous study design and setting in different epidemiologic series.<sup>4</sup>

The purpose of this retrospective study was to evaluate the coincidence of CRC and DD in two regions in Croatia, the continental region and coastal region, and to directly compare the results as a dietary variability observed in the Croatian population, depending on the region of living, creates a favourable situation for the investigation of diseases with suspected nutritional aetiology (sociocultural impact of the Mediterranean environment on the coast and nutritional habits that are more similar to the Western diet – low in fiber with more frequent consumption of meat in the continent). We calculated the prevalence of DD for the group of patients diagnosed with CRC in the continental region as well as for the group in the coastal region. The results were compared and statistical significance defined.

The possible association between DD and CRC could be clinically relevant because a different screening protocol for CRC could be scheduled in patients with DD, and if there is a role of diet and lifestyle, strategies for prevention could be offered.

## Patients, materials and methods

Data were taken from two hospitals, University Hospital (UH) Sveti Duh in the capital city of Croatia – Zagreb (continental region) and University Hospital Centre (UHC) Split in Dalmatia (coastal region) (Table 1).

We have retrospectively analyzed the medical histories of 710 patients that were diagnosed with CRC in UH Sveti Duh in the period from 2011 to 2016. The diagnosis was based on colonoscopy, computed tomography, colonic contrast enema findings or surgical intervention, and subsequently confirmed with histopathological analysis. In the process of diagnosis DD was found in 82 patients.

In UHC Split, 406 patients were hospitalized in the same period, from 2011 to 2016, and diagnosed with CRC by the same means. DD was diagnosed in 131 patients. Patients were stratified according to sex and age. The prevalence of DD found in patients with CRC, for both the continental and coastal region, was calculated (Table 2).

The distribution of DD and CRC according to the affected part of the colon was pointed out for the group of patients with concomitance of both diseases (Table 3).

Statistical analysis was performed using the SAS system for Windows (rel. 8.02, SAS Institute Inc., Cary, NC, SAD). Fisher's exact test was used for dependent and independent samples. Statistical significance was set at  $p < 0.05$ .

The study design was approved by the Local Ethics Committee. Standards of Good Clinical Practice and the Declaration of Helsinki followed.

Table 1 Total number of patients stratified according to age and sex.

Tablica 1. Sveukupan broj bolesnika podijeljen na dob i spol

	Number of patients <i>Broj bolesnika</i>	Gender M F <i>Spol M Ž</i>		Age / Dob			
				<= 40	> 40	<= 65	> 65
Continental region (ZG) <i>Kontinentalno područje (ZG)</i>	710	431	279	13	262	435	
Coastal region (ST) <i>Obalno područje (ST)</i>	406	265	141	11	133	262	
Total <i>Sveukupno</i>	1116	696	420	24	395	697	

Table 2 Prevalence of diverticular disease (DD) in the colorectal cancer group (CRC), with reference to age and sex  
Tablica 2. Prevalencija divertikularne bolesti (DD) kod kolorektalnog karcinoma (CRC) u odnosu na dob i spol

AGE (years) and SEX Dob (godine) i SPOL	Number of patients with CRC Broj bolesnika s CRC		Number of patients with CRC and DD (N) Broj bolesnika s CRC i DD		Rate of patients with CRC and DD (%) Stopa bolesnika s CRC i DD (%)		
	ZG*	ST**	ZG*	ST**	ZG*	ST**	P***
Total Sveukupno	710	406	82	131	11.5	32.3	0.001
Men Muškarci	431	265	51	72	11.8	27.2	0.001
< = 40	5	7	0	0	-	-	-
> 40 < = 65	163	90	10	6	6.1	6.7	n.s.
> 65	263	168	41	66	15.6	39.3	0.001
Women Žene	279	141	31	59	11.1	41.8	0.001
< = 40	8	4	0	0	-	-	-
> 40 < = 65	99	43	6	6	6.1	14.0	n.s.
> 65	172	94	25	53	14.5	56.4	0.001

\* ZG – continental region / ZG kontinentalno područje; \*\* ST – coastal region / ST obalno područje

\*\*\* P < 0,05 Fisher's exact test / P < 0,05 Fisher test točnosti; n.s. = non significant / bez značajnosti

Table 3 Diverticular disease (DD) and colorectal cancer (CRC) distribution in the colon in the CRC with DD group  
Tablica 3. Podjela divertikularne bolesti (DD) i kolorektalnog karcinoma (CRC) u kolonu u CRC i DD skupini

Parts of the colon Djelovi debelog crijeva	Continental region Kontinentalno područje		Coastal region Obalno područje		p
	CRC N (%)	DD N (%)	CRC N (%)	DD N (%)	
Rectum Rektum	15 (18.3)	4 (4.8)	19 (14.5)	8 (6.1)	n.s.
Sigmoid colon Sigmoidno debelo crijevo	35 (42.8)	41 (50.0)	61 (46.6)	74 (56.5)	n.s.
Descending colon Silazno debelo crijevo	11 (13.4)	23 (28.2)	18 (13.7)	28 (21.4)	n.s.
Transverse colon Poprečno debelo crijevo	5 (6.1)	7 (8.5)	11 (8.4)	11 (8.4)	n.s.
Ascending colon Uzlazno debelo crijevo	12 (14.6)	7 (8.5)	14 (10.7)	9 (6.9)	n.s.
Cecum Crijevo	4 (4.8)	-	8 (6.1)	1 (0.7)	n.s.

P < 0,05 Fisher's exact test / P < 0,05 Fisher test točnosti; n.s. = non significant / bez značajnosti

## Results

A total of 710 medical histories of patients diagnosed with CRC from 2011 to 2016 were analyzed in UH Sveti Duh of which 431 were men and 279 women, 82 of them had DD of which 51 were men and 31 women. Furthermore, the patients were stratified

into three age groups <= 40, > 40 <= 65, > 65. Their age-stratified distribution represented the typical age-related risk for CRC and the prevalence of DD increased with age while no DD was identified under the age of 40 (Table 2). The prevalence of DD in the CRC group is presented in Table 2.

A total of 406 medical histories of patients diagnosed with CRC from 2011 to 2016 were analyzed in UHC Split of which 265 were male and 141 female, 131 of them had CRC with DD of which 72 were men and 59 were women. The patients were also stratified into three age groups. Their age-stratified distribution represented the typical age related risk for CRC and the prevalence of DD increased with age while no DD was identified under the age of 40. The prevalence of DD in the CRC group is presented in Table 2.

Comparing the results from these two regions statistically significantly higher rates of DD were found in the coastal cancer group. The same results were found in the group of women as well as in the group of men. In the age-stratified groups statistically significantly higher rates of DD were found in the group > 65 years for both men and women in the coastal region (Table 2).

Colonic diverticulosis and cancer distribution according to the part of the colon for the group of patients with both CRC and DD is shown in Table 3. The left colon was affected more often and there were no statistical differences between the two regions.

### Discussion

The diverticular disease of the colon is among the most common diseases of westernized and industrialised countries. The prevalence amounts to 5-10% of people up to 50 years of age, 30% of those > 50 years of age, and 50% of those > 70 years of age, and 66% of people > 85 years of age.<sup>5</sup> On the other hand, according to “GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012” the estimated world incidence of CRC for both sexes is the Age Standardised Rate (ASR) 17.2/100 000, in Europe ASR 29.5/100 000 and in Croatia ASR 32.9/100 000.<sup>6</sup> Age is a major risk factor for sporadic CRC. It is a rare diagnosis before the age of 40, the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter.<sup>7</sup> Therefore, the concomitance of colonic neoplasia and DD should be common in aged people. But there are data that suggest that this coincidence seems to fall below the expected prevalence.<sup>8</sup>

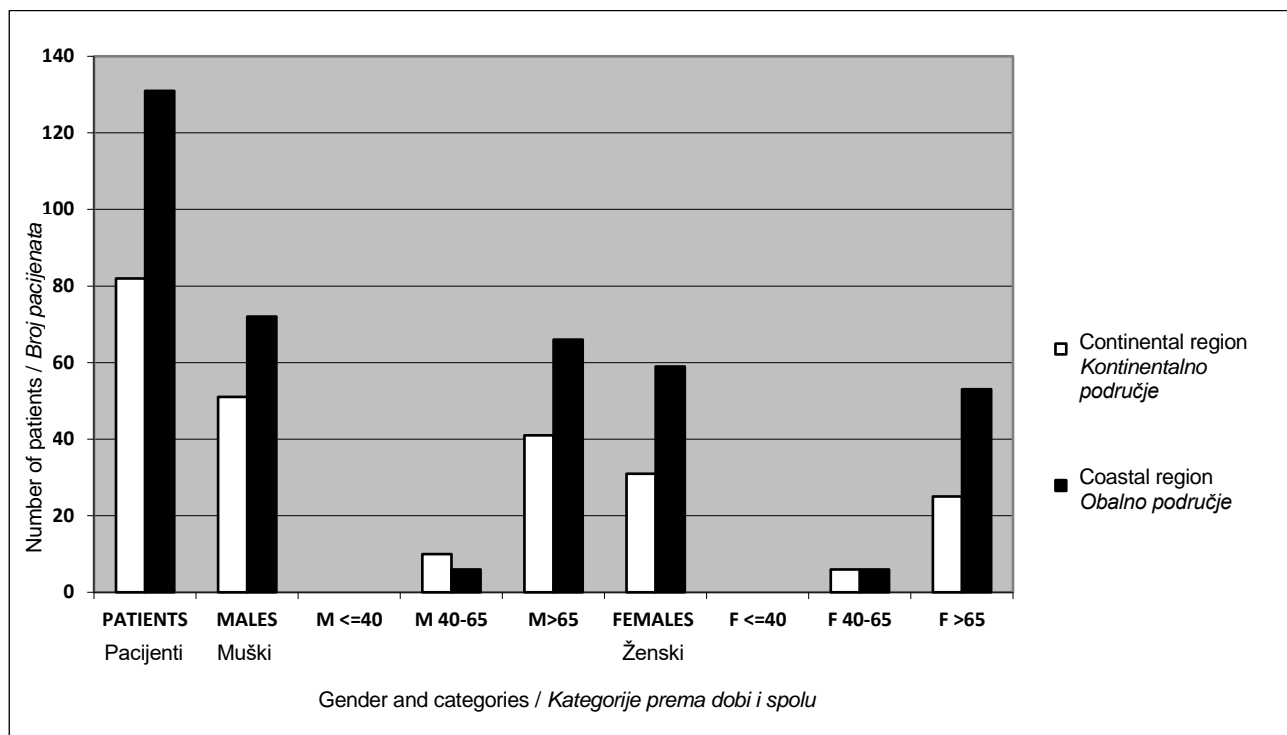
Furthermore, several studies have suggested that nutritional behaviour, especially the increased consumption of a low-fiber diet, is one of the major etiologic factors for CRC and DD. The Western diet, low in dietary fiber and rich in saturated fat, may play a major role.<sup>9-11</sup> On the other hand, the incidence of cancer overall in Mediterranean countries is lower than in Scandinavian countries, the United Kingdom, and

the United States. This is mostly accounted for by the lower incidence among Mediterranean countries of cancer of the large bowel (that we are interested in), breast, endometrium, and prostate. These forms of cancer have been linked to dietary factors, particularly low consumption of vegetables and fruit, and to a certain extent, high consumption of meat.<sup>12</sup> The term Mediterranean diet is well defined and refers to dietary patterns found in olive-growing areas of the Mediterranean region and described in the 1960s and beyond. There are several variants of the Mediterranean diet, but some common components can be identified: high monounsaturated/saturated fat ratio; ethanol consumption at moderate levels and mainly in the form of wine; high consumption of vegetables, fruits, legumes, and grains; moderate consumption of milk and dairy products, mostly in the form of cheese; and low consumption of meat and meat products<sup>13</sup> It is essential for Mediterranean nutrition that it is characterized by the moderate use of meat, milk, cheese, high intake of complex carbohydrates (potatoes, raspberry, pasta, rice), fresh fruits and vegetables, regular use of fish and using fat almost all contained in the form of olive oil.

Continental nutrition is known for its abundance, excessive calories, of red meat. It is assumed to be due to the harsh climate with its long and cold winters. This diet presents 'more specific' fatty foods based on meat, spicy spices and pickled vegetables.

The hypothesis is, therefore, that there should also be a lower rate of DD in the Mediterranean region, although an autopsy study in the population on Crete reported only slightly lower diverticulosis prevalence (22.9%) than which has been reported in most other studies in economically developed countries.<sup>14</sup>

Our results have shown that statistically significant higher rates of DD were found in coastal Croatia, our Mediterranean region, in the overall number of patients with CRC (32.3% vs. 11.5% respect.) and also when they were stratified according to sex as well as in the age group of patients older than 65. If a low-fiber diet is supposed to directly influence the risk of DD and CRC, this cannot explain the divergent finding (Picture 1). The distribution of DD and CRC in the colon is represented in Table 3 and the results have shown that there is no statistical difference in the distribution of both diseases according to the region of living, and the majority of the findings are situated in the left colon, which is similar to the published world data.<sup>15</sup> In conjunction with our results, there were interesting results from Japan that explained the different location of diverticula in Easterners (right hemicolon) or Westerners (left hemicolon) by morphological rather than environmental influences.<sup>15</sup>



Picture 1 Patients with colorectal cancer and diverticular disease (both regions) stratified in age and gender categories

Slika 1. Bolesnici s kolorektalnim karcinomom i divertikularnom bolesti (oba područja) podijeljeni na dob i spol

In addition, Kronos et al. retrospectively analyzed the prevalence of DD in patients with a history of CRC and, comparing it with published epidemiologic data, found a statistically significant reduced rate of diverticula in their cancer group (18.3%) explained with a different composition of extracellular matrix.<sup>8</sup> In comparison to our results of DD prevalence (Table 2), in a postmortem survey of DD of the colon, Hughes found in 200 unselected necropsies the overall incidence of diverticula to be 43%, 45% in the men group and 40% in the women group.<sup>16</sup> There was also another study published in 2001 in which the analysis of the endoscopic reports from 9086 patients showed the prevalence of DD by 27%, 26% in men and 28% in women.<sup>17</sup> These epidemiologic data are especially divergent when compared to the rate of DD in our CRC group from the continental region because the coincident occurrence of both diseases seems to fall below their individual epidemiologic estimates. These findings suggest that patients with CRC and DD could derive from distinct groups and challenge the role of a high fiber diet protecting against both diseases.

It is also worth to mention that, according to literature, there is a higher prevalence rate of DD among females and similar findings are present in our

group from the coastal region while in the continental region there is a slightly higher prevalence among men (11.8% vs. 11.1%, respectively).<sup>18</sup> In the Western countries, on the other hand, CRC incidence is higher in males.<sup>4</sup>

Now we come to the question, what could possibly influence the proposed heterogeneity of both diseases – do they derive from a different composition of the extracellular matrix as it was hypothesized by Kronos et al., or from a different microbiota composition, referring, for example, to the study of the mucosa-associated bifidobacteria in patients with CRC, diverticulitis or IBD showing that colorectal bacteria may play a role in the pathogenesis of several intestinal diseases<sup>8,19</sup> or maybe hormonal factors are also involved in such a phenomenon. Furthermore, the number of questions regarding the etiology of DD still remains, especially related to the role of diet and lifestyle, as these factors offer strategies for prevention. Epidemiologic and observational studies have been most successful in illuminating the role of diet and lifestyle in DD prevalence so far but the epidemiological approach is currently confounded by the lack of available up-to-date data on DD prevalence in different populations.<sup>20</sup> Observing more recent

studies, the results are conflicting and there is a need for more prospective case-control cohort studies upon DD and diet.<sup>21-23</sup> In the colonoscopy-based, cross-sectional study of dietary risk factors for diverticulosis of Peery et al. it was found, contrary to expectation, that a high-fiber diet was associated with a higher (not lower) prevalence of diverticula. Dietary fiber could alter gut bacteria and these changes could be associated with diverticulosis. The bacterial flora is, namely, important for the function and integrity of the epithelial barrier and its blood supply, and is essential for the development of gut motility.<sup>24</sup> Therefore, maybe altering the host microflora could prevent the formation of diverticula. Furthermore, in the last few years, some open-label studies evaluated the role of probiotics in the treatment of DD, but there is a lack of controlled trials.<sup>25</sup> Finally, we should also mention the results from a meta analysis of prospective studies performed up to December 2010 and published in 2011 that investigated the relationship between the intake of dietary fiber and whole grains and the risk of CRC, and concluded that the high intake of dietary fiber, in particular cereal fiber and whole grains, was associated with a reduced risk of CRC.<sup>26</sup> There are proven advantages in eating a high fiber, plant-based diet with respect to constipation, heart disease and cancer<sup>27</sup> but there are still a lot of controversies about DD.

In conclusion, our findings suggest that patients with CRC and DD could derive from distinct groups and the role of a diet has yet to be established. The main limitation of our study, due to the retrospective approach, is in the fact that we did not use a questionnaire on individual eating habits of the study population which could have possibly influenced the results. There is a need for further prospective studies to clarify the role of the diet in the development of CRC and DD and to give new insights in the etiology of both diseases.

We also believe that for future research it would be necessary to make a well-thought-out questionnaire on the dietary habits of patients with diverticulosis of the colon and colorectal cancer, including an analysis of the intestinal microbiota.

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