



Change in the incidence and anatomic distribution of colorectal adenoma and cancer over a period of 20 years – A single center experience

Promene u incidenci i anatomskej distribuciji kolorektalnih adenoma i karcinoma u periodu od 20 godina – iskustvo jednog centra

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Abstract

Background/Aim. In recent years, many studies have demonstrated a proximal shift in the distribution of adenomas and colorectal cancers. The aim of this study was to investigate whether there are differences in the incidence and anatomical distribution of adenomas and colorectal cancers spanning a 20 year time gap. **Methods.** We performed a retrospective observational study of colorectal adenomas and cancers diagnosed during total colonoscopy in a high volume tertiary care facility in two 1-year periods of time – 1990 and 2010. **Results.** During the analyzed period, 4,048 colonoscopies were performed, 1,148 were performed in 1990 and 2,900 were done in 2010. The study included 466 patients with adenomas and 121 patients with colorectal cancers. Frequency of proximal adenoma changed from 16.5% to 32.7% ($p < 0.001$). By analyzing colonoscopies in 2010, an increase in the incidence of adenomas compared to 1990 was noticed. The number of adenomas sized 0–5 mm rose from 32.8% to 56.9% ($p < 0.001$). Frequency of colon carcinoma changed from 5.3% to 2.0% ($p < 0.001$). Incidence of cancers in the proximal colon rose from 21.3% to 48.4% ($p = 0.002$). A higher incidence of cancers in the proximal colon and a lower incidence of distal cancers were observed, while no difference was observed in the incidence of rectal cancers. **Conclusion.** Presence of proximal colon adenoma and cancer is higher, while the overall incidence of colon cancer is lower. This finding should be taken into account when planning the screening for colorectal cancer.

Key words:

colorectal neoplasms; adenoma; carcinoma; diagnosis; incidence.

Apstrakt

Uvod/Cilj. Poslednjih godina mnoge studije su ukazale da je došlo do promene u distribuciji adenoma i karcinoma debelog creva, odnosno da se povećava zastupljenost proksimalnih lezija. Cilj ove studije je bio da se utvrdi postoji li razlika u zastupljenosti i distribuciji adenoma i karcinoma debelog creva u dva vremenska perioda sa razlikom od 20 godina. **Metode.** Sprovedena je retrospektivna opservaciona studija o kolorektalnim adenomima i karcinomima koji su dijagnostikovani kolonoskopski u tercijarnom zdravstvenom centru tokom 1990. i 2010. godine. **Rezultati.** Od ukupno 4,048 kolonoskopija izvedenih tokom dva analizirana perioda 1,148 je urađeno tokom 1990. a 2,900 je urađeno tokom 2010. godine. Studijom je obuhvaćeno 466 bolesnika sa adenomima i 121 bolesnik sa karcinomom debelog creva. Zastupljenost proksimalnih adenoma se promenila sa 16.5% na 32.7% ($p < 0.001$). Analizirajući kolonoskopije iz 2010. godine, uočen je porast incidencije adenoma u poređenju sa nalazom iz 1990. godine. Broj adenoma veličine 0–5 mm je porastao sa 32.8% na 56.9% ($p < 0.001$). Učestalost karcinoma kolona je promenjena sa 5.3% na 2.0% ($p < 0.001$). Zastupljenost karcinoma u proksimalnim partijama debelog creva je porasla sa 21.3% na 48.4% ($p = 0.002$). Uočena je veća incidenca karcinoma u proksimalnom kolonu i manja incidenca distalnih karcinoma kolona, ali ne i razlika u incidenci kod rektalnog karcinoma. **Zaključak.** Pokazana je veća učestalost proksimalnih adenoma i kancera, dok je ukupna učestalost karcinoma kolona manja. Ovaj zaključak je značajan radi sprovođenja skrininga za kolorektalni karcinom.

Ključne reči:

kolorektalne neoplazme; adenom; karcinom; dijagnoza; incidenca.

Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third in men worldwide. According to the World Health Organization GLOBOCAN database in 2012, approximately 1.4 million new cases of CRC were diagnosed and 694,000 people died as a result of CRC¹. Cancer development most commonly begins with adenoma formation^{2,3} and therefore adenoma detection and removal is paramount⁴. Previous studies have shown that adenomas larger than 11 mm have a higher malignant potential^{5,6}. The incidence of CRC increases with age⁷. In recent years, many studies have indicated that there has been a change in the distribution of adenomas and CRC, with a proximal shift of the lesions⁸⁻¹⁹. This knowledge significantly affects colonic screening programs.

The current screening options for bowel cancer include fecal occult blood test (FOBT) and endoscopic assessments of the colon, including flexible sigmoidoscopy and total colonoscopy⁴. FOBT is primarily a non-specific method, while flexible sigmoidoscopy allows one to visualize only the distal parts of the colon, thus potentially leaving proximal lesions undiscovered²⁰. The combination of FOBT with flexible sigmoidoscopy will diagnose 25% of CRCs and advanced neoplasia (adenomas over 1 cm, at least 25% villous, high-grade dysplasia, or invasive cancer)²¹. Consequently, total colonoscopy is favored as a method of choice for screening²².

The aim of this study was to determine whether there are differences in the incidence and distribution of adenomas and CRC comparing the years 1990 and 2010.

Methods

We performed a retrospective observational study of colorectal adenomas and cancers diagnosed during total colonoscopy in the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia, Belgrade, Serbia, during two one-year periods of time: 1990 and 2010.

Two different databases were created during the study. The adenoma database included personal data, localization, number and size. According to size, adenomas were categorized into 0–5 mm, 6–10 mm, 11–20 mm and > 20 mm. The

cancer database included personal data, localization and indication for examination. The data was collected from procedure reports.

Only colonoscopies reaching the cecum were included. Incomplete colonoscopies for any reason, namely inadequate patient preparation, intolerance, or tortuous colon, were excluded. Patients who met the criteria for hereditary non-polyposis CRC syndrome and familial adenomatous polyposis, or those with a past medical history of CRC, ulcerative colitis and Crohn's disease, were excluded from the study.

Lesions located between the cecum and the splenic flexure, were classified as proximal, while lesions arising in the descending colon, sigmoid and rectum were classified as distal.

Certified gastroenterologists using standard endoscopic equipment performed all examinations. Colonoscopes used in 1990 were CF-20HI, and in 2010 were CF-Q180AL Olympus Optical Co., Tokyo, Japan. Additional technologies such as narrow band imaging were not used.

The bowel preparation regimen, four liters of polyethylene glycol (PEG) solution, was similar in the two periods. Sedation using intravenous midazolam or intravenous propofol was administered on a case-to-case basis and was performed by an anesthesiologist.

For continuous variables, we employed the Kolmogorov-Smirnov test to assess normality. For normal variables, means and standard deviations were reported. For non-normal data, medians and interquartile ranges were determined. χ^2 test was used to assess the differences between the two periods. Independent-sample *t*-test was used to assess differences between the means in the two periods. *P* values less than 0.05 were considered as statistically significant.

Results

During the analyzed period, 4,048 colonoscopies were performed, 1,148 were performed in 1990 (first period) and 2,900 were done in 2010 (second period). The study included 466 patients with adenomas (Table 1) and 121 patients with colorectal cancers (Table 2).

Table 1

Demographic and clinical characteristics of patients diagnosed with adenomas			
Characteristics of patients	1990	2010	<i>p</i>
Number of patients	100	366	
male, n (%)	62 (62)	206 (56.3)	0.143
female, n (%)	38 (38)	160 (43.7)	
Female-to-male ratio \geq 70 years	1	0.52	
Female-to-male ratio < 70 years	0.57	0.88	
Age (years), mean (range)	58 (34–82)	61 (19–88)	0.113
Adenomas detected by size, %			
0–5 mm	32.8	56.9	< 0.001
6–10 mm	39.5	28.8	0.063
11–20 mm	14.3	9.6	0.194
> 20 mm	13.4	4.7	0.001
Adenomas detected, %			
adenoma detection rate	14.02	14.69	
total number of adenomas	127	678	
proximal adenomas	16.5	32.7	< 0.001

Table 2

Demographic and clinical characteristics of patients diagnosed with cancers

Characteristics of patients with cancers	1990	2010	<i>p</i>
Number of patients, n	61	60	
male, n (%)	37 (60.7)	33 (55)	0.529
female, n (%)	24 (39.3)	27 (45)	
Female-to-male ratio ≥ 70 years	0.71	0.56	
Female-to-male ratio < 70 years	0.63	1.05	
Age (years), mean (range)	61 (21–84)	66 (19–83)	0.626
Indication for examination, n (%)			
positive FOBT	0 (0)	3 (5)	0.77
rectal bleeding	35 (57.4)	18 (30)	0.002
positive family history	0 (0)	5 (3)	0.021
colopathy	25 (41)	18 (30)	0.207
other	21 (34.4)	25 (41.6)	0.412
Cancers detected			
total number of cancers, n	61	60	< 0.001
proximal cancers, %	21.3	48.4	0.002

FOBT – fecal occult blood test.

In 1990, 100 patients were found to have an adenoma, in contrast to 366 in 2010. In men, adenomas were more common than in women, but without a statistically significant difference in the two observed time periods (Table 1). Median age of the patients was higher in the second than in the first period (58 compared to 61) but it was not statistically significant ($p = 0.113$). Female-to-male ratio is also shown in Table 1. The number of male and female patients by age intervals for 1990 and 2010 is shown in Figure 1.

By analyzing colonoscopy reports in 2010, an increase in adenomas was observed when compared to 1990 (Figure 2). The number of adenomas sized 0–5 mm rose from 32.8% to 56.9%, which was highly statistically significant ($p < 0.001$). A decline in the number of adenomas sized 6–10 mm (from 39.5% to 28.8%), 11–20 mm (from 14.3% to 9.6%) and > 20 mm (from 13.4% to 4.7%) was also noticed (Table 1). The frequency of proximal adenomas changed from 16.5% to 32.7%, which proved to be highly statistically significant ($p < 0.001$).

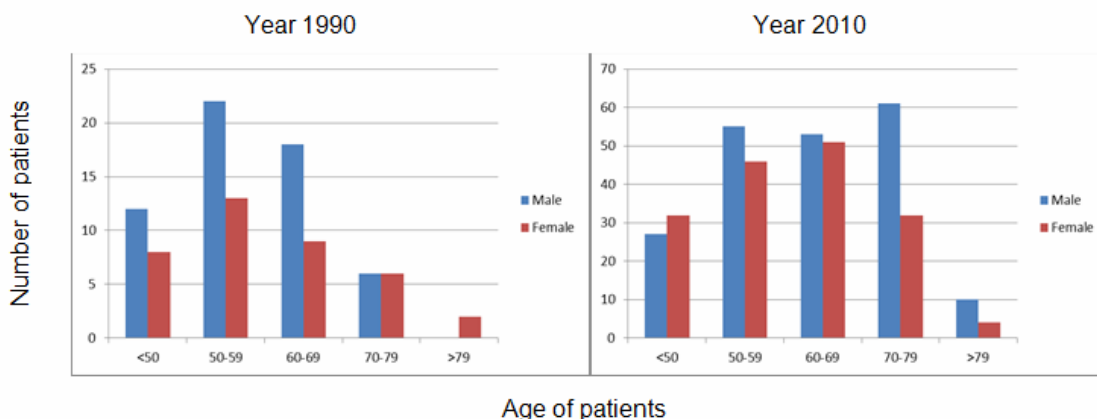


Fig. 1 – Adenomas – Number of male and female patients in age groups.

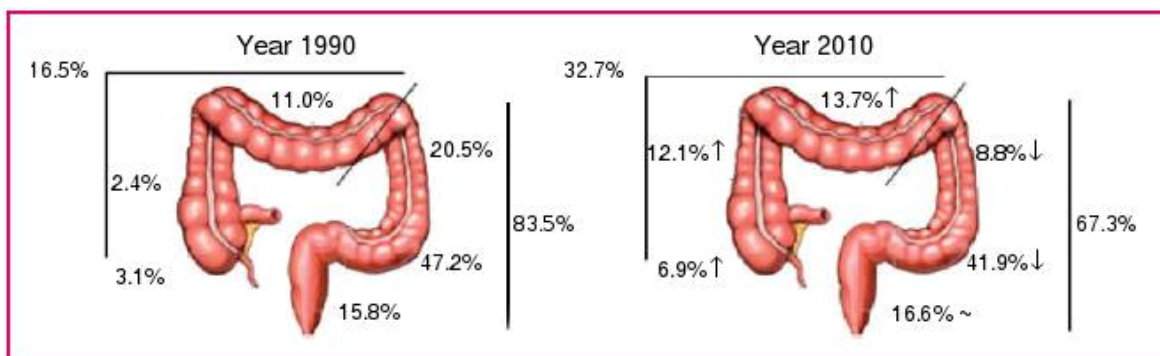


Fig. 2 – Distribution of adenomas according to colon segment.

In 1990, 61 cancers were diagnosed, and in 2010, 60 were discovered, which was statistically significant ($p < 0.001$). Males were diagnosed more often, but with no significant difference between the two time periods (Table 2). Median age of the patients was higher in the second period (61 compared to 69), which was not statistically significant ($p = 0.626$). Female-to-male ratio is shown in Table 2. The number of male and female patients by age intervals for 1990 and 2010 is shown in Figure 3. Analyzing the underlying indications for colonoscopy in 2010, colonoscopies were performed more often because of positive FOB test and family history, which is in contrast to 1990, where colonoscopies were mostly performed due to rectal bleeding (Table 2). The incidence of cancers in the proximal colon rose from 21.3% to 48.4%, which proved to be statistically significant ($p = 0.002$).

In 2010, there was a higher incidence of cancers in the proximal colon and a lower incidence of distal cancers observed, while no difference was observed in incidence of rectal cancers (Figure 4).

Discussion

Colorectal cancer is the fourth most common cause of cancer-related death¹. According to epidemiological data,

the World Health Organization Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) database, in 2012 there is a tenfold variation in the incidence of colorectal cancer worldwide, with the highest values seen in Australia and New Zealand and the lowest values observed in West Africa¹. Mortality, according to the same study, was highest in Central and Eastern Europe and lowest in West Africa¹. In recent decades screening techniques for the diagnosis and removal of adenomas (precancerous lesions) as well as for detection of colon cancer in early stages have been developed. Despite the rapid development of these screening programs, by comparing the epidemiological data from 2008 and 2012, an increase in number of new cases, as well as increased mortality rates from colorectal cancer were observed^{1, 23}. The current screening options are: analysis of stool for occult blood and endoscopic assessment of the colon, including flexible sigmoidoscopy and total colonoscopy⁴.

In this retrospective study, we looked at the incidence and anatomical distribution of adenomas and cancers in various segments of the colon during two 1-year periods (in 1990 and 2010) in our center.

We found a noticeable increase in the occurrence of proximal adenomas during 2010, when compared to 1990. Our results are consistent with studies conducted by de Oliveira et al.⁸ who analyzed the topographic distribution of

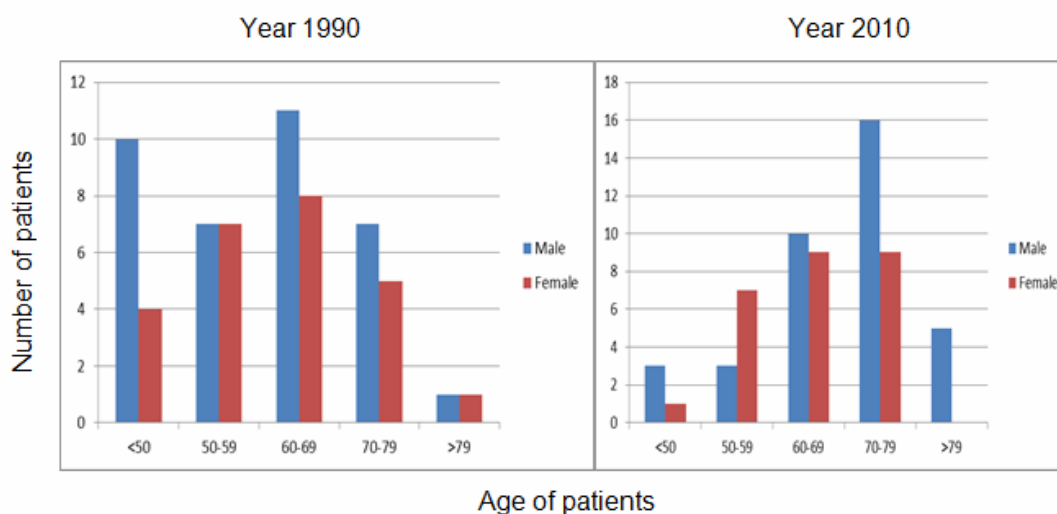


Fig. 3 – Carcinomas – Number of male and female patients in age groups.

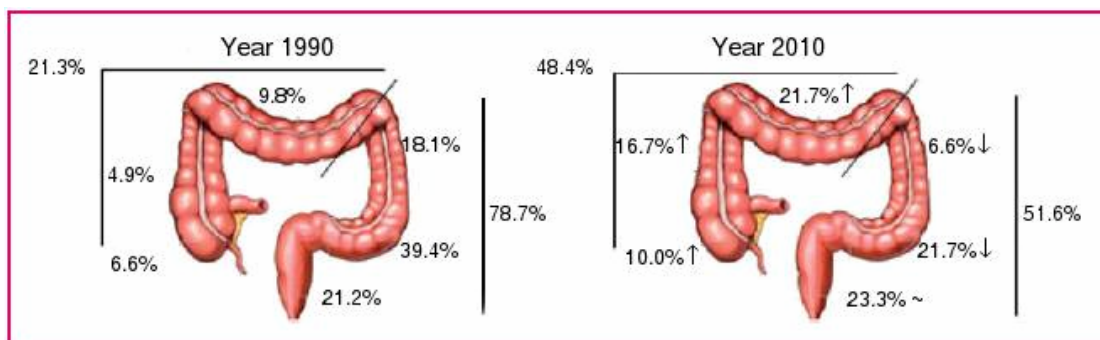


Fig. 4 – Distribution of cancers according to colon segment.

adenomas during two annual periods (2003 and 2012). Their results showed an increase in the presentation of proximal adenomas from 30.6% to 38.8%. By analyzing colonoscopies done in the fifteen-year period from 1996 to 2011, a Romanian study by Visovan et al.¹⁰ presented similar results (from 9.36% to 17.12%). Comparable results were shown by a study conducted in Italy by Fenoglio et al.¹⁵ who analyzed colonoscopies performed in the period 1997–2006 (from 19.2% to 26%). Chen et al.¹⁴ from China also found a proximal shift in adenoma location in the period of 1990–2009 in the population under the age of 50 years (from 15.01% to 20.99%). A study conducted in Italy by Parente et al.¹² showed that in the population aged 60 years and over, the presence of proximal adenomas was higher (37%) when compared to patients aged 50–59 years (29%). In Korea, Kim et al.¹⁹ demonstrated that with the increasing age there was an increase in the incidence of proximally localized adenomas.

Increasing incidence of colorectal cancers in the proximal parts of colon was also been presented in many previously published studies, and is supported in our study. A study carried out in Japan by Iida et al.⁹ analyzed patients with colorectal cancers in the period 2005–2012, and found that aging increases the number of proximal cancers and that this difference was most pronounced among women. Seydaoglu et al.¹¹ showed that in the period of 1993–2008 the incidence of proximal cancers changed (from 19.8% to 25.6%). In an Italian study conducted by Caldarella et al.¹³ the incidence of proximal cancers increased during the observed period of 1985–2005. In the Netherlands, Mensink et al.¹⁶ examined patients from 1981 and 1996 and found that the incidence of proximal cancer changed from 25% to 37%. In Japan, Takada et al.¹⁷ showed that in the period of 1974–1994 there was an increase in proximal cancer in women (up from 44.2% to 49.7%). In the USA, Cucino et al.¹⁸ observed distributions of colorectal cancer in African Americans and Caucasians in the period of 1970–2000. The results showed that there was an increased incidence of proximal cancers in both racial groups.

An explanation for this shift to proximal adenoma and colon cancer is not entirely clear. The reason for the reduction in the incidence of advanced polyps and carcinomas, as well as proximal shift of adenomas and carcinomas may be explained by an increase in the availability of the colonoscopy. Namely, the colonoscopy is more indicated, and polypectomy is more frequently carried out in the early stages of the evolution of polyps. Another reason might be the fact that the flexible rectosigmoidoscopy is accessible examination than colonoscopy, and provides examination of the distal colon. Examination of the proximal colon can be difficult due to technical difficulties or insufficient bowel preparation. Lieberman et al.²⁴ described that endoscopist more often overlooked proximal than distal lesion.

Recently published studies have shown that the physiological microflora of the colon have an impact, too. In fact, several studies have shown that there is a difference in microflora of healthy people and those with adenomas or colorectal cancers. In patients with adenomas an increased abundance of *Bacteroidetes*^{25, 26}, *Firmicutes*, *Proteobacte-*

*ria*²⁷ and *Fusobacterium*^{26, 28} was observed, while *Lactobacillus* and *Eubacterium* were associated with having a protective role²⁶. In patients with colorectal cancers, previous studies showed an increase in the number of bacteria from the genera: *Bacteroides-Prevotella*, *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, *Peptostreptococcus*, *Fusobacterium*²⁷, along with *Microbacterium* and *Anoxybacillus*²⁹. Zeller et al.³⁰ have shown that in patients with colorectal cancers there was an increase in number of *Proteobacteria* and a decrease in number of *Actinobacteria*.

It is believed that through certain receptors and activation of certain signaling pathways microflora participate in the formation of adenomas and colorectal cancers^{26, 27, 31}. The best evaluated of these is the route via toll-like receptors (TLR) that recognize microbial signal molecules-pathogen-associated molecular patterns (PAMPs). TLR activation initiates a sequence of intracellular signals leading to the formation of pro-inflammatory cytokines, the collapse of apoptosis regulation and uncontrolled cell proliferation, which together leads to cancer formation^{27, 31}.

Dietary habits also influence colorectal cancer development. Gut bacteria metabolize proteins and form nitrosamines, thereby promoting carcinogenesis, leading to the conclusion that an increased dietary intake of protein in the form of red meat presents a risk factor for the development of adenomas and cancers of the colon^{26, 32}.

Genetic studies showed that proximal cancers are most commonly associated with microsatellite instability (MSI), and that distal cancers are associated with chromosomal instability (CIN) and chromosome 5q, 17p and 18q³³.

Dejea et al.³⁴ showed that tumors in the ascending colon and hepatic flexure were biofilm-positive in 87% of cases whereas tumors located in the transverse and descending colon displayed biofilm-positivity in only 13%. Biofilms are defined as aggregations of microbial communities encased in a polymeric matrix that adhere to either biological or non-biological surfaces. The authors concluded that principal coordinates analysis revealed that biofilm communities on paired normal mucosa, distant from the tumor itself, cluster with tumor microbiomes as opposed to biofilm-negative normal mucosa bacterial communities also from the tumor host. Therefore, colon mucosal biofilm detection may predict increased risk for the development of sporadic CRC.

Comparing the female-to-male ratio in patients with adenomas and colorectal cancers in the two periods, we found that in patients older than 70 years there was a decline in the ratio as opposed to patients younger than 70 years, where there was an increase. Iida et al.⁹ showed that in age groups younger than 70 years, the female-to-male ratio is relatively low, but it increased in age groups older than 70 years. In our study, colonic adenomas and cancers were equally found in men during both periods; however, there was an increase in the distribution of women in 2010 when compared to 1990. This increase in the number of women suffering from colorectal adenoma and cancer can be explained by their change in lifestyle habits and the increasing number of women who are examined and subsequently diagnosed, given the fact that there was an initial resistance many women felt towards

colonoscopy, which was seen as potentially painful and embarrassing³⁵.

In 2010, we found that there was an increase in the number of adenomas sized 0–5 mm compared to 1990. Another study, which analyzed the size of adenomas, had different results. De Oliveira et al.⁸ showed that the number of adenomas sized ≥ 1 cm increased (from 10.8% to 19.8%) during the time under investigation. In our study, the number of adenoma size 6–10 mm, 11–20 and > 20 mm decreased. Adenoma detection rate (ADR) is an important parameter for colonoscopy. Studies have shown that with an increase in ADR, there is a drop in the risk of diagnosis of advanced stage colorectal cancer³⁶. In our study, ADR remained at the same level in both periods (14.02% in 1990 and 14.69% in 2010).

By analyzing the indications for colonoscopy, we noticed that in both periods the most common indications were rectal bleeding and colonic discomfort. The incidence of rectal bleeding is on the decline, while the incidence of fecal occult blood testing is on the rise, which means that more and more affected patients are detected in early stages. Rec-

tal bleeding is the most common late manifestation of colorectal cancer and as such, it further complicates the treatment of these patients³⁷.

Conclusion

On the basis of our results along with similar studies, we can conclude that the presence of proximal colon adenoma and cancer is increasing. This finding should be taken into account during the planning of CRC screening methods. Total colonoscopy should be employed over other methods. Future studies must focus on resolving the causal link between physiological microflora and the increased incidence of proximal colon cancer.

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