Analysis of Colon Cancer Incidence and Mortality in Croatia

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Abstract

Introduction. Colon cancer is considered one of the most significant health issues in the world where, according to the GLOBOCAN 2020 data, it is diagnosed in 1,931,590 patients annually and is the cause of death in 935,173 patients. Approximately 3,500 new cases of colon cancer are diagnosed each year in Croatia.

Aim. To present and analyze the recent trends in the incidence of colon cancer in Croatia for the period from 2001 to 2018 and trends in mortality for the period from 2001 to 2019.

Methods. The analysis of colon cancer incidence reports for the period from 2001 to 2018 gathered from the Croatian National Cancer Registry and mortality reports obtained from the database of the Croatian Bureau of Statistics and the Croatian Institute of Public Health. The trends in incidence and mortality were processed using the Joinpoint program.

Results. An incidence rate of 626.8 per 100,000, 706.4 per 100,000 for males, and 552.4 per 100,000 for females was recorded. In the year 2018, 13,809 people died from cancer in Croatia, including 8,049 men and 5,760 women. The mortality rates were 337.8 per 100,000, 407.5 per 100,000 for males, and 272.6 per 100,000 for females. In women, colon cancer ranked second in terms of incidence, while in men it was in the third place. The total number of new cases was 2,121 for men and 1,508 for women, totaling 3,629 cases. The share of colon cancer in the number of neoplasms in 2018 was 14.1%.

Conclusion. The trends in the incidence and mortality rates of colorectal cancer in Croatia still show an increasing tendency in standardized rates.

Introduction

Colon cancer is a malignant tumor which most commonly originates from the epithelial cells of the lining of the colon. It has a tendency to spread to other parts of the intestinal wall, surrounding tissues, and lymphatic vessels, and later to distant organs such as the liver or lungs (1).

The highest incidence rates are recorded in highly developed countries, which can be associated with a Western lifestyle. Several risk factors contribute to the development of colon cancer, such as a positive family history, advanced age, male sex, inflammatory bowel diseases, smoking, excessive alcohol consumption, obesity, frequent consumption of red meat and fats, and diabetes. Preventive factors for the development of colon cancer include physical activity, a diet rich in fruits and vegetables, fiber, and grains, endoscopic removal of precancerous lesions, and estrogen hormone replacement therapy in women. Additionally, a protective effect of aspirin has also been documented (2).

The majority of colorectal cancers develop from adenomas (adenoma-carcinoma sequence). In more than 90% of cases of colon cancer, it is an adenocarcinoma. Colon cancer is most commonly localized in the rectum and sigmoid colon (50%), the cecum and ascending colon (20%), the descending colon (15%), and the transverse colon (15%) (2).

The classification of colon cancer is performed using the TNM and Dukes classification systems. In the TNM classification, "T" represents the size of the tumor, "N" indicates the number of involved lymph nodes, and "M" denotes the presence of distant metastases. *In situ* carcinoma refers to cancer which has not penetrated the basal membrane and does not have the ability to metastasize. The Dukes classification includes four stages: stage A involves the involvement of the bowel wall (limited to the mucosa), stage B involves the muscular layer, stage C involves lymph node involvement, and stage D indicates distant metastases. The most important prognostic indicator is the extent of tumor spread at the time of diagnosis (3).

Various treatment modalities are possible for colorectal cancer, including surgical treatment, which involves the removal of the affected part of the colon along with neighboring lymph nodes and associated blood vessels. Other forms of treatment include chemotherapy and radiation therapy, which can be administered before, after, or concurrently with surgical treatment. There is also the possibility of biological therapy, which aims to destroy cancer cells without negatively affecting the remaining healthy cells (4).

In 2007, the National Colorectal Cancer Screening Program was launched in Croatia. The population between 50 and 74 years of age receives a fecal occult blood test every other year by mail, which, after providing a stool sample, is sent back to the address of the local Institute of Public Health. In case blood is found in the stool, and the test is positive, patients are called in for a colonoscopy to establish a final diagnosis and remove any polyps if they are found. During the first cycle of early screening, only 19.9% of the target population participated (5). European guidelines for quality assurance in cancer screening and diagnosis state that in order to implement a well-designed screening program, it is necessary to conduct it in an organized manner, use the most up-to-date data, establish accurate exclusion criteria, and ensure that the program is free of charge and applicable to the entire population. In addition to analyzing occult fecal blood, it is necessary to provide accessible instructions for the population. It is advisable to use a testing procedure which does not require dietary restrictions. According to European guidelines, during organized screening using the guaiac test, there is no need to follow a dietary regimen, but the consumption of vitamin C is not allowed (6). During the second cycle, patients do not receive the test by mail, but a call for testing. If the patient responds, they receive three test kits at their home address.

The frequency and mortality rates of colorectal cancer vary significantly across the world. Globally, it is the third most commonly diagnosed cancer in men and the second most common in women, according to the GLOBOCAN database of the World Health Organization. Incidence and mortality rates are significantly higher in men than in women.

The highest incidence rates are in Australia and New Zealand, Europe, and North America, while the lowest rates are in Africa and South Central Asia. These geographic differences appear to be attributed to variations in diet and environmental exposure, low socioeconomic status, and lower rates of cancer

screening. In the United States, the lifetime incidence of colorectal cancer in patients with an average risk level is approximately 4%. The incidence of colorectal cancer is approximately 25% higher in the male population than in the female population, and about 20% higher in African Americans than in Caucasians. The frequency is higher in patients with specific inherited conditions which predispose them to the development of cancer. A gradual shift towards right-sided colon cancer has been observed in the USA and other countries, with the most significant relative increase in incidence noted for primary cecal cancers. This change in the anatomical distribution of colorectal cancer may be partly associated with the improvements in diagnosis and treatment, as well as increased screening with the removal of adenomatous polyps in the distal colon. Colonoscopy is more effective in preventing left-sided than right-sided colorectal cancer, which could also contribute to the shift in the distribution of colon cancer. Part of the difference is likely due to quality aspects related to colonoscopy (poorer preparation on the right side, incomplete colonoscopy, anatomical configurations which compromise visibility), but biology may also vary between right and left colorectal cancer. For example, serrated adenomas, which are flatter and more challenging to visualize endoscopically, and typically carry BRAF V600E mutations and lead to microsatellite-unstable colorectal cancer, are more common in the right colon. In the USA, colorectal cancer incidence rates had been declining at approximately 2% annually, but that rate of decline slowed to about 1% per year during the period from 2013 to 2017. Incidence rates in most other Western countries remained stable or slightly increased during that period. In contrast, colorectal cancer incidence rates have rapidly increased in several historically low-risk regions, including Spain and several countries within Eastern Asia and Eastern Europe (7).

In Croatia, colon cancer ranks second in terms of incidence for both sexes. Despite advanced treatment methods, there continues to be an increase in both incidence and mortality on a global scale (7).

Age is the primary risk factor for sporadic colorectal cancer. It is rare before the age of 40, with the incidence starting to significantly increase between 40 and 50 years of age, and age-specific incidence rates continue to rise in each subsequent decade. Recent data from the Surveillance, Epidemiology, and End Results (SEER) database of the United States and other cancer registries in Western countries indicate that colorectal cancer incidence is increasing in the under-50 age group while decreasing in older age groups. In the USA, the incidence of colorectal cancer in men and women under the age of 50 has consistently increased at a rate of 2% per year from 1995 to 2016. Some registries report an increase in the incidence of colorectal cancer even among young adults up to the age of 39, although the absolute number of cases in this age group is still much lower than in adults aged 50 and older. These increases in incidence can mainly be attributed to left-sided colon cancer, particularly rectal cancer.

More than 86% of individuals under the age of 50 diagnosed with colorectal cancer are symptomatic, and the disease is diagnosed in later stages, suggesting that the increased incidence is real and not attributable to earlier detection. The reasons for this trend can be multifactorial, involving genetic influences and changes in environmental exposure and lifestyle. It is estimated that up to 35% of these cancers in young adults in the USA are linked to known hereditary syndromes, and the reasons for these increases remain unknown. Interestingly, these trends have also been observed in developing countries, which are traditionally considered to have lower rates of colorectal cancer compared to Western countries. The literature suggests that the ratios of early and late-onset cases in several low-resource countries are significantly higher than the international average in general, and particularly in Western countries. A meta-analysis of 20 studies concluded that significant risk factors for early-onset colorectal cancer (EOCRC) include a family history of colorectal cancer in first-degree relatives (relative risk [RR] 4.21, 95% CI 2.61-6.79), hyperlipidemia (RR 1.62, 95% CI 1.22-2.13), obesity (RR 1.54, 95% CI 1.01-2.35), and alcohol consumption (RR 1.71, 95% CI 1.62-1.80). Several other potential risk factors (e.g., hypertension, metabolic syndrome, ulcerative colitis, chronic kidney disease, unhealthy dietary patterns, insufficient vitamin D intake, sedentary behavior, and occupational exposure to organic dust) have been examined in only one or two studies. A pooled analysis of 13 population studies concluded that EOCRC is associated with irregular use of non-steroidal anti-inflammatory drugs, higher red meat consumption, lower education, alcohol abstinence, and increased alcohol use (7).

Colorectal cancer mortality rates have been progressively declining since the mid-1980s in the United

States and many other Western countries. This improvement in outcomes can be attributed, at least in part, to the detection and removal of colon polyps, the early detection of colorectal cancer, and more effective primary and adjuvant treatments. However, at least in the USA, the decline in colorectal cancer mortality began long before widespread screening and before effective adjuvant therapy became widely used. Nevertheless, especially in the USA, the overall decline in mortality masks trends in young adults. In data derived from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, colorectal cancer mortality rates per 100,000 individuals under the age of 50 decreased by approximately 2% annually from 2000 to 2004, and then increased by 1% annually until 2018. The increase applied to Caucasians and Latino Americans, unlike African Americans and Asian/Pacific Islanders, whose mortality rates either remained stable or decreased during the same time period. Similar trends have been reported by the American Cancer Society and the National Center for Health Statistics. Globally, the USA has one of the highest survival rates for colorectal cancer. Data collected by the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute show that nearly 65% of all patients treated for colorectal cancer (all stages and locations combined) between 2011 and 2017 survive for five years. Unlike these data, mortality rates continue to rise in many countries with limited resources and healthcare infrastructure, especially in Central and South America and Eastern Europe, as evidenced by the data from the WHO GLOBOCAN international database (7).

Since colon cancers develop slowly, in the early stages, there are often no noticeable symptoms or they are attributed to other, less serious conditions. Signs which may indicate colon cancer include anemia, low hemoglobin levels, fatigue, the presence of blood in the stool, changes related to stool consistency (diarrhea, constipation, or a feeling of incomplete bowel emptying), bloating and gas, nausea, abdominal pain, and weight loss (8). Today, numerous diagnostic methods are used for the purpose of detecting cancer. The test for detecting occult (hidden) blood in the stool is one of the cheapest and simplest methods for detecting colon cancer. Due to its simplicity and cost-effectiveness, it is used as a method for timely colorectal cancer detection. Digital rectal examination is a procedure in which a physician, usually a general practitioner, manually examines the end of the colon using a finger, especially when there is suspicion of colon cancer. That examination can help detect cancers located at the end of the colon. Colonoscopy is the most reliable method for detecting colorectal cancer because it provides the best view of changes in the colon, allows for the removal of pathological changes and the collection of samples for histological analysis. Irigography is a radiological method for detecting pathological changes in the colon (9).

When a diagnosis of colon cancer is made, it is necessary to assess the extent of the disease and decide on the method of treatment. The treatment of colorectal cancer often requires surgery to remove the portion of the colon affected by the tumor, along with the associated blood vessels and lymph nodes. In some patients, in addition to surgery, chemotherapy may be necessary. Chemotherapy involves the use of specific drugs to destroy cancer cells and prevent their further growth and proliferation. Radiotherapy is a treatment method that involves the use of ionizing radiation. High doses of radiation are used to destroy genetic material, and thus cancer cells. Targeted biological therapy is a very modern method of treating colon cancer today. This form of treatment involves the use of specific antibodies which selectively destroy cancer cells without negatively affecting the body (10).

Colon cancer prevention

The aim of primary and secondary prevention measures is to reduce the number of individuals suffering from colorectal cancer, decrease mortality, and improve the quality of life for the affected individuals. Primary prevention refers to reducing the risk of developing colorectal cancer. To prevent or at least reduce the risk of developing cancer, it is recommended to consume a diet rich in fiber, such as starch, fruits, and vegetables. Fiber does not excrete bile acids, but promotes faster bowel movement, reducing the contact time of potential carcinogenic substances with the intestinal mucosa, thereby lowering the chances of their absorption. In addition to a proper diet, it is necessary to engage in physical activity, regulate bowel movements, avoid alcohol and cigarettes, and lead a healthier lifestyle. The aim of secondary prevention is the early detection of any changes in the lining of the colon, which includes a systematic program for the timely detection of cancer while the disease is still in its early stages and more easily treatable.

The National Colorectal Cancer Screening Program was adopted during the session of the Government of the Republic of Croatia on 4 October 2007, following the Recommendation of the Council of Europe (2003) and the European guidelines for quality assurance in colorectal cancer screening and diagnosis. The program aims to detect cancer in its early stages, improve the chances of curing patients, enhance the quality of life and survival, and reduce mortality.

The target group consists of men and women aged 50 to 74 years (approximately 1,300,000 individuals). The screening test is conducted using a fecal occult blood test (FOBT) card to detect hidden blood in the stool. All individuals who receive a positive stool blood test result within the screening program are scheduled for a colonoscopy, which includes the removal of polyps and a histopathological diagnosis (11).

Aim

The aim of the research was to present and analyze the trends in colon cancer incidence in Croatia from 2001 to 2018, as well as the mortality rates from 2001 to 2019.

Methods

The research includes an analysis of the incidence data for colon cancer during the period from 2001 to 2018, obtained from the Croatian National Cancer Registry, as well as the mortality data from 2001 to 2019, obtained from the Croatian Bureau of Statistics and the Croatian Institute of Public Health us-ing the most recent data available. Age-standardized incidence and mortality rates were calculated using the direct standardization method, utilizing Croatia's population census from the year 2011. The trends in incidence and mortality were analyzed using the Join-point program, version 4.4.0.0, from January 2017.

The population data used in the research was obtained from the 2011 population census conducted by the Croatian Bureau of Statistics.

Results

Incidence

During the period from 2001 to 2018, there were 57,552 cases of colon cancer recorded in Croatia. The percentage of men was 57.68% (33,196), while women made up 42.31% (24,356). The highest incidence rate is observed in older age, particularly in the range between 80 and 84 years. The average age of those affected in 2018 was 69.6 years. The data shows that incidence and mortality are higher in men compared to women.

Figure 2. depicts the incidence of colon cancer in men and women in the age group of 50 to 74 years in Croatia from 2001 to 2018. It shows an increase of 1.0% per year in men, 1.0% per year in women, and a total annual increase of 1.1%.

Figure 3. illustrates the trend in the incidence of colon cancer in men and women from 2001 to 2018. It is evident that the incidence of colon cancer has been on the rise on average for both sexes.

The overall age-standardized colon cancer incidence rate for both sexes (standardized to the 2011 population census) in the mentioned period is statistically significantly increasing for both sexes (1.1% per year in men, 1.0% per year in women), with an overall annual increase of 1.2% when considering both sexes together.

0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0.0	0.0	0.5	0.0	0.4	2.1	4.5	9.5	17.5	34.4	60.6	91.1	174.2	248.5	255.8	340.4	359.7	359.5

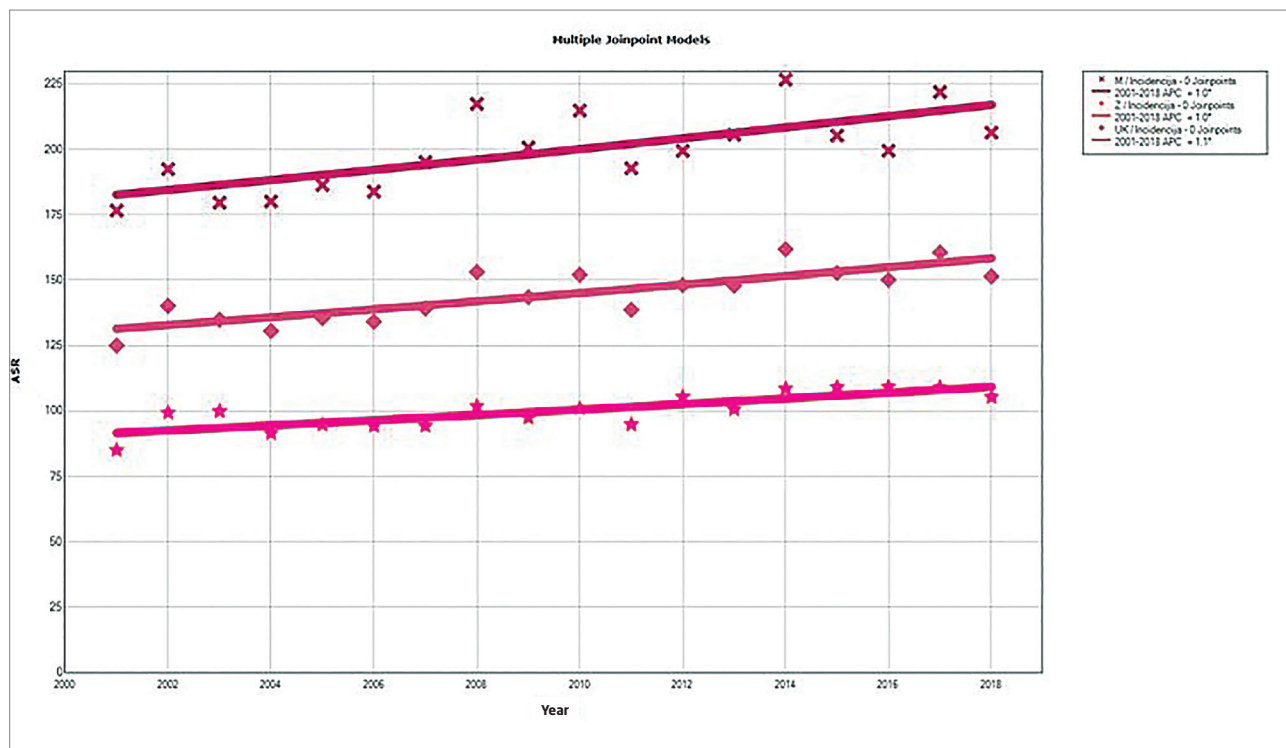Figure 1. **Age-specific incidence rate (data for the year 2018), (13)**

Figure 2. **Joint point analysis of colon cancer incidence in men and women in the age group of 50 to 74 years in Croatia in the period from 2001 to 2018.**
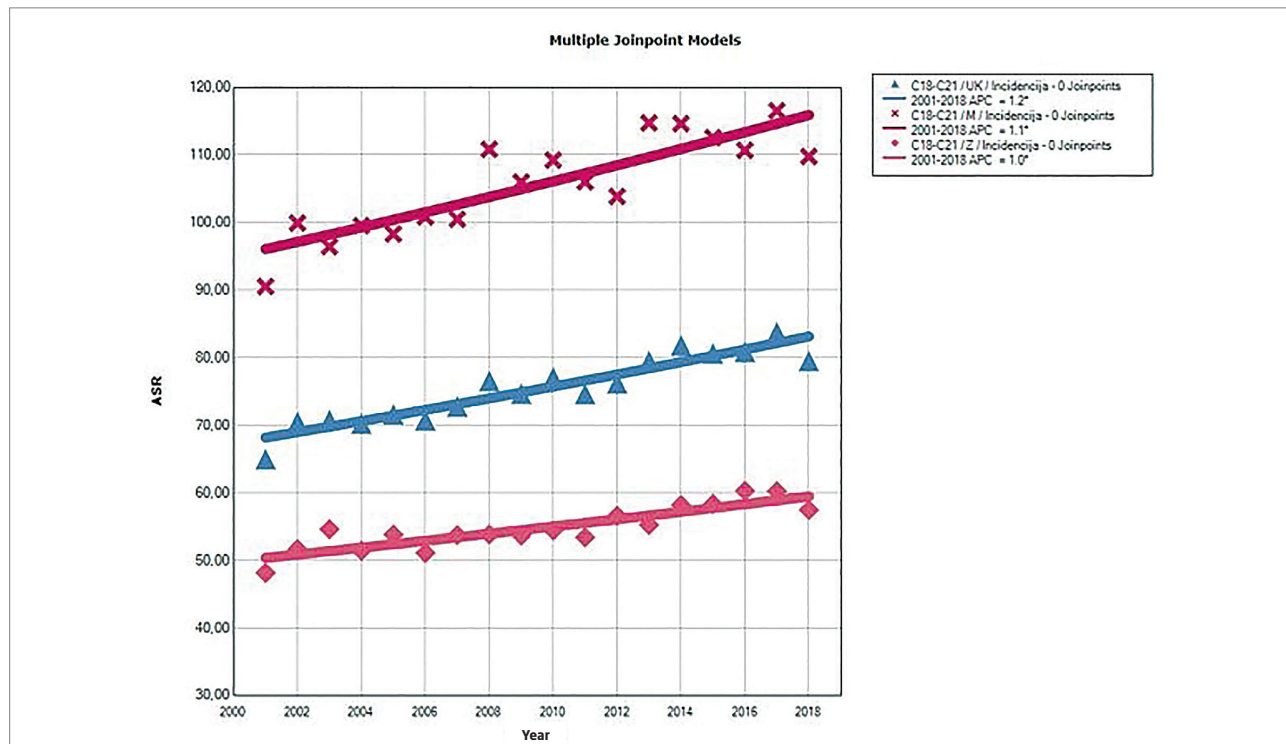

Figure 3. **Joint point analysis of colon cancer incidence in men and women in Croatia in the period from 2001 to 2018.**

Mortality

From 2001 to 2019, there were 35,830 deaths due to colon cancer in Croatia. The percentage of men was 57.82% (20,718), while women accounted for 42.18% (15,112). The highest mortality rate is observed in the elderly population, between 75 and 79 years of age, both in men and women.

Figure 4. shows that the overall age-standardized mortality rate (standardized to the 2011 population census) for colon cancer significantly increased in men by 0.7% per year throughout the mentioned period. For women, there was an annual increase of 1.0% until 2012, and from 2012 to 2019, there was a non-statistically significant decrease of -0.8% per year. We conclude that the mortality trend is stable because a decrease is not yet evident.

Figure 5. displays the analysis of colon cancer mortality in men and women in the age group of 50 to 74 years in Croatia from 2001 to 2019. In men, an increase of 0.2% per year was observed, while in women, it was 0.3% per year, and we conclude that neither trend is statistically significant.

When considering both genders together, we observe a statistically significant increase from 2001 to 2015 (1.5% per year). However, from 2015 to 2019, there is a non-statistically significant decrease of -0.3% per year. It is interpreted as a stable mortality trend because a decrease is not yet evident.

Discussion

Wong and colleagues published an epidemiological study for the periods from 2007 to 2016, from 2006 to 2015, or from 2005 to 2014, depending on data availability, on the incidence and mortality of colon cancer in 36 countries (13).

The incidence of colon cancer increased in 10 out of the 36 analyzed countries (all in Asia or Europe), with the highest increase observed in India, followed by Poland. All of these 10 countries showed moderate to high scores on the Human Development Index (HDI). Six countries showed a decrease in the incidence of colon cancer. Those countries had the high-est HDI scores, with the United States experiencing the largest decrease, followed by Israel. Seven countries (including all North American countries) showed a decrease in incidence among individuals aged 50 and older. Eight countries showed an increase in the incidence of colon cancer among individuals under 50 years of age, including the United Kingdom and India. Germany, Australia, the United States, Sweden, Canada, and the United Kingdom showed a decrease or stable incidence among individuals aged 50 and older, but a significant increase among individuals under 50 years of age. Only Italy showed a decrease in the incidence of colorectal cancer among individuals under 50 years of age. Among women, 12 out of 36 countries (all from Asia and Europe) showed an increase in the incidence of colon cancer, while 7 countries showed a decrease. India showed the highest increase in colon cancer incidence among women, followed by Slovenia. Out of the 36 countries, 5 showed an increase in rectal cancer incidence, and 8 showed a decrease. Ecuador and Thailand experienced the most significant increase in rectal cancer incidence. The frequency of rectal cancer among individuals under 50 years of age significantly increased in Finland, Australia, Canada, the United States, and the Netherlands. Four countries showed an increase in the incidence of rectal cancer among women, with Ecuador experiencing the highest increase, followed by Thailand. The frequency of rectal cancer in women decreased in 8 countries. Among women under 50 years of age, the incidence of rectal cancer increased despite a decrease in women aged 50 and older in Costa Rica, Slovenia, Japan, Slovakia, Canada, and the United States. A total of 24 countries reported a decrease in mortality, including North America, Oceania, and most European countries. Furthermore, some countries in Asia, Latin America, and Southern Europe showed a significant increase in colorectal cancer mortality (14).

Conclusion

Colorectal cancer is a malignant neoplasm which annually affects more than 1,900,000 people worldwide, making it the third most common cancer among men and the second most common among women. In developing countries, the incidence and mortality rates of colorectal cancer are increasing, which
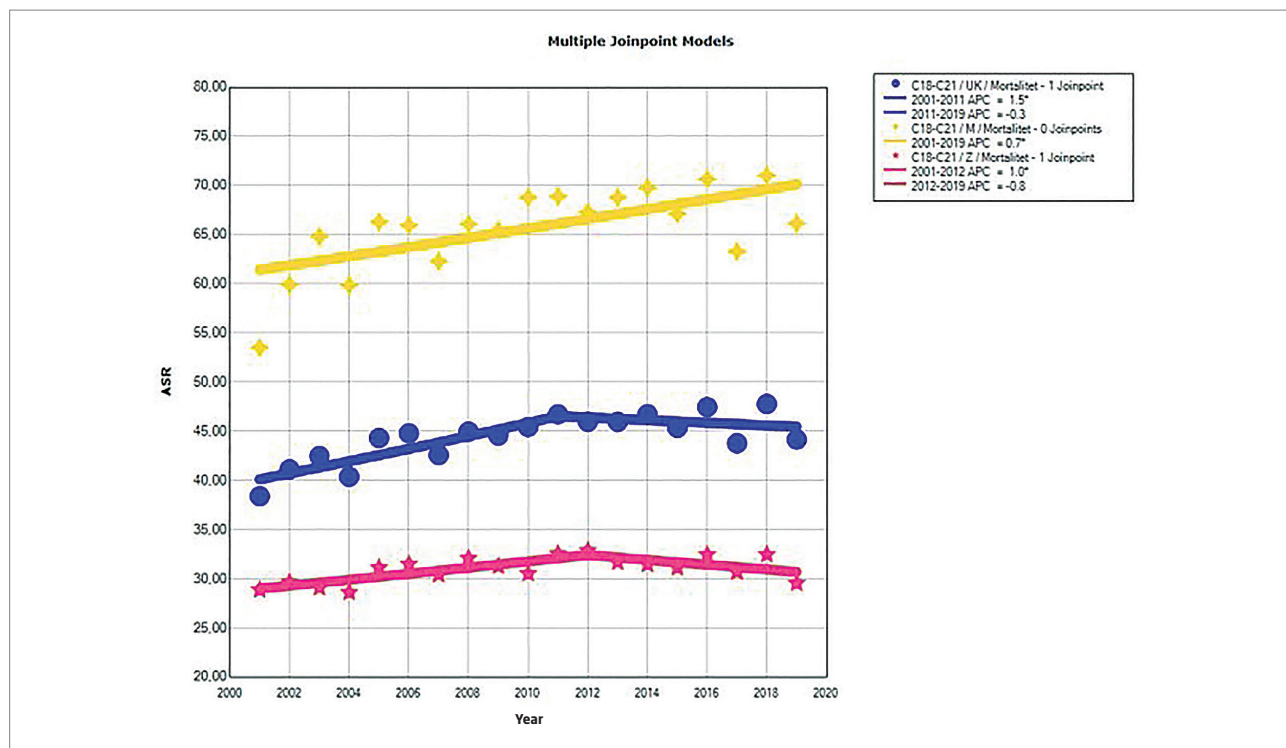
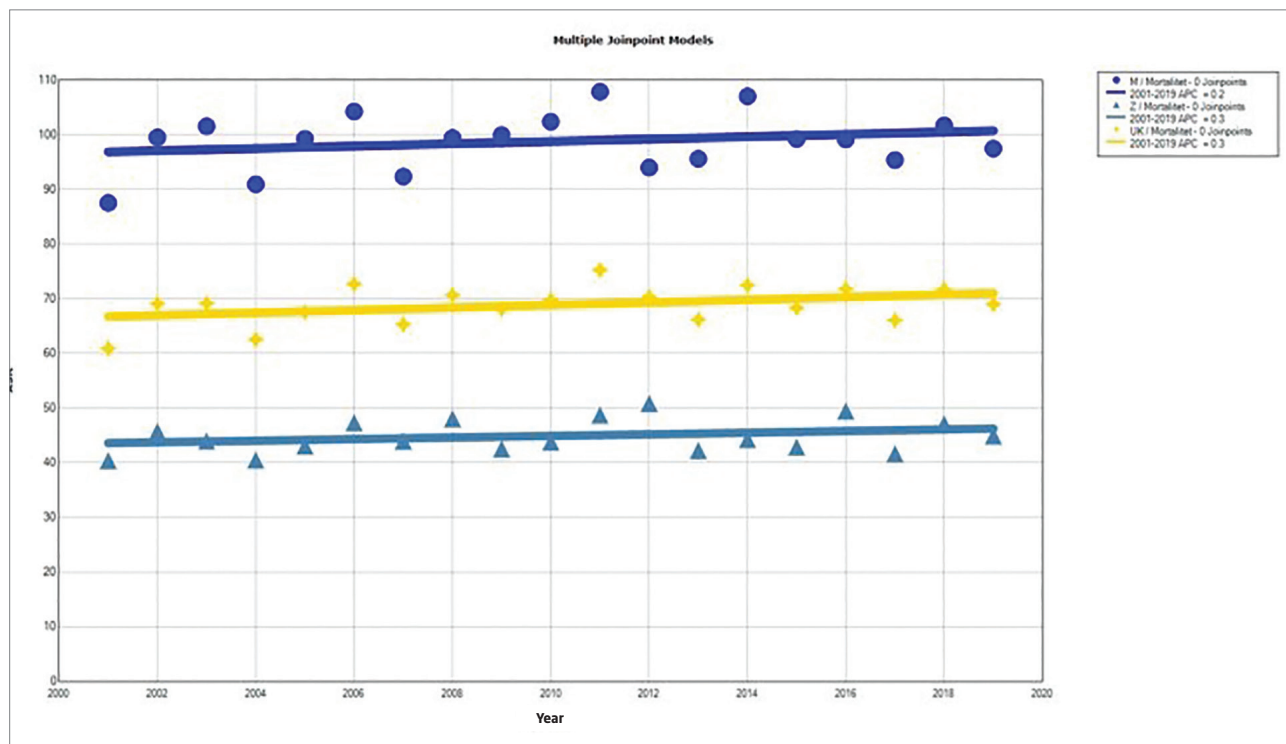Figure 4. **Joint point analysis of colon cancer mortality in men and women in Croatia from 2001 to 2019.**

Figure 5. **Joint point analysis of colon cancer mortality in men and women in the age group of 50 to 74 years in Croatia from 2001 to 2019.**

subsequently leads to a gradual reduction in the disparity compared to industrialized Western countries. In Croatia, colon cancer is the second most common cause of death from malignant diseases in both men and women. In women, it ranks second in terms of incidence, while in men, it ranks third. The trends in the incidence and mortality rates of colorectal cancer in Croatia still show an increasing tendency in standardized rates. According to epidemiological data, it is clear that the prevention of colorectal cancer is one of the main public health activities in Croatia. The increased incidence and mortality of colorectal cancer highlight the crucial role of a multidisciplinary approach, ensuring the availability of new treatment models, and emphasizing secondary prevention (population-based screening) and primary prevention (changing dietary habits and levels of physical activity). Education of the general population about the importance of colorectal cancer is necessary.

It is important to focus on the prevention and early detection of the disease, which can be achieved through the National Colorectal Cancer Screening Program.

During the period from 2001 to 2018, there were 57,552 cases of colon cancer recorded in Croatia. The percentage of men was 57.68%, while women made up 42.31%. The highest incidence is observed in older age groups, with the peak incidence occurring between 80 and 84 years of age.

In 2019, 1,258 men and 837 women in Croatia died from colorectal cancer (including the anus).

According to the World Health Organization's estimation, by the year 2030, approximately 2.5 million people worldwide will be diagnosed with colorectal cancer, and around 1.2 million will die from it.

With the help of the obtained results, we believe that the importance of addressing the concern related to colon cancer will be further highlighted, encouraging all healthcare system stakeholders to systematically implement measures for primary, secondary, and tertiary prevention.

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PRIKAZ INCIDENCIJE I MORTALITETA RAKA DEBELOG CRIJEVA U REPUBLICI HRVATSKOJ

Sažetak

Uvod. Karcinom debelog crijeva smatra se jednim od najvećih zdravstvenih problema u svijetu, gdje, prema podacima Globocana 2020, godišnje bude dijagnosticiran kod 1 931 590 bolesnika te je uzrok smrti kod 935 173 bolesnika. U Republici Hrvatskoj godišnje se dijagnosticira oko 3500 novih slučajeva karcinoma debelog crijeva.

Cilj. Prikazati i analizirati zadnje trendove incidencije karcinoma debelog crijeva u RH za razdoblje od 2001. do 2018. i trendove mortaliteta za razdoblje od 2001. do 2019.

Metode. Analiza izvještaja o incidenciji karcinoma debelog crijeva za razdoblje od 2001. do 2018. objedinjena je iz Registra za rak RH, dok su izvještaji o mortalitetu preuzeti iz baze podataka Državnog zavoda za statistiku i Hrvatskog zavoda za javno zdravstvo. Trendovi incidencije i mortaliteta obrađeni su uz pomoć programa Joinpoint.

Rezultati. Zabilježena je stopa incidencije 626,8 / 100 000, 706,4 / 100 000 za muškarce i 552,4 / 100 000 za žene. U RH je 2018. od karcinoma umrlo 13 809 osoba, od čega 8049 muškaraca i 5760 žena. Stope mortaliteta iznosile su 337,8 / 100 000, odnosno 407,5 / 100 000 (M) i 272,6 / 100 000 (Ž). Kod žena se karcinom debelog crijeva po incidenciji nalazio na drugom mjestu, dok se kod muškaraca nalazio na trećem mjestu. Ukupan broj novooboljelih iznosio je 2121 za muškarce te 1508 za žene, sveukupno 3629 slučajeva. Udio karcinoma debelog crijeva u broju novotvorina 2018. iznosio je 14,1 %.

Zaključak. Trendovi pojavnosti karcinoma debelog i završnog crijeva u RH još uvijek imaju tendenciju porasta u standardiziranim stopama incidencije i mortaliteta.