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TRENDS IN MORTALITY RATES OF COLORECTAL CANCER IN CENTRAL SERBIA DURING THE PERIOD 1999–2014: A JOINPOINT REGRESSION ANALYSIS

UMIRANJE USLED KOLOREKTALNOG RAKA U CENTRALNOJ SRBIJI U PERIODU 1999–2014: "JOINPOINT" REGRESIONA ANALIZA

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SUMMARY

Introduction/Aim: Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide and one of the major causes of cancer-related mortality. The aim of this study was to analyze the trends in mortality rates of colorectal cancer in central Serbia in the period 1999-2014.

Methods: Mortality data for colorectal cancer, for the period 1999 - 2014, were taken from the of the Institute of Public Health of Serbia "Dr Milan Jovanović – Batut". Joinpoint regression analysis was used to estimate annual percent changes (APCs) in mortality and to identify critical stages in time where significant changes in trend occurred.

Results: In central Serbia, in the period between 1999 and 2014, colorectal cancer was the second most common cause of mortality in both men and women. The average standardized mortality rate was 18.2 in men (per 100,000) and 10.5 in women (per 100,000). Rates were 1.7 times higher in men, with a remarkable annual increase of colorectal cancer mortality rate of 1.3% in the period 1999-2014, while in women the mortality rates were steady. In men, a significant increase in mortality rates was present in colon (APC 1.8%) as well as in rectosigmoidal junction cancer (APC 3.3%). Rise of 1.7% was present in colon carcinoma in men 35-74 years of age as well as an increase both in men and women 75 years of age and older in the period 1999-2014.

Conclusion: Findings of present study revealed increasing mortality rates of colorectal cancer in Serbia. The implementation of nationally organized screening programmes is of paramount importance and should be conducted with higher efficacy in Serbia. Primary prevention measures should mainly focus on maintaining

SAŽETAK

Uvod/Cilj: U svetu, rak kolorektuma je treći vodeći uzrok umiranja kod muškaraca i drugi kod žena, i predstavlja jedan od vodećih uzroka umiranja među svim malignim tumorima. Cilj ovog rada je da se analizira trend mortaliteta usled raka kolorektuma u centralnoj Srbiji u periodu 1999-2014. godine.

Metode: Od Instituta za javno zdravlje Srbije „Dr Milan Jovanović – Batut” preuzeti su podaci o mortalitetu za rak kolorektuma za period 1999-2014. godine. U cilju određivanja godišnje procentualne promene (APCs) umiranja i za identifikovanje kritičnih perioda kada su se dogodile značajne promene umiranja korišćena je joinpoint regresiona analiza.

Rezultati: U centralnoj Srbiji, u periodu između 1999. i 2014. godine, rak kolorektuma je bio drugi vodeći uzrok umiranja, među svim malignim tumorima, kako za muškarce tako i za žene. Prosečna standardizovana stopa mortaliteta je bila 18,2 na 100.000 za muškarce i 10,5 na 100.000 za žene. Stope su bile 1,7 puta više kod muškaraca nego žena. U periodu 1999-2014, dolazi do značajnog porasta stope mortaliteta od raka kolorektuma od 1,3% godišnje kod muškaraca, dok je kod žena trend umiranja bio stabilan. Kod muškaraca je uočen značajan porast stope mortaliteta za rak kolona (APC – 1,8%) i rak rektosigmoidalnog prelaza (APC – 3,3%). Takođe, značajan porast umiranja beleži se kod muškaraca u uzrasta 35-74 godina, kao i kod muškaraca i žena uzrasta 75 i više godina.

Zaključak: Rezultati ovog istraživanja ukazuju na porast mortaliteta usled kolorektalnog raka u Srbiji. Rad na boljoj primeni nacionalnog organizovanog skrininga mora biti od najvećeg značaja u Srbiji. Mere primarne prevencije treba uglavnom usredsrediti na održavanje

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healthy body weight and a balanced diet as well as smoking and alcohol cessation.

Keywords: *colorectal cancer, colon cancer, rectal cancer, mortality, trend, joinpoint regression*

optimalne telesne težine i uravnoteženu ishranu, kao i na prestanak pušenja i konzumiranja alkohola.

Ključne reči: *rak kolorektuma, rak kolona, rak rektuma, mortalitet, trend, jointpoint regresiona analiza*

Introduction

Colorectal cancer is one of the major causes of cancer-related mortality. It is the most common malignant disease of the gastrointestinal tract, the third most common cancer in men and the second most common cancer in women (1). Highest mortality rates for colorectal cancer both in men and women are determined in Central and Eastern Europe and the lowest in Middle Africa (1). Data shows a decline of colorectal cancer mortality rates in high income/high-risk countries such as the United States and European countries, as well as countries of the Western Pacific region (2,3). This marked decrease in mortality rates is a result of colorectal prevention, earlier diagnosis using screening, decreased prevalence of risk factors and improved treatment (1,3,4). However, mortality rates are still on the rise in low-income countries of South America such as Mexico, Brazil, Chile and Eastern Europe such as Romania and Russia (2,3,5,6).

Mortality differs significantly by sex and race (7). Rates are 30% to 40% greater in men than in women altogether, though this disproportion varies by age (8). Smoking, high consumption of alcohol, diabetes, obesity, physical inactivity, high intake of red and processed meat and lack of dietary fiber intake all represent risk factors for colorectal cancer (3,9). Colorectal cancer is mostly curable if detected at an early stage, therefore, screening and early detection are excellent measures for the secondary prevention, in contrast with most of the other cancers (10).

The aim of this study was to analyze the trends in mortality rates of colorectal cancer in central Serbia in the period 1999-2014. For the assessment of the efficacy of screening implementation in Serbia and access to effective treatment, it is essential to know the data regarding the colorectal cancer mortality trends. Also changes in mortality over time could be due to demographic characteristics, lifestyle, disease awareness and some other factors. This is the first study in which we wanted to assess whether mortality of colon, rectosigmoid junction and rectal cancers shared the same trends in order to suggest better preventive measures.

Methods

Mortality data for colorectal cancer (colon cancer code – C18, rectosigmoid junction cancer code – C19 and rectum cancer code – C20, according to the X International Classification of Diseases), and other leading malignant tumors (lung and bronchus cancer – C34, breast cancer – C50, prostate cancer – C61, stomach cancer – C16, pancreas cancer – C25, cervical cancer – C53 and all cancers except non-melanoma skin cancer – C44) as well as the population data, regarding sex and age for the period between 1999-2014, were collected from the Public Health Institute of Serbia “Dr Milan Jovanović Batut”. Crude, age-specific and standardized mortality rates of colorectal cancer were calculated, as well as those of colon, rectosigmoid junction, and rectum cancer. Standardized rates of mortality were calculated with the direct standardization method, by using the world population for standard population (11).

The trends in age-specific and standardized mortality rates were calculated by using joinpoint regression analysis (Joinpoint Regression Program, Version 4.5.0.1. June, 2017; Statistical Research and Applications Branch, National Cancer Institute), according to the method of Kim et al (12). The annual percent change (APC) was determined by joinpoint regression analysis, as well as points in which comes to significant changes in trends. The maximum number of joinpoints was adjusted to two. Grid Search method was used. The minimum number of data from the beginning of the series was adjusted to three, whereas the smallest number of data between two joinpoints was 4. Permutation test was used for the selection of the best model of joinpoints with the general level of significance from 0.05 and 4499 accidentally arranged sets. Moreover, 95% confidence intervals were measured for each APC estimate in order to determine whether APC for each segment is different from 0.

Results

In Central Serbia, during the period 1999-2014, 128,197 men and 97,277 women died because of cancer. The average number of cancer deaths was 8,013 per year in male

population and 6,080 per year in female population. The average number of cancer deaths of colorectal cancer was 952 (11.9% of all

men with cancer) in males and 675 in females (11.1% of all women with cancer) (Table 1).

Table 1. Average number of deaths due to the most common cancers and their percentage among all new cases of cancers in Central Serbia by sex, 1999-2014

The most common cancers	Males		The most common cancers	Females	
	Average number of deaths	% of new cases among all cases		Average number of deaths	% of new cases among all cases
Most common cancers (ICD 10)			Most common cancers (ICD 10)		
Lung and Bronchus cancer (C34)	2395	29.9	Breast cancer (C50)	1103	18.1
Colorectal cancer (C18-C20)	952	11.9	Lung and Bronchus cancer (C34)	775	12.7
Prostate cancer (C61)	634	7.9	Colorectal cancer (C18-C20)	675	11.1
Stomach cancer (C16)	530	6.6	Cervical cancer (C53)	353	5.8
Pancreas (C25)	387	4.8	Stomach cancer (C16)	301	5.0
Others	3117	38.9	Others	2874	47.3
All cancers except non-melanoma skin cancer (C44)	8013	100.0	All cancers except non-melanoma skin cancer (C44)	6080	100.0

ICD 10 – International Classification of Diseases-10 codes

During the observed period, colorectal cancer was the second leading cause of mortality in male (behind lung and bronchus cancer) and third in female (behind breast cancer and lung and bronchus cancer) populations.

In male population between 1999-2014, the average annual number of deaths was 473 for colon cancer (the average crude

rate – 18.0/100,000, and the standardized rate – 9.0/100,000), 43 for rectosigmoid junction cancer (the average crude rate – 1.6/100,000, and standardized rate – 0.8/100,000) and 437 for rectal cancer (the average crude rate – 16.7/100,000, and standardized rate – 8.4/100,000) (Table 2).

Table 2. Number of cancer deaths, crude and standardized (World population) mortality rates (per 100,000) of colon, rectosigmoid junction, rectal and colorectal cancer, males, Central Serbia, 1999-2014

Cancer	Rectosigmoid											
	Colon			junction			Rectal			Colorectal cancer		
Years	No	CR	SR	No	CR	SR	No	CR	SR	No	CR	SR
1999	348	13	7.3	37	1.4	0.8	366	13.6	7.6	751	28	15.8
2000	400	15	8.5	44	1.6	0.9	390	14.6	8	834	31.1	17.4
2001	371	13.9	7.7	33	1.2	0.7	376	14.1	7.6	780	29.3	15.9
2002	429	16.1	8.5	29	1.1	0.6	421	15.8	8.2	879	33	17.2
2003	405	15.3	8.2	32	1.2	0.7	418	15.8	8.4	855	32.2	17.2
2004	443	16.7	8.7	36	1.4	0.7	408	15.4	8.1	887	33.5	17.5
2005	458	17.3	9	32	1.2	0.7	467	17.7	9.1	957	36.2	18.7
2006	466	17.7	9.2	41	1.6	0.8	418	15.9	8	925	35.2	18
2007	494	18.1	9.1	20	0.8	0.4	436	16.6	8.4	950	36.2	17.9
2008	533	20.4	10.1	34	1.3	0.6	428	16.4	8.3	995	38.1	19
2009	517	19.9	9.4	39	1.5	0.8	498	19.1	9.5	1054	40.5	19.8
2010	517	19.9	9.7	43	1.7	0.8	506	19.5	9.5	1066	41.1	20.1
2011	494	19.1	9.3	63	2.4	1.1	437	16.9	8.2	994	38.5	18.6
2012	569	22.1	10.1	67	2.6	1.2	498	19.4	8.9	1134	44.1	20.1
2013	564	22.1	9.8	62	2.4	1.1	505	19.7	9	1131	44.2	19.9
2014	551	21.6	9.8	69	2.7	1.2	408	16	7.3	1028	40.4	18.3
Average	473	18.0	9.0	43	1.6	0.8	437	16.7	8.4	952	36.4	18.2

No – Number of new cases, CR – Crude mortality rate, SR – Standardized mortality rate

In female population in the same period of time, annually the average number of deaths was 360 for colon cancer (the average crude rate – 13.1/100,000, and the standardized rate 5.6/100,000), 32 for rectosigmoid junction cancer (the average crude rate – 1.2/100,000, and the standardized rate – 0.5/100,000) and 283 for rectal cancer (the average crude rate – 10.3/100,000, and the standardized rate – 4.4/100,000) (Table 3).

In Central Serbia, in the period between 1999-2014, there were 952 deaths of colorectal cancer annually in male population and 675 deaths of colorectal cancer annually in female population. The average standardized mortality rate (per 100,000) for colorectal cancer (C18-C20) was 18.2 for males and was 1.7 times higher for males than for females (10.5) (Tables 2 and 3).

Table 3. Number of cancer deaths, crude and standardized (World population) mortality rates (per 100,000) of colon, rectosigmoid junction, rectal and colorectal cancer, females, Central Serbia, 1999-2014

Cancer	Colon			Rectosigmoid junction			Rectal			Colorectal		
Years	No	CR	SR	No	CR	SR	No	CR	SR	No	CR	SR
1999	285	10.6	6.1	32	1.2	0.7	244	9.1	5.2	561	19.9	9.7
2000	286	10.2	4.6	24	0.9	0.3	278	9.9	4.7	588	20.8	9.6
2001	270	9.6	4.5	23	0.8	0.4	273	9.7	4.4	566	20.2	9.2
2002	313	11.2	4.8	23	0.8	0.4	266	9.5	4.1	602	21.5	9.2
2003	326	11.7	5.2	27	1	0.4	301	10.8	4.8	654	24.7	12.9
2004	364	13	5.7	19	0.7	0.3	264	9.5	4.2	647	23.2	10.2
2005	442	15.9	6.8	30	1.1	0.4	287	10.3	4.4	759	27.2	12.6
2006	373	13.4	5.8	47	1.7	0.6	292	10.5	4.5	712	25.6	11
2007	363	13.1	5.6	20	0.7	0.2	284	10.3	4	667	24.1	9.8
2008	426	15.4	6.5	32	1.2	0.5	295	10.7	4.4	753	27.3	11.4
2009	400	14.5	5.9	26	0.9	0.5	317	11.5	4.6	743	27	11
2010	391	14.3	5.8	27	1	0.4	293	10.7	4.3	711	25.9	10.5
2011	415	15.2	6.4	46	1.7	0.7	257	9.4	4	718	26.3	11.1
2012	379	14	5.4	47	1.7	0.7	306	11.3	4.4	732	27	10.5
2013	356	13.2	5	38	1.4	0.5	286	10.6	4.1	680	25.2	9.7
2014	371	13.8	5.3	45	1.7	0.7	280	10.4	4.1	696	25.9	10.1
Average	360	13.1	5.6	32	1.2	0.5	283	10.3	4.4	675	24.5	10.5

No – Number of new cases, CR – Crude mortality rate, SR – Standardized mortality rate

According to the results of the joinpoint regression analysis in the period between 1999-2014, there was a remarkable increase in men of colon carcinoma mortality rates of 1.8 % as well as rectosigmoidal junction carcinoma of 3.3 % annually (1999-2007 drop of 4.4 %, 2007-2014 increase of 12.9%) Mortality rates for rectal carcinoma were sustainable. In female population, the mortality rates for colon carcinoma and carcinoma of rectosig-

moidal junction were steady during the period of 1999-2014, while a significant annual drop of 0.9% was observed in the mortality rates of rectal carcinoma. In men, when all localizations were observed together, during the period 1999-2014 a notable increase in mortality rates of 1.3% annually in colorectal carcinoma was detected, while in females' the mortality rates of colorectal carcinoma were steady (table 4).

Table 4. Joinpoint regression analysis: trends in standardized mortality rates of colorectal cancer by site and sex, Central Serbia, 1999-2014

Cancer sites (ICD 10)	Males		Females	
	Period	APC (95%CI)	Period	APC (95%CI)
Colon (C18)	1999-2014	1.8 [^] (1.2 to 2.3)	1999-2001	-14.1 (-32.1 to 8.7)
			2001-2005	10.3 (-1.9 to 24.1)
			2005-2014	-2.0 (-4.1 to 0.1)
			1999-2014	-0.6 (-4.5 to 3.3)
Rectosigmoid junction (C19)	1999-2007	-4.4 [^] (-8.4 to -0.2)	1999-2014	3.0 (-1.1 to 7.2)
	2007-2014	12.9 [^] (7.1 to 18.9)		
	1999-2014	3.3 [^] (0.3 to 6.4)		
Rectum (C20)	1999-2014	0.6 (-0.3 to 1.5)	1999-2014	-0.9 [^] (-1.6 to -0.2)
Colorectal (C18-C20)	1999-2014	1.3 [^] (0.8 to 1.8)	1999-2014	0.4 (-0.8 to 1.6)

APC – Annual Percent Change, 95%CI – 95% Confidence interval, [^]The Annual Percent Change (APC) is significantly different from 0 at alpha=0.05, ICD 10 – International Classification of Diseases-10 codes

As stated in the results of the joinpoint regression analysis, when analyzed age-specific rates, there was a remarkable rise in colon carcinoma mortality rates of 1.7% annually between 1999 and 2014 in men age between 35-74 as well as 2.5% rise annually in men 75

years of age and older. Mortality rates were stable for rectosigmoidal junction and rectal carcinoma in all age-specific groups in the observed period (Table 5).

Table 5. Joinpoint regression analysis: trends in age-specific mortality rates of colorectal cancer by site and age groups, males, Central Serbia, 1999-2014

Cancer sites (ICD-10)	<35		35-74		75+	
	Average age-specific rate/ 100,000*	AAPC* (95%CI)	Average age-specific rate/ 100,000*	AAPC* (95%CI)	Average age-specific rate/ 100,000*	AAPC* (95%CI)
Colon (C18)	0.3	-15.1 (-33.8 to 8.9)	23.0	1.7 [^] (1.1 to 2.3)	109.3	2.5 [^] (1.4 to 3.6)
Rectosigmoid junction (C19)	0.0	-**	2.0	3.1 (-0.7 to 6.9)	10.1	8.4 (-4.4 to 22.8)
Rectum (C20)	0.2	0.5 (-11.4 to 14.1)	21.1	0.0 (-1.2 to 1.1)	99.9	0.8 (-0.2 to 1.9)
Colorectal (C18-C20)	0.4	-0.9 (-5.5 to 4.0)	46.7	1.2 [^] (0.6 to 1.7)	219.3	1.8 [^] (1.1 to 2.6)

ICD 10 – International Classification of Diseases-10 codes, AAPC – Average annual percent change, 95%CI – 95% Confidence interval, [^]The Average Annual Percent Change (AAPC) is significantly different from 0 at alpha=0.05, *period 1999-2014, **values of the most rates are zero

Age-specific rates, when analyzed, were stable and without any significant alterations for colon carcinoma mortality rates in females age younger than 35 years and 35 to 74 years. In female population 75 years of age and older during the period 1999-2014 occurs a remark-

able rise of 1.4% annually in colon carcinoma mortality rates. In women, there were no notable changes in any age group in rectosigmoidal junction and rectal carcinoma mortality rates (Table 6).

Table 6. Joinpoint regression analysis: trends in age-specific mortality rates of colorectal cancer by site and age groups, females, Central Serbia, 1999-2014

Females	<35		35-74		75+	
Cancer sites (ICD-10)	Average age- specific rate/ 100,000*	AAPC* (95%CI)	Average age- specific rate/ 100,000*	AAPC* (95%CI)	Average age- specific rate/ 100,000*	AAPC* (95%CI)
Colon (C18)	0.2	-3.7 (-16.1 to 10.5)	14.8	0.4 (-3.8 to 4.7)	65.4	1.4 [^] (0.0 to 2.8)
Rectosigmoid junction (C19)	0.0	-**	1.3	2.3 (-1.8 to 6.7)	5.7	1.7 (-4.2 to 7.9)
Rectum (C20)	0.1	-**	12.0	-1.3 (-2.7 to 0.1)	52.1	-0.4 (-1.7 to 0.8)
Colorectal (C18-C20)	0.3	2.3 (-5.5 to 10.8)	27.7	0.5 (-0.8 to 1.7)	123.2	0.6 (-0.3 to 1.5)

ICD 10 – International Classification of Diseases -10 codes, AAPC – Average annual percent change, 95%CI – 95% Confidence interval, [^]The Average Annual Percent Change (AAPC) is significantly different from 0 at alpha=0.05, *period 1999-2014, **values of the most rates are zero

Average age-specific rates for colorectal carcinoma in males younger than 35 years were 0.4/100,000, in males 35-74 years 46.7/100,000 and in males of 75 and more were 219.3/100,000. Age-specific rates for colorectal carcinoma in males are stable for males younger than 35 years but show significant increase of 1.2% in males age 35-74 years and 1.8% in males of 75 years and above. Average age-specific rates for colorectal carcinoma (C18-C20) in males younger than 35 years were 0.3/100,000, in males 35-74 years 26.7/100,000 and in males of 75 and older were 123.2/100,000. In females, colorectal carcinoma (C18-C20) age-specific rates were stable in all three age groups.

Discussion

Approximate total number of cancer deaths in Europe in 2012 was 1.75 million, 56% of which in men (976,000) and 44% in women (779,000) (13). In Central Serbia, during the period from 1999 to 2014, the annual

average number of cancer deaths was 8,013 in male population and 6,080 in female population, with 57 % being males and 43% being females. European data from 2012 shows that lung cancer was the most common cause of death from cancer in men (254,000; 26.1%), with colorectal cancer in the second place (113,000; 11.6 %) and prostate (92,000; 9.5%) (13). In central Serbia the percentages were very similar in men regarding lung cancer (2395; 29,9 %) colorectal cancer (952; 11.9%) and prostate cancer (634, 7,9%). In female population in Europe, breast cancer was the leading cause of death in 2012 (131,000; 16,8%), the second most common cause was colorectal cancer (102,000; 13,0%) and lung cancer was the third (almost 100,000; 12,7%)(13). In central Serbia breast cancer was the most common cause of death in female population (1103; 18,1%), lung cancer (775, 12,7%) was second and colorectal cancer (675, 11,1%) the third.

A significant variation in the mortality rates across Europe exists, with the high-

est rates in Hungary (30.1/100,000) Slovakia (26.9/100,000), Croatia (26.7/100,000), and Slovenia (22.9/100,000) in men, and in Hungary (14.5/100,000), Denmark (13.0/100,000), Russian Federation (12.6/100,000) and Republic of Moldova (12.6/100,000) in women, while the lowest rates are observed in Greece (9.2/100,000 in men 6.1/100,000 in women) Cyprus (8.6/100,000 in men 5.3/100,000 in women) and Albania (4.8/100,000 in men 3.9/100,000 in women)(14). Mortality rates for both sexes in Central Serbia were similar to those in Eastern European countries (Latvia, Lithuania, Ukraine, and Belarus) (14). It is clear that there is a great variation in mortality rates worldwide, as well as between countries of Europe, which points to variability in the national health system policies (e.g. organized screening for colorectal cancers), availability and quality of treatment, regional variations in the prevalence of major risk factors, disparities in human development and age structure (15). When observing specific regions, highest standardized mortality rates worldwide both in men and women were estimated in Central and Eastern Europe (14.9/100,000 for both sexes) while lowest were in Middle Africa (3.9/100,000 for both sexes) (15).

Mortality rates in Central Serbia observed in present study were 1.7 times higher in male than in female population. This trend is equivalent to almost all countries with exceptions such as Kuwait, Cuba, and Qatar (14). Findings from clinical and preclinical studies indicate that there are sex- and gender-associated differences in colorectal cancer development with both genetic and environmental factors playing roles in sex and gender differences in colon cancer (8). Biological and pathophysiological differences in colorectal cancer development are not clearly investigated according to sex (15). It will be important to improve colorectal cancer screening guidelines which should consider special importance to gender-specific points for colorectal cancer screening.

Our results from Central Serbia show a significant increase in mortality rates in males of 1.3% annually while in female population mortality rates were steady. Comparing to the data from Italy between 1999 and 2016 where mortality rates have been decreasing, 0.6 % per year in males and 1.2% per year in females, data from our study is worrisome (16). Also, in the United States, between 2001 and 2010, colorectal carcinoma mortality rates decreased by approximately 3% annually both in men and women (17). Worldwide data shows

that during the last 15 years mortality rates significantly decreased in developed countries such as the United States and countries of Western and Northern Europe (18,19). On the contrary, continuous rise was present in Eastern and Central European countries, such as Russia (by 0.6% per year)(19). Additionally, increased trends were present in Central and South American countries such as Mexico and Brazil, while in Slovenia and Slovakia rates were high but remained constant for both gender (2,4). These enormous differences in the global distribution of colorectal cancer are largely attributed to diverse risk factor exposure as well as strength of each individual health system. Positive lifestyle changes must be encouraged as well as the promotion of screening tests. Socioeconomic circumstances also affect the ability to save lives due to the fact that countries have limited resources and thus cancer-preventing measures and treatment options are limited (17). As in the United States, Canada, Australia and Norway, there was a significant increase in mortality rates in people younger than 50 years of age in Central Serbia since the early 2000s (4,8).

There are numerous factors that affect the risk for colorectal carcinoma. Decrease in behavioral risk factors and more frequent promotion of positive factors is crucial in lowering the risk and mortality of colorectal carcinoma. Physical inactivity is one of the most reported behavioral factors related to colon cancer. Scientific literature shows that physically active people have a 25% lower risk of colon cancer than the least active people (20). Only every other person in Serbia (50.2%) take at least 30 minutes to walk (21). Being overweight or obese is connected with a higher risk of colorectal carcinoma both in men and women, although more importantly observed in men (22). A number of people that were overweight in Serbia in 2013 was alarmingly high at 56.3% (pre-obese and obese) while the percentage of obesity was a lot higher in men (41.4%) than in women (29.1%) which can justify higher mortality rates in man(21). More important than overall obesity is the abdominal obesity (23,24). Waist circumference as an estimate of abdominal obesity is growing, with values being 94cm in men and 80cm in women in central Serbia (21). Moderate daily fruit and vegetable intake is protective against colon but not rectal cancer (25). In central Serbia, every second person (54.4 %) does not eat or rarely eats fruits (21) which can also be one of the reasons why colon cancer mortality rates increased. There is a lot of research

data which indicate that tobacco smoking can cause colorectal cancer (26). In Serbia, tobacco smoking has been one of the highest prevailing risk factors for a number of years (21). In the age group from 18-64 years of age 43.6 % of men smoke and 38.8 % of women (21). Comparing to the data from 2006 prevalence of daily smokers increased by 3% while in the European Union there was a decrease of 1% (21). Alcohol also, as one of the behavioral factors, is associated with colorectal cancer (3,8). It is estimated that alcohol consumption increases the chance of developing colorectal cancer by 60% (27). Even small doses can increase the risk, but the relationship between alcohol and colorectal cancer is dose-dependent (27). Daily alcohol consumption is present in 8.3% of male and 1.3 % of female population in central Serbia (6) which can also be an indicator of why rates were higher in men (21).

Screening can prevent cancer by the detection and removal of precancerous growths and decrease cancer mortality by detecting cancer at an early stage when treatment is more successful (28). Numerous cost-effective tests can be performed. Randomized clinical trial in the United Kingdom reported that a single sigmoidoscopy in people with age between 55 and 65, decreases colorectal incidence by 33% and mortality by 43% (29). Colonoscopy like sigmoidoscopy allows direct visual examination of the colon and rectum but it has its own limitations such as bowel bleeding especially when a polyp is removed (29). Colonoscopy was found to be an appropriate test in high-risk individuals or as second procedure following a noninvasive test (28). A fecal occult blood test can also detect blood in stool due to the fact that polyps and cancerous tumors bleed from time to time into the intestine. In the United States screening prevalence has been increasing. Data from 2010 reveal that 9% of people older than 50 reported screening with a fecal occult blood test and 56.4 % reported doing sigmoidoscopy or colonoscopy in the past 10 years (30). In Serbia, in 2013 7.6% of the population aged 50-74 performed a fecal occult blood test and only 7.4% of the population has done a colonoscopy in the past 10 years (21,30).

Conclusion

Serbia belongs to the group of countries with high mortality rates of colorectal cancer. In men, when all localizations observed together (colon, rectosigmoid junction, rectum), the mortality rates increased by 1.3% in the

period from 1999-2014, while in women no significant changes in mortality rates occurred. Absence of decrease in colorectal mortality rate in Central Serbia indicates poor effect of national prevention and screening strategies. Working towards improving diet, physical activity, body weight as well as alcohol and smoking cessation are the most important preventive measures. Better implementation of nationally organized screening programmes in Serbia is of the greatest importance.

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